tongue appears smooth in pernicious anemia. Group B vitamin deficiency is associated with oral mucositis and ulcers, glossitis, and burning sensations of the tongue. Scurvy, caused by severe vitamin C deficiency, is associated with gingival swelling, bleeding, ulceration, and tooth loosening. Lack of vitamin D in utero or infancy impairs tooth development. Enamel hypoplasia may result from high levels of fluoride or from disturbances in calcium and phosphate metabolism, which can occur in hypoparathyroidism, gastroenteritis, and celiac disease. The mouth also can reflect the effects of tobacco use, perhaps providing the only visible evidence of its adverse effects.

Oral Manifestations of HIV Infection and of Osteoporosis

The mouth can serve as an early warning system, diagnostic of systemic infectious disease and predictive of its progression, such as with HIV infection. In the case where oral cells and tissues have counterparts in other parts of the body, oral changes may indicate a common pathological process. During routine oral examinations and perhaps in future screening tests, radiographic or magnetic resonance imaging of oral bone may be diagnostic of early osteoporotic changes in the skeleton. The following sections provide details.

HIV Infection

The progressive destruction of the body's immune system by HIV leads to a number of oral lesions, such as oral candidiasis and oral hairy leukoplakia, that have been used not only in diagnosis but also in determining specific stages of HIV infection (CDC 1992, 1994, Montaner et al. 1992, Redfield et al. 1986, Royce et al. 1991, Seage et al. 1997). Oral candidiasis is rarely seen in previously healthy young adults who have not received prior medical therapy such as cancer chemotherapy or treatment with other immunosuppressive drugs (Klein et al. 1984). It was associated with AIDS as early as 1981 in the first report of the syndrome (CDC 1981a) and was frequently noted among otherwise asymptomatic HIV-positive populations (Duffy et al. 1992, Feigal et al. 1991). Oral candidiasis may be the first sign of HIV infection and often occurs as part of the initial phase of infection—the acute HIV syndrome (Tindall et al. 1995). It tends to increase in prevalence with progression of HIV infection when CD4 lymphocyte counts fall (Glick et al. 1994a, Lifson et al. 1994). It also appears to be the most common oral manifestation in pediatric HIV infection (Kline 1996, Leggott 1995, Ramos-Gomez et al. 1996) and has been demonstrated to proceed to esophageal candidiasis, a sign of overt AIDS (Saah et al. 1992). Both the pseudomembranous and the erythematous forms of candidiasis appear to be important predictors of progression of HIV infection (Dodd et al. 1991, Klein et al. 1984, 1992).

Like oral candidiasis, oral hairy leukoplakia in HIV-positive persons heralds more rapid progression to AIDS (Glick et al. 1994a, Greenspan et al. 1987, Lifson et al. 1994, Morfeldt-Manson et al. 1989). Oral hairy leukoplakia is an oral lesion first reported in the early days of the AIDS epidemic (Greenspan D et al. 1984, Greenspan JS et al. 1985). Since its discovery, hairy leukoplakia has been found in HIV-negative persons with other forms of immunosuppression, such as organ or bone marrow recipients and those on long-term steroid therapy (Epstein et al. 1988, Greenspan et al. 1989, Itin et al. 1988, King et al. 1994, Zakrzewska et al. 1995), and less frequently among immunocompetent persons (Eisenberg et al. 1992, Felix et al. 1992).

In a comprehensive review of periodontal conditions, Mealey (1996) noted that linear gingival erythema and necrotizing ulcerative periodontitis may be predictive of progression of HIV infection. Necrotizing ulcerative periodontitis, a more serious periodontal condition observed in HIV-infected persons, is a good predictor of CD4+ cell counts of under 200 per cubic millimeter, and in one study was a strong predictor of rapid progression to death (Glick et al. 1994a,b, Winkler and Robertson 1992, Winkler et al. 1988). In addition, the numerous ulcerative and nonulcerative conditions that affect the oral cavity (Aldous and Aldous 1991, Coates et al. 1996, Cruz et al. 1996, Gandolfo et al. 1991, Itin et al. 1993, Mealey 1996) may affect the biologic activity of HIV and are affected by its treatments.

Other oral conditions, unexpected in the oral cavity, have been noted in the early stages of HIV infection. The increased incidence of Kaposi's sarcoma among young men in New York and California was one of the earliest signs of the AIDS epidemic (CDC 1981b). In addition, some conditions create a problem for differential diagnosis. For example, because involvement of the gingiva is common, early non-Hodgkin's lymphoma lesions are frequently mistaken for common periodontal or dental infections (Epstein and Silverman 1992).

The changing face of the HIV epidemic and changes in the therapies used to manage complications are reflected in changes in the oral manifestations, which warrant continued surveillance and research. The increasing resistance of microorganisms

to antibiotics and antifungals is challenging. On the other hand, the completion of the *Candida albicans* genome may yield better treatments for this opportunistic infection.

Osteoporosis and Oral Bone Loss

With growing numbers of Americans living longer, there have been concomitant increases in the numbers affected by age-related chronic degenerative diseases. Prominent among these conditions are bone and joint diseases. It is likely, for example, that some temporomandibular joint disorders are manifestations of osteoarthritis, rheumatoid arthritis, or myofascial pain. Paget's disease, characterized by enlarged and deformed bone, can be particularly painful and debilitating when it affects the cranial and jaw bones.

Osteoporosis, a degenerative disease characterized by the loss of bone mineral and associated structural changes, has long been suspected as a risk factor for oral bone loss. In addition, measures of oral bone loss have been proposed as potential screening tests for osteoporosis (Jeffcoat 1998). Osteoporosis affects over 20 million people in the United States, most of whom are women, and results in nearly 2 million fractures per year (National Institute of Arthritis, Musculoskeletal and Skin Diseases 2000). The disease is more prevalent in white and Asian American women than in black women.

Oral bone loss has been reported to be more prevalent in women than in men. Studies by Ortman et al. (1989) found a higher percentage of women than men with severe alveolar ridge resorption. This finding parallels the findings of Humphries et al. (1989), who showed that loss of bone mineral density with age in edentulous adult mandibles was more significant in women than in men. Also, the association between estrogen status, alveolar bone density, and history of periodontitis in postmenopausal women has been studied (Payne et al. 1997).

Most of the studies in this area have examined bone loss in women, and most investigators have reported a correlation between oral and skeletal bone loss measured in a variety of ways. Studies of non-osteoporotic women by Kribbs et al. (1990) showed that mandibular bone mass is significantly correlated with skeletal bone mass. Dual photon absorptiometry measurements of jawbone volume in women with osteoporosis have shown that reduction in mandibular bone mass is directly related to the reduction in total skeletal mass density (Kribbs and Chesnut 1984, Kribbs et al. 1983, von Wowern 1985, 1988, von Wowern et al. 1994). Kribbs et al. (1989) further showed that mandibular mass is correlated with all skeletal measures in osteoporotic women and that the height of the edentulous ridge is correlated with total body calcium and mandibular bone mineral density. Hirai et al. (1993) found that the presence of skeletal osteoporosis strongly affects the reduction of the residual ridge in edentulous patients. A small case-control study comparing older female patients with osteoporotic fractures and non-osteoporotic women without fractures found greater periodontal attachment loss in the osteoporotic women than in the controls (von Wowern et al. 1994).

Studies that have controlled for confounding factors also have found correlations between oral bone loss and skeletal bone density. Controlling for pack-years of smoking, education, body mass, and years since menopause, Krall et al. (1994, 1996) found a significant positive relationship between number of teeth and bone mineral density of the spine and the radius. In a cohort of 70 postmenopausal women, Wactawski-Wende et al. (1996) measured skeletal bone mineral density at the Ward's triangle area of the femur and compared it with periodontal disease assessed by attachment loss and the height of alveolar bone measured by radiographs. After adjusting for age, years since menopause, estrogen use, body mass index, and smoking, the investigators concluded that osteopenia (low bone mass) is related to alveolar crestal height and tooth loss in postmenopausal women.

Methods used to measure oral and skeletal bone loss have varied among investigators and have shown different outcomes. Kribbs (1990) found that patients in an osteoporotic group had lost more teeth, had less mandibular bone, and had a thinner bone measured at a part of the jaw (cortex at the gonion) than a comparable non-osteoporotic group. However, using periodontal attachment loss as an indicator of mandibular bone loss, they found no differences between the osteoporotic and the non-osteoporotic group. Mohajery and Brooks (1992) compared non-osteoporotic postmenopausal women with women with mild to moderate osteoporosis and found no correlation between mandibular and skeletal bone mineral density. This study raises questions about the quantification of mild and moderate osteoporosis. Defining healthy periodontal tissues as having no periodontal pockets deeper than 5 millimeters, Hildebolt et al. (1997) studied postmenopausal women with healthy periodontal tissues and found no relationship between periodontal attachment loss and postcranial bone mineral density. However, preliminary studies from the oral ancillary study of the NIH Women's Health Initiative report significant correlations between mandibular basal bone mineral density and hip bone mineral density

($r = 0.74$, $P < .001$) (Jeffcoat et al. in press). In this study, digital subtraction radiography methods were used for mandibular bone measurements, and dual-energy X-ray absorptiometry (DXA) scans were used for the hip bone measurements. The authors of this study propose the possibility that high-quality intraoral radiographs may be used in the future for screening osteopenia.

Larger cross-sectional studies, as well as longitudinal and mechanism studies, are needed to better define the relationship between osteoporosis, osteopenia, and oral bone loss, periodontal disease, and tooth loss. The role of factors involved in the regulation of bone mineral density in men as well as in postmenopausal women needs to be evaluated further with reference to oral bone loss, tooth loss, and periodontal disease. Variables such as sex, race, dietary calcium and phosphorus, vitamin D intake, exercise, body mass index, smoking, genetics, medication use, reproductive history, and psychosocial factors need to be assessed in depth. In addition, reliable and valid criteria and imaging technologies for assessing osteoporosis and oral bone loss are needed to better elucidate the full relationship between skeletal and mandibular bone mineral density, periodontal disease, alveolar ridge resorption, and tooth loss.

TABLE 5.2
Saliva/oral fluids: sampled analytes and current FDA-approved tests

Category	Analytes	FDA-Approved Tests
Drugs of abuse[a]	Alcohol	Cannabinoids
	Amphetamines	Cocaine
	Barbiturates	Cotinine
	Benzodiazepines	Methamphetamine
	Cocaine	Opiates
	LSD	PCP
	Marijuana	Ethanol
	Nicotine	
	Opiates	
	PCP	
Antibodies[b]	HIV	HIV antibodies
	HPV	
	HHV-8/KSH	
	C. parvum	
	Helicobacter pylori	
Hormones[c]	Cortisol	Estriol
	Progesterone	
	Testosterone	
	Substance P	
	Met-enkephalin	
Environmental toxins[d]	Cadmium	
	Lead	
	Mercury	
Therapeutics[e]	Antipyrine	
	Carbamazepine	
	Ciprofloxacin	
	Irinotecan	
	Lithium	
	Methotrexate	
	Phenytoin	
	Phenobarbital	
	Theophylline	

[a] Cone et al. 1993, 1997.
[b] Constantine et al. 1997.
[c] Dabbs 1993, Ellison 1993.
[d] Gonzalez et al. 1997, Joselow et al. 1968.
[e] Wilson 1993.
Source: Constantine et al. 1997.

Oral-fluid-based Diagnostics: The Example of Saliva

The diagnostic value of salivary secretions to detect systemic diseases has long been recognized (Mandel 1990), and oral fluids and tissues (buccal cells) are increasingly being used to diagnose a wide range of conditions. Saliva- and oral-based diagnostics use readily available samples and do not require invasive procedures. Researchers have detected antibodies in saliva that are directed against viral pathogens such as human immunodeficiency virus (Malamud 1997) and hepatitis A virus (O'Farrell et al. 1997) or B virus (Richards et al. 1996). Saliva is being used to detect antibodies, drugs, hormones, and environmental toxins (Malamud and Tabak 1993) (Table 5.2). The simplest tests are those that detect the presence or absence of a substance in the saliva, such as various drugs. Greater technical challenges are presented for tests that will be used for therapeutic monitoring since accurate levels of a substance and/or its metabolites are needed. In these instances the saliva/plasma concentration ratio must be determined experimentally (Haeckel 1993). Tests beyond those listed in Table 5.2 are currently on the market, but do not yet have FDA approval. Saliva is also the fluid of choice to assess the integrity of the mucosal immune system (Mandel 1990).

Most recently, oral fluids have been used as a source of microbial or host DNA. With the advent of polymerase chain reaction methods, the DNA contained within a single cell is sufficient for detection of viruses (e.g., Kaposi's sarcoma-associated herpes virus, Koelle et al. 1997; Epstein-Barr virus, Falk et al. 1997; mumps virus, Afzal et al. 1997) or bacteria (e.g., *Helicobacter pylori*, Reilly et al. 1997). Similarly, DNA extracted from sloughed buccal epithelial cells can be used to genotype persons. This has found application in forensics (Roy et al. 1997) and may be

used for diagnostic purposes in the future (van Schie and Wilson 1997).

Saliva has the potential of replacing blood, the current standard for testing many diseases and conditions (e.g., diabetes, infectious disease, Parkinson's disease, alcoholic cirrhosis, Sjögren's syndrome, and cystic fibrosis sarcoidosis). Important goals for the future are the development of new diagnostic tests for early disease detection, defining individual patient risk of adverse response to drugs, monitoring therapeutic progress, and determining outcomes of treatment. Key issues in the development of a new generation of saliva diagnostics include their selectivity, sensitivity, response time, dynamic range (values of interest), representative sampling, and, perhaps most important, their reliability or stability as well their ability to assess multiple substances simultaneously.

Conclusion

For the clinician the mouth and face provide ready access to physical signs and symptoms of local and generalized disease and risk factor exposure. These signs and symptoms augment other clinical features of underlying conditions. Comprehensive care of the patient requires knowledge of these signs and symptoms, their role in the clinical spectrum of general diseases and conditions, and their appropriate management. Oral biomarkers and surrogate measures are also being explored as means of early diagnosis. With further development and refinement, oral-based diagnostics such as salivary tests can become widely used and acceptable tools for individuals, health care professionals, researchers, and community programs. The continued refinement of imaging techniques also has the potential of using oral imaging to identify early signs of skeletal bone degeneration.

THE MOUTH AS A PORTAL OF ENTRY FOR INFECTION

Chapter 3 provides an overview of the effects of oral microbial infections with viruses, bacteria, and fungi. More than 500 bacterial strains have been identified in dental biofilm, and more than 150 bacterial strains have been isolated from dental pulp infections. More recently, 37 unique and previously unknown strains of bacteria were identified in dental plaque (biofilm) (Kroes et al. 1999). Most oral lesions are opportunistic infections, that is, they are caused by microorganisms commonly found in the mouth, but normally kept in check by the body's defense mechanisms. These microorganisms can induce extensive localized infections that compromise general well-being in and of themselves. However, they also may spread to other parts of the body if normal barriers are breached. The oral mucosa is one such barrier that provides critical defense against pathogens and other challenges (Schubert et al. 1999). Salivary secretions are a second major line of defense. Damage to the oral mucosa from mechanical trauma, infection, or salivary dysfunction with resulting derangements in lubricatory and antimicrobial functions of saliva, as a result of chemotherapy, radiation, and medications causing hyposalivation, allows a portal of entry for invading pathogens.

Oral Infections and Bacteremia

Oral microorganisms and cytotoxic by-products associated with local infections can enter the bloodstream or lymphatic system and cause damage or potentiate an inappropriate immune response elsewhere in the body. Dissemination of oral bacteria into the bloodstream (bacteremia) can occur after most invasive dental procedures, including tooth extractions, endodontic therapy, periodontal surgery, and scaling and root planing. Even routine oral hygiene procedures such as daily toothbrushing, subgingival irrigation, and flossing may cause bacteremia. However, these distant infections have been seen more often in high-risk patients such as those who are immunocompromised.

Oral bacteria have several mechanisms by which they invade mucosal tissues, perhaps contributing to their ability to cause bacteremias. For example, oral bacteria and their products may invade the periodontal tissues directly. *Actinobacillus actinomycetemcomitans* has been found in gingival connective tissue in patients with localized juvenile periodontitis (Christersson et al. 1987a,b, Meyer et al. 1991, Riviere et al. 1991). Invasion of tissue by *Porphyromonas gingivalis* has also been described in vivo (Saglie et al. 1988) and in vitro (Njoroge et al. 1997, Sandros et al. 1993, 1994, Weinberg et al. 1997). Although oral bacteria can enter the blood through injured or ulcerated tissue, bacterial invasion of periodontal tissues represents another possible mechanism.

In the immunocompetent individual, bacteremia originating from the oral cavity is usually transient and harmless. However, if the individual's immune system is compromised, the normally harmless oral bacteria may pose a significant risk. The morbidity and mortality associated with oral foci of infections are hard to assess. This is due to the formidable task

of tracking the source of an infection unless the responsible pathogen is indigenous to a specific anatomic location.

Viridans group streptococci (VGS) have a low degree of virulence but can be associated with morbidity and mortality under certain circumstances. Increased pathogenicity of *Streptococcus viridans* is most prominent in individuals with neutropenia (low blood counts of circulating white blood cells called neutrophils) and has been associated with a toxic-shock-like syndrome (TSLS) or viridans streptococcal shock syndrome (VSSS), as well as with adult respiratory distress syndrome (ARDS) (Bochud et al. 1994).

Although a high degree of morbidity is associated with viridans streptococcal bacteremia, a low incidence of mortality has been reported (Heimdahl et al. 1989). Several studies have shown that under adverse circumstances oral flora and oral infections are associated with increased incidence of morbidity and even mortality (Engelhard et al. 1995, Lucas et al. 1998, Martino et al. 1995, Ruescher et al. 1998, Sparrelid et al. 1998, Sriskandan et al. 1995). Reduction of oral foci of infection decreases systemic complications, specifically in severely neutropenic patients undergoing chemotherapy (Heimdahl et al. 1984). In addition, hospital stays for patients with oral mucositis undergoing autologous bone marrow transplants were longer than for those without oral mucositis (Ruescher et al. 1998).

Other cohorts identified at increased risk for systemic complications due to oral bacteria include hospitalized patients unable to perform adequate oral hygiene, those receiving saliva-reducing medications, and those taking antibiotics that alter the oral flora. A positive dental plaque culture for aerobic pathogens was significantly associated with the development of hospital-acquired pneumonia and bacteremia in a study of individuals in an intensive care unit (ICU) (Fourrier et al. 1998).

In addition, several case reports have been published implicating indigenous oral flora in the development of brain abscesses (Andersen and Horton 1990, Andrews and Farnham 1990, Baker et al. 1999, Gallagher et al. 1981, Goteiner et al. 1982, Saal et al. 1988). This serious condition is associated with a mortality rate of almost 20 percent and full recovery in only slightly more than 50 percent of all patients (Goteiner et al. 1982). These data are based on single case reports and most probably represent rare events. However, they provide additional examples that point to the potential pathogenicity of the normal oral flora during special adverse circumstances.

Oral Infections as a Result of Therapy

Chemotherapy

Oral mucositis can be a major dose-limiting problem during chemotherapy with some anticancer drugs, such as 5-fluorouracil, methotrexate, and doxorubicin. It is estimated that approximately 400,000 patients undergoing cancer therapy each year will develop oral complications (NIH 1990). Infection of ulcerated mucous membranes often occurs after chemotherapy, especially since patients are usually immunocompromised. Bacterial, fungal, and viral causes of mucositis have been identified (Feld 1997). The mechanism by which cancer-chemotherapy-induced mucositis occurs is likely associated with the rapid rate of turnover of oral epithelial cells. In addition, other components likely include upregulation of pro-inflammatory cytokines and metabolic by-products of colonizing oral microflora (Sonis 1998). Chemotherapy alters the integrity of the mucosa and contributes to acute and chronic changes in oral tissue and physiologic processes (Carl 1995). The ulcerated mucosa is susceptible to infection by microbial flora that normally inhabit the oral cavity, as well as by exogenous organisms, and exacerbates the existing mucositis. Further, these microflora can disseminate systemically (Pizzo et al. 1993, Rolston and Bodey 1993). Compromised salivary function can further elevate risk for systemic infection of oral origin.

Both indigenous oral flora and hospital-acquired pathogens have been associated with bacteremias and systemic infection (Schubert et al. 1999). Changes in infection profiles in myelosuppressed (immunosuppressed) cancer patients tend to occur in cyclic fashion over many years. This evolving epidemiology is caused by multiple factors including use of antibiotics. Gram-positive organisms including viridans streptococci and enterococci are currently associated with systemic infection of oral origin in myelosuppressed cancer patients. In addition, gram-negative pathogens including *P. aeruginosa, Neisseria* spp., and *Escherichia coli* remain of concern.

Cancer patients undergoing bone marrow radiation who have chronic periodontal disease may also develop acute periodontal infections with systemic complications (Peterson et al. 1987). The extensive ulceration of gingival sulcular epithelium associated with periodontal disease is not directly observable clinically, yet may represent a source for disseminated infection by an extensive array of organisms. Inflammatory signs may be masked due to the underlying bone marrow suppression.

Viruses are also associated with clinically important oral disease in patients receiving chemotherapy (Rolston and Bodey 1993, Pizzo et al. 1993). Infections caused by herpes simplex virus, varicella-zoster virus, and Epstein-Barr virus typically result from reactivation of a latent virus, whereas cytomegalovirus infections can result via reactivation of a latent virus or a newly acquired virus. The severity of the infection, including fatal outcome, depends on the degree of immunocompromise.

Many agents and protocols have been investigated to manage or prevent mucositis (Peterson 1999, Schubert et al. 1998). For example, various biologic response modifiers, including transforming growth factor β3 or keratinocyte growth factor, have been under recent study in randomized clinical trials. Allopurinol mouthwash and vitamin E have been cited as agents that can decrease the severity of mucositis, although more extensive testing is necessary. Prostaglandin E2 was not shown to be effective in prophylaxis of oral mucositis following bone marrow transplant; however, more recent studies indicate possible efficacy when administered via a different dosing protocol. Oral cryotherapy appears to be efficacious in reducing severity of oral mucositis caused by 5-fluorouracil and related compounds (Rocke et al. 1993).

Local application of capsaicin preparations may be effective in controlling oral mucositis pain as distinguished from tissue injury itself (Berger et al. 1995). Capsaicin and its analogs are the active ingredients in chili peppers. Capsaicin's clinical potential derives from the fact that it elevates the threshold for pain in areas to which it is applied.

Radiation Therapy

Radiation therapy disrupts cell division in healthy tissue as well as in tumors and also affects the normal structure and function of craniofacial tissues, including the oral mucosa, salivary glands, and bone. Oral-facial complications are common after radiation therapy to the head and neck. The most frequent, and often the most distressing, complication is mucositis, but adverse reactions can affect all oral-facial tissues (Scully and Epstein 1996).

Radiation can cause irreversible damage to the salivary glands, resulting in dramatic increases in dental caries. Oral mucosal alterations may become portals for invasion by pathogens, which may be life-threatening to immunosuppressed or bone-marrow-suppressed patients. A less common but very serious adverse consequence is destruction of bone cells and bone death, called osteoradionecrosis (ORN). ORN can result in infection of the bone and soft tissue and can require surgery to excise the dead tissue, which can in turn leave the face badly disfigured as well as functionally impaired (Field et al. 2000). The likelihood of ORN is increased with trauma to the bone, including that caused by tooth extraction (Murray et al. 1980a, b). The risk is especially marked when the trauma occurs near the time of radiation (Epstein et al. 1987). Management includes elimination of acute or potential dental and periodontal foci of disease, increased patient participation in oral hygiene, use of oral topical fluorides for caries prevention, and use of antiviral, antifungal, or antimicrobial therapy for management of infections associated with mucositis.

Combined Cancer Therapies

Rapid developments have occurred in the use of blood cell growth factors for treatment of various conditions, including the anemia of end-stage renal disease, the neutropenia occurring with cancer care, and the bone marrow toxicity and mucositis that can follow aggressive chemotherapy or radiation therapy (Sonis et al. 1997, Williams and Quesenberry 1992). Sonis et al. (1997) found that topical application of transforming growth factor beta (TGF-β) in the hamster model of oral mucositis significantly reduced basal cell proliferation and reduced the severity of mucositis associated with 5-fluorouracil treatment.

Other growth factors considered for use in reducing mucositis include granulocyte-monocyte colony-stimulating factor and granulocyte colony-stimulating factor. Bone morphogenetic proteins are also in development for alleviating the toxicity and mucositis that follow chemotherapy and radiation therapy. Other approaches to reducing mucositis and adverse oral effects of chemotherapy and radiation therapy include fractionating the dose of radiation, and combining chemotherapy with growth factors or with less toxic oncostatic agents. Although the oral mucositis occurring in chemotherapy and in head and neck radiation patients shares many characteristics, distinct differences also exist (NIH 1990, Schubert et al. 1998, Wilkes 1998). For example, in contrast to chemotherapy-associated lesions, radiation damage is anatomically site-specific; toxicity is localized to irradiated tissue volumes. The degree of damage depends on treatment-regimen-related factors, including the type of radiation used, the total dose administered, the fractionation, and field size. Thus, research involving both cohorts of cancer patients remains essential to enhancing patient management.

Development of new technologies to prevent cancer-therapy-induced oral mucositis could

substantially reduce the risk for oral and systemic infections, oral pain, and the number of hospital days. Improvement in quality of life and reduction in health costs are also likely and desirable outcomes.

The new technologies could also provide a setting in which novel classes of chemotherapeutic drugs, utilized at increased doses, could be implemented. These advances in turn could lead to enhanced cancer patient survival and lengthen the duration of disease remission.

Pharmaceuticals

A number of medications used to treat systemic diseases can cause oral complications, ranging from xerostomic effects to alterations in the surface structure of the enamel or mucosa. More than 400 over-the-counter and prescription drugs have xerostomic side effects (Sreebny and Schwartz 1997). These include tricyclic antidepressants, antihistamines, and diuretics. The dimensions and impact of these side effects vary depending on the response of the individual patient and the duration of medication use.

Staining of the teeth or mucosa is associated with a variety of drugs, including tranquilizers, oral contraceptives, and antimalarials. The antibiotic tetracycline can cause enamel hypoplasia when taken by the mother during pregnancy and by children during tooth development. The antimicrobial mouthrinse agent chlorhexidine also can stain the teeth, but this staining is external and can be removed by dental prophylaxis.

Other drugs have been associated with gingival overgrowth, including cyclosporin, which has been used as an immunosuppressant in the United States since 1984 to prevent rejection of transplanted organs and bone marrow. This drug has also been used in other countries for treatment of type 2 diabetes, rheumatoid arthritis, psoriasis, multiple sclerosis, malaria, sarcoidosis, and several other diseases with an immunological basis (Adams and Davies 1984). Other drugs that cause gingival overgrowth include calcium ion channel blocking agents used in the treatment of angina pectoris and postmyocardial syndrome, such as nifedipine and verapamil (Lucas et al. 1985), and phenytoin (sodium 5,5-phenylhydantoin), used in the treatment of epilepsy and also for management of other neurological disorders. Treatment often consists of using an alternate drug, although this is not always possible. Conservative periodontal therapy can reduce the inflammatory component of enlargement; however, surgery is often required. Oral candidiasis is typically caused by opportunistic overgrowth of *Candida albicans*. Drugs that cause systemic bone marrow suppression, oral mucosal injury, or salivary compromise collectively promote the risk for clinical infection. In addition, antibiotics and concurrent steroid therapy often alter oral flora, thereby creating an environment for fungal overgrowth. In high-risk cancer patients, fungal infection can cause severe morbidity and even death.

Infective Endocarditis

The purported connection between oral infection and a specific heart disease, infective endocarditis, has a long history. Endocarditis is caused by bacteria that adhere to damaged or otherwise receptive surfaces of the tissue that lines heart valves (the endocardium) (Weinstein and Schlesinger 1974). Dental and other surgical procedures may predispose susceptible patients to infective endocarditis by inducing bacteremias (Lacassin et al. 1995). However, bacteremias from oral infections that occur frequently during normal daily activities, coincidental even with chewing food, toothbrushing, and flossing, contribute more substantially to the risk of infective endocarditis (Bayliss et al. 1983, Dajani et al. 1997, Strom et al. 1998). Oral organisms are common etiologic agents of infective endocarditis (Bayliss et al. 1983). For example, strains of *S. sanguis*, as well as gram-negative oral bacteria including *Haemophilus aphrophilus*, *A. actinomycetemcomitans*, *E. corrodens*, *Capnocytophaga* spp., and *Fusobacterium nucleatum*, have been associated with bacterial endocarditis (Barco 1991, Geraci and Wilson 1982, Kaye 1994, Moulsdale et al. 1980).

Infective endocarditis occurs with different incubation periods, which differ in causative bacteria and signs and symptoms. For example, *Staphylococcus aureus* endocarditis may have a rapid onset and fatal course if it affects the left side of the heart. With a more indolent course, patients may often be unaware of infection and may experience fever, night chills, myalgia, and arthralgia for a considerable period of time before diagnosis. The infection is often curable if diagnosed and treated early.

The classic risk factors for endocarditis include cardiac valve disorders (valvulopathies) that include rheumatic and congenital heart disease, complex cyanotic heart disease in children, and mitral valve prolapse with regurgitation. Recent studies indicate that the use of certain diet drugs (fenfluramine and dexfenfluramine) has induced cardiac valvulopathy, which may in some cases be transient. Among at-risk persons, bacteremias are more likely to occur in those with periodontal disease (Silver et al. 1977). However, the oral pathogens causing periodontitis have only rarely been shown to cause endocarditis.

Prevention of infective endocarditis from oral bacteria depends on limiting the entry and dissemination of bacteria through the bloodstream and lymphatic circulation. Antibiotic prophylaxis for dental procedures that are likely to provoke bacteremia has historically been recommended (Dajani et al. 1997, Durack 1995). A recent study, however, suggests that receiving dental treatment does not significantly increase the risk of infective endocarditis, even in patients with valvular abnormalities (Strom at al. 1998). Further research is necessary to determine whether some heart or valvular conditions or certain dental procedures, such as surgery or scaling, would require coverage with pre-procedural antibiotics and others would be precluded.

Oral Infections and Respiratory Disease

Pathogens in the oral cavity can also gain access to the airway, sometimes with serious consequences. In adults, bacterial pneumonias are strongly associated with aspiration of bacteria into the lower respiratory tract, which is normally sterile. Common respiratory pathogens such as *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Mycoplasma pneumoniae*, and *Haemophilus influenzae* can colonize the oropharynx and the lower airway. In addition, oral bacteria including *A. actinomycetemcomitans* (Yuan et al. 1992), *Actinomyces israelii* (Morris and Sewell 1994, Zijlstra et al. 1992), *Capnocytophaga* spp. (Lorenz and Weiss 1994), *Eikenella corrodens* (Joshi et al. 1991), *Prevotella intermedia*, and *Streptococcus constellatus* (Shinzato and Saito 1994) can be aspirated into the lower airways (Scannapieco 1998, 1999).

Chronic obstructive pulmonary disease, characterized by obstruction of airflow due to chronic bronchitis or emphysema and by recurrent episodes of respiratory infection, has been associated with poor oral health status (Hayes et al. 1998, Scannapieco et al. 1998). A positive relationship between periodontal disease and bacterial pneumonia has been shown by Scannapieco and Mylotte (1996).

Although oral bacteria, including periodontal pathogens, have the potential for causing respiratory infections, the frequency and nature of such infections are not known and merit further study.

Oral Transmission of Infections

Besides being a portal of entry for infections, the mouth is an important source of potentially pathogenic organisms and is often the vehicle by which infection is delivered to the bodies of others. Microorganisms were not discovered in the mouth until the seventeenth century, when van Leewenhoek examined dental plaque using a microscope he had constructed. In 1884, Koch demonstrated that tuberculosis could be transmitted by airborne droplets from the mouth and respiratory tract. Since that time, we have learned that many common respiratory infections, such as influenza, the common cold, pneumonia, and tuberculosis, can be transmitted from oral secretions. Before the development of effective vaccines, orally transmitted diseases such as chickenpox, measles, mumps, polio, and diphtheria were a major source of morbidity and mortality in childhood. Viral diseases such as hepatitis B, herpes labialis, acute herpetic gingivostomatitis, cytomegalovirus, and infectious mononucleosis may also originate from oral contact.

Disease-causing microorganisms can be spread by direct contact (with saliva or blood from the mouth) or indirect contact (with saliva- or blood-contaminated surfaces, including hands or lips), droplet infection (from coughing, sneezing, or even normal speech), or by aerosolized organisms. These organisms can be inhaled, ingested, or taken in through mucous membranes in the eyes, nose, or mouth or through breaks in the skin. A number of diseases can be spread via oral sexual contact, including gonorrhea, syphilis, trichomoniasis, chlamydia, and mononucleosis.

As mentioned earlier, the oral mucosa and saliva provide significant defense against disease transmission. Epidemiological and animal studies are providing evidence, however, that the oral cavity may be the site for transmission of serious systemic infections despite the protective factors in saliva (see Chapter 2). Infection with HIV provides a case in point (Baba et al. 1996, Dillon et al. 2000, Pope et al. 1997, Ruprecht et al. 1999, Stahl-Hennig et al. 1999, Baron et al. 2000).

Early in the 1980s, when AIDS was first identified in the United States, concern was expressed about casual (i.e., nonsexual) transmission of HIV (CDC 1983, 1985). Detailed household studies did not demonstrate transmission of HIV, even when family members shared eating utensils and toothbrushes with an HIV-affected member (Fischl et al. 1987, Rogers et al. 1990, Sande 1986). Similarly, surveillance data collected over time showed no evidence of casual transmission (Ward and Duchin 1997).

Only one nonoccupational episode of HIV transmission has been attributed to blood-contaminated saliva (CDC 1997); this incident involved intimate kissing between sexual partners. There have been a few cases of HIV transmission from performing oral

sex on a person infected with HIV, and it is also possible to become infected with HIV by receiving oral sex. In the San Francisco Options Study of men who have sex with men identified within 12 months of HIV seroconversion, oral transmission represented 7.8 percent of primary HIV infections (Dillon et al. 2000). Rothenberg et al. (1998) reviewed epidemiologic studies and reports of 38 cases of oral transmission of HIV in the literature. They concluded that although oral-genital contact may be less efficient than needle-sharing or anal intercourse for the transmission of HIV, its increased use by men who have sex with men (Ostrow and DiFranceisco 1996, Schwarcz et al. 1995) and in crack cocaine smokers (Faruque et al. 1996a,b) may increase its contribution to HIV transmission over time. Several studies provide evidence that when the oral environment is compromised, the mouth can be a potential site of transmission of infectious microbes. Data from Faruque et al. (1996a,b) and Wallace et al. (1996) suggest that there is a positive association between the presence of oral lesions resulting from crack cocaine use, receptive oral intercourse, and HIV transmission. A case report has documented the passage of HIV from a partner who is HIV-positive to one who is HIV-negative in the presence of periodontal disease but in the absence of other risk factors (Padian and Glass 1997). Because the type, duration, and frequency of oral contact in past studies may not have been specified, the risk could be somewhat higher for oral transmission of HIV than previously reported. The risk might also vary depending on factors such as viral load, infectious dose, area of exposure, and presence or absence of oral lesions. Additional studies are needed to evaluate the risk of oral-genital transmission of HIV; some are under way (J. Greenspan, K. Page-Schafer, personal communication, 1999).

Other sexually transmitted diseases (STDs) can occur through oral contact. For example, pharyngeal infection with *Chlamydia trachomatis* has been found in 3 to 6 percent of men and women attending STD clinics. Most infections are asymptomatic (Holmes et al. 1999). Another common sexually transmitted infection, herpes simplex virus, commonly infects the pharynx and is seen in 20 percent of patients with primary genital herpes. The painless chancre of primary syphilis can be found in the oral cavity; however, there are no data on the prevalence of this site of infection for *Treponema pallidum*. Among persons with gonorrhea, pharyngeal infection occurs in 3 to 7 percent of heterosexual men, 10 to 20 percent of heterosexual women, and 10 to 25 percent of men who have sex with men (Holmes et al. 1999). Gonococcal infection can cause acute pharyngitis, but is usually asymptomatic. The transmission of pharyngeal gonorrhea to sex partners had been thought to be rare. However, in one study, 17 of 66 men who had sex with men who had urethral gonorrhea reported insertive oral sex as their only risk factor in the past 2 months (Lafferty et al. 1997).

Conclusion

The role of the mouth as a portal of entry for infection presents ever-new challenges for study. Although oral tissues and fluids normally provide significant barriers and protection against microbial infections, at times these infections can not only cause local disease but, under certain circumstances, can disseminate to cause infections in other parts of the body. The control of existing oral infections is clearly of intrinsic importance and a necessary precaution to prevent systemic complications.

ASSOCIATIONS AMONG ORAL INFECTIONS AND DIABETES, HEART DISEASE/STROKE, AND ADVERSE PREGNANCY OUTCOMES

Recent studies have reported associations between oral infections—primarily periodontal infections—and diabetes, heart disease and stroke, and adverse pregnancy outcomes, but sufficient evidence does not yet exist to conclude that one leads to the other. This section characterizes the nature of these associations by describing the quality of the evidence supporting the reports. Both observational and experimental studies were accepted as admissible evidence. Table 5.3 presents the hierarchy of evidence used to interpret these associations. Where there are operative mechanisms proposed that support an association between oral infectious agents and the systemic conditions in question, they are introduced at the outset. These are followed by animal studies and then by epidemiologic or population-based studies. The evidence for each association is presented in the table in rank order according to the rigor of the study design.

The Periodontal Disease–Diabetes Connection

There is growing acceptance that diabetes is associated with increased occurrence and progression of periodontitis—so much so that periodontitis has been called the "sixth complication of diabetes" (Löe 1993).

The risk is independent of whether the diabetes is type 1 or type 2. Type 1 diabetes is the condition in which the pancreas produces little or no insulin. It usually begins in childhood or adolescence. In type 2 diabetes, secretion and utilization of insulin are impaired; onset is typically after age 30. Together, these two types of diabetes affect an estimated 15.7 million people in the United States and represent the seventh leading cause of death (NIDDK 1999). The goal of diabetic care is to lower blood glucose levels to recommended levels. Some investigators have reported a two-way connection between diabetes and periodontal disease, proposing that not only are diabetic patients more susceptible to periodontal disease, but the presence of periodontal disease affects glycemic control. This section explores the bidirectional relationship, beginning with the effects of diabetes on periodontal disease.

Effects of Diabetes on Periodontitis Prevalence and Severity

Several reviews have described candidate mechanisms to explain why individuals with diabetes may be more susceptible to periodontitis (Grossi and Genco 1998, Manouchehr-Pour and Bissada 1983, Murrah 1985, Oliver and Tervonen 1994, Salvi et al. 1997, Wilton et al. 1988). These include vascular changes, alterations in gingival crevicular fluid, alterations in connective tissue metabolism, altered host immunological and inflammatory response, altered subgingival microflora, and hereditary patterns. Studies were classified by type of diabetes and age of study population (see Table 5.4).

Type 1 Diabetes. Ten reports focused principally on children and adolescents with type 1 diabetes, comparing them with groups of similar ages without diabetes (Cianciola et al. 1982, de Pommereau et al. 1992, Faulconbridge et al. 1981, Firatli 1997, Firatli et al. 1996, Goteiner et al. 1986, Harrison and Bowen 1987, Novaes et al. 1991, Pinson et al. 1995, Ringelberg et al. 1977). All but one of the studies (Goteiner et al. 1986) reported greater prevalence, extent, or severity of at least one measure or index of periodontal disease (e.g., gingival inflammation, probing pocket depth, loss of periodontal attachment, or radiographic evidence of alveolar bone loss) among subjects with diabetes, even though these investigations were conducted in a variety of countries across several continents.

Another set of studies on the relationship between type 1 diabetes and periodontal disease included subjects with and without diabetes between the ages of 15 and 35 (Cohen et al. 1970, Galea et al. 1986, Guven et al. 1996, Kjellman et al. 1970, Rylander et al. 1987, Sznajder et al. 1978). All six studies reported greater prevalence, extent, or severity of at least one measure or index of periodontal disease.

A third set of studies conducted in Scandinavia looked at the relationship between periodontal disease and type 1 diabetes (or diabetes reported as requiring insulin therapy without specification of diabetes type) in adults between 20 and 70 years old. Three of the four studies were cross-sectional (Glavind et al. 1968, Hugoson et al. 1989, Thorstensson and Hugoson 1993), and one was a treatment follow-up study (Tervonen and

TABLE 5.3
Hierarchy of evidence used in analyzing and interpreting results

Quality of Evidence	
I:	Evidence obtained from at least one properly randomized controlled trial.
II-1:	Evidence obtained from well-designed controlled trials without randomization.
II-2:	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.
II-3:	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.
III:	Opinions of respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.
Strength of Recommendation	
A:	There is good evidence to support the recommendation.
B:	There is fair evidence to support the recommendation.
C:	There is insufficient evidence to recommend for or against, but recommendations may be made on other grounds.
D:	There is fair evidence to support the recommendation that the intervention be excluded.
E:	There is good evidence to support the recommendation that the intervention be excluded.

Source: Adapted from U.S. Preventive Services Task Force 1996.

TABLE 5.4

Summary of studies of the association between diabetes and periodontal diseases, classified by strength of evidence, diabetes type, and age group

	Country	Study Design	Diabetes Type[a]	Number of Subjects a. Diabetes b. Control	Ages[b] a. Diabetes b. Control	Measure of Periodontal Disease Status: Diabetes Effect[c]	Other Diabetes-Related Variables Considered	Evidence Level[d]
Firatli 1997	Turkey	Prospective	1	a. 44 b. 20	a. 12.2 (mean) b. 12.3 (mean)	Ging: 0s Ppd: 0s Lpa: 1s	Glycemic control Duration of diabetes	II-2
Cohen et al. 1970	USA	Prospective	1*	a. 21 b. 18	a. 18, 35 b. 18, 35	Ging: 1s Lpa: 1r, 1s	None	II-2
Tervonen and Karjalainen 1997	Finland	Prospective	1	a. 36 b. 10	a. 24, 36 b. 24, 36	Ging: 0e Ppd: 1r Lpa: 1e	Glycemic control Duration of diabetes Diabetes complications	II-2
Novaes et al. 1996	Brazil	Prospective	2	a. 30 b. 30	a. 30, 77 b. 30, 67	Ppd: 1s, 1r Lpa, 1s, 1r	Glycemic control	II-2
Nelson et al. 1990	USA	Prospective	2	a. 720 b. 1,553	a. 15, 55+ b. 15, 55+	XRBL: 1i, 1p	None	II-2
Taylor et al. 1998a	USA	Prospective	2	a. 24 b. 338	a. 15, 57 b. 15, 57	XRBL: 1i, 1r	None	II-2
Taylor et al. 1998b	USA	Prospective	2	a. 21 b. 338	a. 15, 49 b. 15, 49	XRBL: 1i, 1r	Glycemic control	II-2
Goteiner et al. 1986	USA	Cross-sectional	1	a. 169 b. 80	a. school ages b. 5, 18	Ging: 0s Lpa: 0p, 0s PDI: 0s	None	III
Harrison and Bowen 1987	USA	Cross-sectional	1	a. 30 b. 30	a. 4, 19 b. 4, 19	Ging: 1s Lpa: 1p	Glycemic control	III
Novaes et al. 1991	Brazil	Cross-sectional	1	a. 30 b. 30	a. 5, 18 b. 5, 18	Ging: 1s Ppd: 0s XRBL: 1s	None	III
Cianciola et al. 1982	USA	Cross-sectional	1	a. 263 b. 208	a. <10, >19 b. <10, >19	Ging: 1p Lpa: 1p XRBL: 1p, 1s JPS: 1p, 1s	Duration of diabetes	III
de Pommereau et al. 1992	France	Cross-sectional	1	a. 85 b. 38	a. 12, 18 b. 12, 18	Ging: 1e Lpa: 0e, 0p, 0s XRBL: 0e, 0p, 0s	Glycemic control Duration of diabetes	III
Ringelberg et al. 1977	USA	Cross-sectional	1	a. 56 b. 41	a. 10, 16 b. 10, 12	Ging: 1s MGI: 1s	None	III
Firatli et al. 1996	Turkey	Cross-sectional	1	a. 77 b. 77	a. 12.5 (mean) b. 12.6 (mean)	Ging: 0s Ppd: 1s Lpa: 1s	Duration of diabetes	III
Pinson et al. 1995	USA	Cross-sectional	1	a. 26 b. 24	a. 7-18 b. 7-18	Ging: 1s Ppd: 0s Lpa: 0s	Glycemic control Duration of diabetes	III
Faulconbridge et al. 1981	England	Cross-sectional	1	a. 94 b. 94	a. 5, 17 b. 5, 17	Ging: 1s	Duration of diabetes	III
Kjellman et al. 1970	Sweden	Cross-sectional	1*	a. 105 b. 52	a. 15, 24 b. 15, 24	Ging: 1e Ppd: 0s XRBL: 0s	Glycemic control Diabetes complications	III
Guven et al. 1996	Turkey	Cross-sectional	1	a. 10	a. 18, 27	Ging: 1e	None	III

(continues)

TABLE 5.4 continued

	Country	Study Design	Diabetes Type[a]	Number of Subjects a. Diabetes b. Control	Ages[b] a. Diabetes b. Control	Measure of Periodontal Disease Status: Diabetes Effect[c]	Other Diabetes-Related Variables Considered	Evidence Level[d]
Rylander et al. 1987	Sweden	Cross-sectional	1	a. 46 b. 41	a. 18, 26 b. 19, 25	Ging: 1e, 1p Ppd: 0e Lpa: 1e, 1p XRBL: 0p	Diabetes complications	III
Sznajder et al. 1978	Argentina	Cross-sectional	1*	a. 20 b. 26	a. 9, 29 b. 9, 29	Ging: 1s Lpa: 0s	None	III
Galea et al. 1986	Malta	Cross-sectional	1*	a. 82 b. unknown	a. 5, 29 b. 5, 29	Ppd: 1p	Glycemic control Duration of diabetes Diabetes complications	III
Hugoson et al. 1989	Sweden	Cross-sectional	1	a. 154 b. 77	a. 20, 70 b. 20, 70	Ging: 1e Ppd: 1e, 1p, 1s XRBL: 1s	Duration of diabetes	III
Glavind et al. 1968	Denmark	Cross-sectional	1*	a. 51 b. 51	a. 20, 40 b. 20, 40	Ging: 0s Ppd: 0s Lpa: 1s XRBL: 1s	Duration of diabetes Diabetes complications	III
Thorstensson and Hugoson 1993	Sweden	Cross-sectional	1	a. 117 b. 99	a. 40, 70 b. 40, 70	Ging: 0e Ppd: 1e, 1s XRBL: 1s	Duration of diabetes Onset age	III
Morton et al. 1995	Mauritius	Cross-sectional	2	a. 24 b. 24	a. 26, 76 b. 25, 73	Ging: 1p Ppd: 1s Lpa: 1s	None	III
Shlossman et al. 1990	USA	Cross-sectional	2	a. 736 b. 2,483	a. 5, 45+ b. 5, 45+	Lpa: 1p XRBL: 1p	None	III
Emrich et al. 1991	USA	Cross-sectional	2	a. 254 b. 1,088	a. 15, 55+ b. 15, 55+	Lpa: 1p, 1s XRBL: 1p, 1s	None	III
Wolf 1977	Finland	Cross-sectional	1,2	a. 186 b. 156	a. 16, 60 b. 16, 60	Ging: 1s Lpa: 1s XRBL: 1s	Glycemic control Duration of diabetes Diabetes complications	III
Benveniste et al. 1967	USA	Cross-sectional	1,2*	a. 53 b. 71	a. 5, 72 b. 5, 72	Ging: 0s Ppd: 0p, 0s	None	III
Finestone and Boorujy 1967	USA	Cross-sectional	1,2*	a. 189 b. 64	a. 20, 79 b. 20, 79	PI: 1s	Glycemic control Duration of diabetes Diabetes complications	III
Belting et al. 1964	USA	Cross-sectional	1,2*	a. 78 b. 79	a. 20, 79 b. 20, 79	PI: 1s	Diabetes severity	III
Oliver and Tervonen 1993	USA	Cross-sectional	1,2	a. 114 b. 15,132	a. 20, 64 b. 20, 64	Ppd: 1e, 1p Lpa: 1e, 0p, 0s	None	III
Yavuzyilmaz et al. 1996	Turkey	Cross-sectional	1,2	a. 17 b. 17	a. 25, 74 b. 19, 29	Ppd: 1s	None	III
Bridges et al. 1996	USA	Cross-sectional	1,2	a. 118 b. 115	a. 24, 78 b. 24, 78	Ging: 0s Ppd: 0s Lpa: 1s	Glycemic control Duration of diabetes	III
Sandler and Stahl 1960	USA	Cross-sectional	1,2*	a. 100 b. 3,894	a. 20, 69 b. 20, 69	PDR: 1e	None	III
Bacic et al. 1988	Yugoslavia	Cross-sectional	1,2	a. 222 b. 189	a. <20, 60+ b. <20, 60+	Ppd: 1e, 1p, 1s	Glycemic control Duration of diabetes Diabetes complications	III
Hove and Stallard 1970	USA	Cross-sectional	1,2*	a. 28 b. 16	a. 20, 40+ b. 20, 40+	Ging: 0s Ppd: 0s XRBL: 0s	Duration of diabetes Diabetes severity	III

	Country	Study Design	Diabetes Type[a]	Number of Subjects a. Diabetes b. Control	Ages[b] a. Diabetes b. Control	Measure of Periodontal Disease Status: Diabetes Effect[c]	Other Diabetes-Related Variables Considered	Evidence Level[d]
Mackenzie and Millard 1963	USA	Cross-sectional	9	a. 124 b. 92	a. 32, 78 b. 32, 78	XRBL: 0s	None	III
Sznajder et al. 1978	Argentina	Cross-sectional	9	a. 63 b. 39	a. 30, 49 b. 30, 50	Ging: 1s Lpa: 1s	None	III
Dolan et al. 1997	USA	Cross-sectional	9	Weighted a. 107 b. 554	a. 45, 75+ b. 45, 75+	Lpa: 1e, 1p, 1s	None	III
Grossi et al. 1994	USA	Cross-sectional	9	a. 1,426 b. 69	All: 25, 74; unknown for diabetes	Lpa: 1s, 1p	None	III
Tervonen and Knuuttila 1986	Finland	Cross-sectional	9	a. 50 b. 53	a. <30, 40+ b. <30, 40+	Ging: 1e Ppd: 1e, 1p XRBL: 0s	Glycemic control	III
Campbell 1972	Australia	Cross-sectional	9	a. 70 b. 102	a. 17, 39 b. 17, 39	PI: 1p, 1s	None	III
Albrecht et al. 1988	Hungary	Cross-sectional	9	a. 1,360 b. 625	a. 15, 65+ b. 15, 65+	Ging: 1s PI: 0s	None	III
Szpunar et al. 1989 (NHANES I)	USA	Cross-sectional	9	a. 474 b. 15,174	a. 6, 65+ b. 6, 65+	PI: 1s	None	III
Szpunar et al. 1989 (HHANES)	USA	Cross-sectional	9	a. 322 b. 8,040	a. 15, 65+ b. 12, 65+	PI: 1s	None	III

[a] Diabetes type: 1 = type 1 diabetes mellitus; 2 = type 2 diabetes mellitus; 1,2 = both type 1 and type 2 diabetes mellitus; 9 = diabetes type not specified and not clearly ascertainable from other information in the report; * = diabetes type not specified but ascertained by reviewer from other information in the report.

[b] Ages: subjects' ages presented as minimum, maximum reported for those with diabetes and controls unless otherwise specified.

[c] Measure of periodontal disease status. Measures used include Ging = gingivitis or gingival bleeding; Ppd = probing pocket depth; Lpa = loss of periodontal attachment; XRBL = radiographic bone loss; JPS = juvenile periodontal score; MGI = modified gingival index; PI = Russell's periodontal index; PDR = periodontal disease rate (proportion of teeth affected by periodontal disease). The number following the measure corresponds to greater disease in those with diabetes (1) or no difference between those with diabetes and controls (0). The letter following the number corresponds to the parameter(s) assessed in the study: e = extent; i = incidence; p = prevalence; s = severity; r = progression.

[d] Levels of evidence are delineated in Table 5.3.

Karjalainen 1997). All four studies reported greater prevalence, extent, or severity of at least one measure of periodontal disease.

Type 2 Diabetes. There are fewer reports on the relationship between type 2 diabetes and periodontal disease, particularly where type 2 diabetes is explicitly identified or discernible from the ages of subjects. Seven studies limited to subjects with type 2 diabetes included a comparison group without diabetes. Two of these studies included only adult subjects (Morton et al. 1995, Novaes et al. 1996); the remaining five were large population-based studies of diabetes and periodontal disease in Pima Indians, a group with the highest known prevalence of type 2 diabetes in the world. The Pima Indian studies included subjects aged 5 years and older (Shlossman et al. 1990) or 15 and older (Emrich et al. 1991, Nelson et al. 1990, Taylor et al. 1998a,b). All seven studies reported greater prevalence, extent, or severity of periodontal disease among subjects with diabetes for at least one measure of periodontal disease. Three of these studies were longitudinal (Nelson et al. 1990, Taylor et al. 1998a,b) and showed that the progression of periodontal disease was greater in diabetes patients than in individuals without diabetes.

In addition to finding significant differences in various measures of periodontal status between subjects with and without type 2 diabetes, a number of these reports also provide estimates of association and risk. Using periodontal attachment loss as the measure, Emrich et al. (1991) estimated that people with type 2 diabetes were 2.8 times more likely to have destructive periodontal disease (odds ratio, 2.8; 95 percent CI, 1.9 to 4.1). When they used radiographic bone loss as the measure and controlled for

other important covariates, the estimate rose to 3.4 (odds ratio, 3.4; 95 percent CI, 2.3 to 5.2). Nelson et al. (1990) quantified the increased risk of advanced periodontal disease in Pima Indians with and without type 2 diabetes, finding the prevalence of periodontal disease in subjects with diabetes to be 2.6 times greater (95 percent CI, 1.0 to 6.6) than that of subjects without diabetes. Taylor et al. (1996), in another analysis of data from the Pima Indians, reported that type 2 diabetes was a significant risk factor for more severe alveolar bone loss progression (odds ratio, 4.2; 95 percent CI, 1.8 to 9.9), in addition to being a significant risk factor for the prevalence of alveolar bone loss.

Studies of Individuals with Type 1 or Type 2 Diabetes. Twelve reports included analyses in which subjects with type 1 and type 2 diabetes were not separated. All of these studies were cross-sectional and included adults; two studies included children or adolescents as well (Benveniste et al. 1967, Wolf 1977). Nine of the 12 studies reported greater prevalence, extent, or severity of periodontal disease among the diabetic subjects for at least one measure or index of periodontal disease (Bacic et al. 1988, Belting et al. 1964, Bridges et al. 1996, Finestone and Boorujy 1967, Hove and Stallard 1970, Oliver and Tervonen 1993, Sandler and Stahl 1960, Yavuzyilmaz et al. 1996, Wolf 1977).

Hove and Stallard (1970) and Benveniste et al. (1967) did not find significant differences in periodontal disease between subjects with and without diabetes. The Hove and Stallard report included 28 subjects with diabetes and 16 without diabetes and may not have had enough statistical power to detect clinical differences, although they were able to detect a significantly higher prevalence of gingival vascular changes in subjects with diabetes. Benveniste et al. (1967) commented that their results may have been influenced by use of relatives without diabetes as the comparison group and that the subjects with diabetes were all under reasonably good control with either insulin or dietary regulation. Both factors may have minimized differences between the groups.

Diabetes Type Not Specified. The final set of reports on the association between diabetes and periodontal diseases consists of seven cross-sectional studies in which the type of diabetes was not specified and was not easily determined from other information provided. Four of the seven studies included only adults (Dolan et al. 1997, Grossi et al. 1994, Mackenzie and Millard 1963, Tervonen and Knuuttila 1986). In the other three studies, subjects ranged in age from childhood to older adulthood (Albrecht et al. 1988, Campbell 1972, Szpunar et al. 1989). Szpunar et al. (1989) presented analyses of two separate national surveys (the National Health and Nutrition Examination Survey, NHANES I, conducted between 1971 and 1974, and the Hispanic Health and Nutrition Examination Survey, HHANES, conducted between 1982 and 1984).

All seven studies found subjects with diabetes to have increased prevalence, extent, and severity of periodontal disease. The statistical significance of the diabetes effect was markedly diminished in the final linear regression model used by Szpunar et al. (1989) in analysis of the NHANES I data. Two of the population-based surveys, Grossi et al. (1994) and Dolan et al. (1997), provided epidemiologic estimates of the association of diabetes and attachment loss severity with odds ratios of 2.3 (95 percent CI, 1.2 to 4.6) and 1.9 (95 percent CI, 1.3 to 3.0), respectively, while controlling for other covariates.

Conclusion. Diabetes is a risk factor for the occurrence and prevalence of periodontal diseases. Although there is insufficient evidence of a causal association, the findings of greater prevalence, severity, or extent of at least one manifestation of periodontal disease in individuals with diabetes is remarkably consistent in the overwhelming majority of studies. Furthermore, there are no studies with superior design features in the literature to refute this assessment. The studies were conducted in distinctly different settings, with subjects from different ethnic populations and of different ages, and with a variety of measures of periodontal status. This inevitable variation in methodology and study populations limits the possibility that the same biases apply in all the studies. There is a need for further research using stronger designs that also control for confounding variables such as socioeconomic status.

Glycemic Control

Several lines of evidence support the plausibility that periodontal infections contribute to problems with glycemic control, thus compromising the health of diabetic patients. It has been reported that the chronic release of tumor necrosis factor alpha (TNF-α) and other cytokines such as those associated with periodontitis interferes with the action of insulin and leads to metabolic alterations (Hotamisligil et al. 1993, Flier 1993). Other studies have noted relationships between insulin resistance and active inflammatory connective tissue diseases (Hallgren and Lundquist 1983, Svenson et al. 1987), other clinical diseases (Beck-Nielsen 1992, Beisel 1975), acute

infection (Drobny et al. 1984, Sammalkorpi 1989), and periodontal disease (Grossi et al. 1999). Grossi and Genco (1998) have proposed a model whereby periodontal infection contributes to hyperglycemia and complicates metabolic control in diabetes.

Clinical Studies. The effects of periodontal infection on glycemic control have been investigated in a small number of clinical studies that looked at metabolic control at baseline and following various periodontal treatments (see Table 5.5; Aldridge et al. 1995, Christgau et al. 1998, Grossi et al. 1996, 1997, Miller et al. 1992, Seppala and Ainamo 1994, Seppala et al. 1993, Smith et al. 1996, Westfelt et al. 1996, Williams and Mahan 1960, Wolf 1977). One report is based on an epidemiological cohort study (Taylor et al. 1996).

The randomized controlled trials of Grossi et al. (1997) involving populations with type 2 diabetes found that use of the systemic antibiotic doxycycline to treat periodontitis patients with diabetes resulted in a transient (3 to 6 months) improvement in glycemic control. On the other hand, the two controlled trials conducted in London by Aldridge et al. (1995) involving patients with type 1 diabetes found no effect. Taken together, these three studies provide inconsistent results and are limited in how well they generalize to broader populations. A small uncontrolled study of 10 patients by Miller et al. (1992) also reported an improvement in glycemic control of diabetic patients whose periodontal disease was treated with mechanical therapy and systemic doxycycline. Five of the above-mentioned studies did not include control groups (Miller et al. 1992, Seppala et al. 1993, Smith et al. 1996, Williams and Mahan 1960, Wolf 1977), and four were not specifically designed to address the relationship between periodontal therapy and glycemic control (Grossi et al. 1996, Seppala et al. 1993, Smith et al. 1996, Westfelt et al. 1996), although the data collected allowed the investigators to address the issue. One nonrandomized but controlled clinical trial of nonsurgical periodontal therapy found no significant influence on medical data for the diabetic patients (Christgau et al. 1998). A clear relationship between improvement in periodontal health and glycemic control has not been shown. The studies seem to suggest that antibiotic treatments may help in glycemic control. A recent longitudinal study indicates inflammation may be a precursor to the onset of type 2 diabetes (Schmidt et al. 1999). Thus periodontal infection may contribute to that inflammation.

Conclusion. The body of literature concerning the relationship between periodontal infection and impaired glycemic control is varied in the strength, quantity, breadth, and consistency of evidence presented. The preliminary evidence, while encouraging, does not support a clear-cut conclusion that treating periodontal infection can contribute to management of glycemic control in type 1 or type 2 diabetes. As the table indicates, only studies using systemic antibiotic treatment affected glycemic control favorably. The results suggest that infections other than periodontitis may be implicated or that intensive treatment of periodontal infections with systemic antibiotics is necessary to affect glycemic control favorably. Further rigorous controlled studies in diverse populations are warranted.

The Oral Infection–Heart Disease and Stroke Connection

During the past decade, infectious agents have become recognized as causes of systemic diseases, without fever or other traditional signs of infection. *Helicobacter pylori* is associated with peptic ulcers and, along with *Chlamydia pneumoniae* and cytomegalovirus, is now thought to be associated with increased risk for cardiovascular disease as well as malignancies (Wu et al. 2000). Studies investigating the relationship between oral and dental infections and the risk for cardiovascular disease suggest that there is potential for oral microorganisms, such as periodontopathic bacteria, and their effects to be linked with heart disease.

Mechanisms of Action

Infectious agents are thought to affect the risk of heart disease through several possible mechanisms. Bacteria or viruses originating in tissues such as the lungs or oral mucosa may directly infect blood vessel walls. Such infection may be largely asymptomatic, but may cause local vascular inflammation and injury, which would contribute to the development of lipid-rich plaques and atherosclerosis. Bacteria or viruses may also interact with white blood cells or platelets, both of which integrate into the developing atherosclerotic plaque. Cells of the blood vessel wall and white blood cells and platelets can release prostaglandins (especially PGE_2), interleukins (especially IL-1), thromboxane B2 (TBX_2), and tumor necrosis factor alpha (TNF-α). Bacterial products in the blood may also stimulate liver production of other pro-inflammatory or pro-coagulant molecules such as C-reactive protein and fibrinogen. Microbes may also stimulate expression of tissue factor, which would activate coagulation. During the process of

TABLE 5.5
Effects of periodontal disease and its treatment on glycemic control: clinical and epidemiological evidence

	Study Design[a]	Diabetes Type	Number of subjects a. Treatment (ages) b. Control (ages)	Follow-up Time	Periodontal Therapy	Metabolic Control Outcome	Effects on Metabolic Control	Evidence Level[b]
Aldridge et al. 1995, Study 1	RCT	Type 1	a. 16 (16-40) b. 15 (16-40)	2 months	Experimental group: oral hygiene instruction, scaling, adjustment of restoration margins, and reinforcement after 1 month; control group: no treatment	Glycated hemoglobin, fructosamine	Periodontal treatment had no effect on change in glycated hemoglobin.	I
Aldridge et al. 1995, Study 2	RCT	Type 1	a. 12 (20-60) b. 10 (20-60)	2 months	Experimental group: oral hygiene instruction, scaling and root planing, extractions, root canal therapy; control group: no treatment	Glycated hemoglobin	Periodontal treatment had no effect on change in glycated hemoglobin.	I
Grossi et al. 1996, 1997	RCT	Type 2	a. 89 (25-65) b. 24 (25-65)	12 months	Experimental groups received either systemic doxycycline or placebo and ultrasonic bactericidal curettage with irrigation using either water, chlorhexidine, or povidone-iodine	Glycated hemoglobin	The three groups receiving doxycycline and ultrasonic bacterial curettage showed significant reductions ($P < 0.04$) in mean glycated hemoglobin at 3 months.	I
Christgau et al. 1998	Treatment study, non-RCT	Type 1 and type 2	a. 20 (30-66) b. 20 (30-66)	2 months	Scaling/root planing; subgingival irrigation with chlorhexidine; oral hygiene instruction; and extractions	Glycated hemoglobin	No effect on glycated hemoglobin.	II-1
Westfelt et al. 1996	Treatment study, non-RCT	Type 1 and type 2	a. 20 (45-65) b. 20 (45-65)	5 years	Baseline oral hygiene instruction, scaling and root planing followed by periodic prophylaxis, oral hygiene instruction, localized sub-gingival plaque removal, and surgery at sites with bleeding on probing and a periodontal probing depth of >5 mm	Glycated hemoglobin	"The mean value of HbA1c between baseline and 24 months was not significantly different from that between 24 and 60 months."	II-1
Smith et al. 1996	Treatment study, non-RCT	Type 1	a. 18 (26-57) b. 0	2 months	Scaling and root planing with ultrasonics and curets; oral hygiene instruction	Glycated hemoglobin	Found no statistically or clinically significant change in glycated hemoglobin.	II-1
Taylor et al. 1996	Historical prospective cohort	Type 2	No treatment or control subjects 49 (severe periodontitis) 56 (less severe periodontitis)	2-4 years	Not applicable	Glycated hemoglobin	Those with severe periodontitis were ~6 times more likely to have poor glycemic control at follow-up.	II-2
Miller et al. 1992	Treatment study, non-RCT	Type 1	a. 10 (not given) b. 0	8 weeks	Scaling and root planing, systemic doxycycline	Glycated hemoglobin, glycated albumin	Found decrease in glycated hemoglobin and glycated albumin in patients with improvement in gingival inflammation ($P < 0.01$). Patients with no improvement in gingival inflammation had either no change or increase in glycated hemoglobin post treatment.	III

coagulation, platelets would become trapped in the growing clot or thrombus. Microthrombus formation is one of the key factors in the development of atherosclerotic plaques. As atherosclerotic plaques enlarge, the lumen of the coronary blood vessels narrows and the blood supply to the heart muscle becomes reduced. A frank heart attack or myocardial infarction results when a larger part of the coronary artery

	Study Design[a]	Diabetes Type	Number of subjects a. Treatment (ages) b. Control (ages)	Follow-up Time	Periodontal Therapy	Metabolic Control Outcome	Effects on Metabolic Control	Evidence Level[b]
Seppala et al. 1993, Seppala and Ainamo 1994	Treatment study, non-RCT	Type 1	a. 38 for 1 year; 22 for 2 years[c] 26 PIDD-1y (48 ± 6) 12 CIDD-1y (43 ± 5) 16 PIDD-2y 6 CIDD-2y b. 0	2 years	Scaling and root planing, periodontal surgery, and extractions	Medical history for baseline control status; glycosylated hemoglobin A1 and blood glucose for assessing response to treatment	Reported an improvement of the HBA1 levels of the PIDD and CIDD subjects ($P < 0.068$, t-test).	III
Williams and Mahan 1960	Descriptive clinical study	Not specified	a. 9 (20-32) b. 0	3-7 months	Extractions, scaling and curettage, gingivectomy, systemic antibiotics	Insulin requirement; diabetes control (not operationally defined)	7 of 9 subjects had "significant" reduction in insulin requirements.	III
Wolf 1977	Treatment study, non-RCT	Type 1 and type 2	a. 117 (16-60) b. 0	8-12 months	Scaling and home care instruction, periodontal surgery, extractions, endodontic treatment, restorations, denture replacement or repair	Blood glucose, 24-h urinary glucose, insulin dose	Compared 23 subjects with improved oral infections with 23 who had no improvement after treatment for oral infection and inflammation. The subjects with improved oral inflammation and infection tended to demonstrate diabetes control improvement ($P < 0.1$). However, Wolf states in discussion, "treatment of periodontal inflammation and periapical lesions ... does little to improve the control of diabetes."	III

[a] RCT = randomized controlled trial.

[b] Levels of evidence are delineated in Table 5.3. Note that because this body of literature is small, this review does not distinguish between "well-designed" studies and otherwise in assigning the evidence levels.

[c] PIDD = poorly controlled insulin-dependent diabetes; CIDD = controlled insulin-dependent diabetes.

lumen becomes occluded. Failing to receive enough blood, the heart muscle dies, resulting in an infarct.

Animal Studies

Bacteria originating in the oral cavity may also contribute to platelet clotting or thrombosis, as proposed by Herzberg et al. (1983, 1994). These investigators have suggested that the association between periodontal disease and cardiovascular disease may be due in part to the potential for oral bacteria such as *S. sanguis* and *P. gingivalis* to induce platelet aggregation. Platelets aggregate in response to these bacteria as a result of mistaken identity: a protein structure on the surface of certain common strains of *S. sanguis* and *P. gingivalis* mimics the platelet-interactive regions of collagen molecules (Erickson and Herzberg 1993, Herzberg et al. 1994). Exposure of flowing blood to collagen triggers clotting, the central event in stopping blood flow. When an experimental bacteremia was created with a strain of *S. sanguis* that carried the collagen-like protein, rabbits showed changes in blood pressure, electrocardiogram readings, heart rate, and cardiac contractility (Herzberg and Meyer 1996, 1998). Platelets also aggregated in the circulation, resulting in significant declines in platelet counts. From the electrocardiographic tracings, rabbit heart muscle also appeared to have suffered ischemic damage. The investigators concluded that oral bacteria carrying the collagen-like protein induced platelet aggregation or clotting in the bloodstream. These clots were of sufficient size to obstruct coronary arteries and produce ischemic heart damage, an early warning sign of a heart attack or an infarction. Because *S. sanguis* is present in large numbers in dental plaque and is a causative agent in infective endocarditis, it is likely that these bacteria

have an opportunity to induce platelet clotting during human bacteremias from oral sources. Bacteria-induced platelet clotting could contribute to microthrombosis during the development of atherosclerotic plaques and occlusive thrombus formation with occasional myocardial infarction.

Population-based Studies

Any study investigating the possibility of a unique role for oral pathogens as risk factors for cardiovascular disease, including atherosclerosis and the formation of a blood clot in a coronary artery of the heart, which typically precedes myocardial infarction, must take into consideration such known risk factors as smoking, hypertension, obesity, diabetes, genetic susceptibility, and elevated cholesterol. Genco (1998) and Beck et al. (1998) have recently reviewed studies examining the associations between oral conditions (including periodontitis) and atherosclerosis and coronary heart disease, the latter of which affects 12 million people in the United States and is the leading cause of death. These are summarized in Table 5.6.

Of the ten studies cited in the table, six are prospective cohort studies, in which oral health status was established at the outset (baseline) of the study period and the subjects were followed at periodic intervals to a previously defined endpoint, for example, diagnosis of coronary heart disease or an acute myocardial infarction, or death. Beck et al. (1996) combined data from the Veterans Administration Dental Longitudinal Study and its parent longitudinal study, the Normative Aging Study, for a total of 203 cases and 891 noncases, to determine whether periodontal disease, judged by measuring alveolar crestal bone, is a risk factor for cardiovascular disease. After adjusting for age, blood pressure, cholesterol, and body mass index, the investigators found that subjects with periodontal disease were 1.5 times more likely to develop coronary heart disease over a 25-year period than controls (odds ratio of 1.5). Similarly, after adjusting for age, smoking, and blood pressure, the investigators found that veterans with periodontal disease were 1.9 times more likely to develop fatal coronary heart disease (odds ratio of 1.9).

In a longitudinal study to eliminate the potential confounding effects of smoking, Genco et al. (1997) measured the incidence of periodontal disease and cardiovascular disease in 1,372 American Indians of the Gila River Indian Reservation. Although diabetes is prevalent in this population, cigarette smoking is rare in these individuals (a fact confirmed in this study), so it was considered not to be a risk factor for either cardiovascular disease or periodontal disease in this study. Periodontal disease was measured at baseline, and the incidence of cardiovascular disease was followed over the next 10 years. When the analysis was restricted to individuals under age 60, the risk of cardiovascular disease was 2.7 times higher in subjects with periodontal disease than in those with little or no periodontal infection. This association was seen even after adjusting for other risk factors for cardiovascular disease or periodontal disease such as age, sex, cholesterol, weight, high blood pressure, diabetes, and insulin use. The investigators concluded that periodontal disease is an important risk factor for cardiovascular disease for individuals under 60 in this group, second only to the presence of long-term diabetes. Further analysis of death due to cardiovascular disease is needed in this population to complete the study.

Mattila and coworkers have conducted both prospective and retrospective studies. A prospective study (Mattila et al. 1995) showed that new episodes of myocardial infarction occurred more frequently in subjects with more extensive "dental" disease. The authors used a measure of dental disease that included a composite index that assessed caries, periodontitis, pericoronitis, and periapical lesions. The composite index estimates the combined infectious load that contributes to many possible oral infections. After combining the prospective study data with data from an earlier retrospective study (Mattila et al. 1989) and adjusting for age, triglyceride levels, cholesterol, C-reactive protein, smoking, social class, diabetes, and hypertension, the investigators found a significant association between dental infections and acute myocardial infarction in men under age 50 ($P < 0.01$). A more recent study (Mattila et al. 2000) compared 85 patients with proven coronary heart disease and 53 matched controls. This case-control study showed that dental indices were higher among coronary heart disease patients than controls, but the differences were not statistically significant. Participants in the study were older, which the authors believed was the most likely reason for the results. In the first National Health and Nutrition Examination Survey, 9,670 subjects were followed for over 14 years. DeStefano et al. (1993) found that there was a 25 percent increased risk of cardiovascular disease in individuals with periodontitis compared with those with minimal periodontal disease. The strongest association was seen in men under 50 (relative risk, 1.7). A limitation of this study, which the authors acknowledge, was the lack of baseline data on smoking, a major risk factor for both periodontal and cardiovascular disease. Morrison et al. (1999) evaluated a retrospective cohort study using participants in the

TABLE 5.6
Summary of studies assessing the association between oral conditions, atherosclerosis, and coronary heart disease

	Study Design[a]	Subjects (cases/ controls)	Oral Condition	Cardiovascular Outcome	Adjustments[b]	Association (odds ratio or relative risk)	Evidence Level[c]
DeStefano et al. 1993	Prospective	1,786/7,974	Russell's periodontal index	Coronary heart disease (admission to hospital or death)	Age, sex, race, education, poverty, marital status, cholesterol, BMI, diabetes, smoking	1.72 (1.1-2.68) (only for men under age 50)	II-2
Mattila et al. 1995	Prospective	52/162	Dental index (caries, periodontal disease, pulpal infection)	New acute myocardial infarction or death	Smoking, hypertension, age, sex, triglycerides, socioeconomic status, diabetes, lipids, BMI, previous MI	Yes, $P < 0.01$	II-2
Joshipura et al. 1996	Prospective	757/44,119	Periodontal disease (self-reported), tooth loss due to self-reported periodontal disease	New coronary heart disease	Age, BMI, exercise, smoking, alcohol, vitamin C, family history, MI	1.67 (1.03-2.71)	II-2
Beck et al. 1996	Prospective	203/891	Alveolar crestal bone loss	New coronary heart disease, fatal coronary heart disease, stroke	Age, BMI, total cholesterol, socioeconomic status, DBP, LDL, smoking, cholesterol	1.5 (1.04-2.14) 1.9 (1.0-3.43) 2.8 (1.45-5.48)	II-2
Genco et al. 1997	Prospective	68/1,304	Alveolar crestal bone loss	New coronary heart disease	Age, sex, smoking, BMI, diabetes, cholesterol, hypertension	2.68 (1.35-5.60)	II-2
Morrison et al. 1999	Retrospective	10,000	Severe gingivitis; periodontitis; edentulousness	New coronary heart disease; cerebrovascular deaths	Age, sex, serum total cholesterol, smoking, diabetes, hypertension	1.37 (0.80-2.35) for periodontitis 1.90 (1.17-3.10) for edentulousness for fatal CHD	II-2
Joshipura et al. 1999	Prospective	42,151	Number of teeth lost	Ischemic stroke	Age, smoking, obesity, alcohol, exercise, aspirin, family history, profession, hypertension, hypercholesterolemia	≤10 teeth 1.75 (1.03-2.99) 11-15 teeth 1.95 (1.07-3.64) 17-24 teeth 1.48 (1.02-2.13)	II-2
Mattila et al. 1989	Case-Control	100/102	Dental index (caries, periodontal disease, pulpal infections)	Acute myocardial infarctions	HDL, smoking, C-reactive protein, hypertension, age, cholesterol, diabetes, social class	Yes, $P < 0.01$	II-2
Grau et al. 1997	Case-Control	166/166	Dental index (caries, periodontal disease, periapical infections)	Stroke	Diabetes, preexisting vascular disease, socioeconomic status, smoking	Odds ratio 2.6 (1.18-5.70)	II-2
Mattila et al. 2000	Case-control	85/53	Dental index (caries, periodontal disease, pulpal infections)	New coronary heart disease	Age, sex, smoking, socioeconomic class, hypertension, number of teeth, serum lipid levels	—	II-2

[a]For the prospective studies, the total number of subjects in the cohort is the sum of the two numbers given, the first number of which represents the subjects followed to the endpoint. For the case-control studies, the first number represents the cases, and the second the controls.
[b]BMI = body mass index; MI = myocardial infarction; LDL = low-density lipoproteins; HDL = high-density lipoproteins.
[c]Levels of evidence are delineated in Table 5.3.

1970-72 National Canada Survey. In the younger cohort, those under age 69, they found that gingivitis, periodontitis, and edentulousness were related to fatal coronary heart disease in a statistically significant manner. However, in analyzing those over age 70, none of these dental conditions was associated with fatal heart disease. These results were adjusted for age, sex, serum total cholesterol, smoking status, diabetes status, hypertension status, and province of residence. This pattern of higher risk observed among younger subjects may, to some extent, reflect the relative instability of risk estimates. However, it is also possible that periodontal disease, like other co-morbid relative risks for coronary heart disease, generally declines with age (Semenciw et al. 1988).

Wu et al. (1999) found periodontal disease to be a potential factor for coronary heart disease and stroke based on an analysis of the first National

Health and Nutrition Examination Survey and its 21-year follow-up. In this analysis, periodontitis was found to be a significant risk factor for cerebrovascular disease, in particular nonhemorrhagic stroke. Compared with no periodontal disease, relative risk (95 percent CI) for incident nonhemorrhagic stroke was 2.11 (1.30 to 3.42) for periodontitis. There was no significant relationship for gingivitis or edentulousness, which were 1.24 (0.74 to 2.08) and 1.41 (0.96 to 2.06), respectively. The increased relative risk for total cerebrovascular disease and nonhemorrhagic stroke was not seen for hemorrhagic stroke. Similar relative risks for total cerebrovascular disease and nonhemorrhagic stroke associated with periodontitis were seen in white men and women and African Americans. A conclusive statement about a cause-and-effect relationship between periodontitis and the risk of developing cerebrovascular disease, in particular nonhemorrhagic stroke, cannot be made at this time. The consistency of the findings in different racial groups and the strength of the association warrant further examination of the potentially important association between these two clinical conditions, which are highly prevalent in the adult population.

In the largest cohort studied, Joshipura et al. (1996) found that among a group of male health professionals who were relatively homogeneous socioeconomically and who self-reported preexisting periodontal disease, those with 10 or fewer teeth were at increased risk of new coronary heart disease, compared with those with 25 or more teeth (relative risk, 1.67). These results were adjusted for standard cardiovascular disease risk factors.

In a case-control study of 166 patients with acute cerebrovascular disease and 166 age- and sex-matched controls, Grau et al. (1997) found that "poor dental status" was independently associated with cerebrovascular ischemia. These results were based on a subgroup of patients and controls who completed the dental examination. A modified form of the Total Dental Index was used to measure dental status. In an 8-year follow-up of 42,151 male health professionals who were free of cardiovascular disease at baseline, Joshipura et al. (1999) reported that edentulousness was associated with an increased risk of ischemic stroke after adjusting for age, smoking, obesity, alcohol, exercise, aspirin, family history of cardiovascular disease, profession, hypertension, and hypercholesterolemia.

Conclusion

None of the studies reviewed to date achieves the level of rigor that can unequivocally establish periodontitis as an independent risk factor for cardiovascular disease or stroke. The methods used to measure or identify periodontal disease ranged widely from self-report, to composite indices that included dental caries experience, to precise measures of periodontitis severity. Nevertheless, there were consistent findings of increased odds ratios and significant probability (P) values pointing to an association of periodontal and other oral infections with an increased risk for cardiovascular disease. Further studies are needed to determine whether periodontal disease alone or in the presence of other oral infections is an independent risk factor for cardiovascular or cerebrovascular disease. Research to elucidate the underlying pathological mechanisms is also essential. Studies must also clarify the potentially confounding effects of sex, age, socioeconomic level, and race/ethnicity.

Periodontal Disease and Adverse Pregnancy Outcomes

Preterm birth and low birth weight are considered the leading perinatal problems in the United States (Gibbs et al. 1992). Although infant mortality rates have decreased substantially over the past generation, the incidence of low birth weight (just under 300,000 cases in 1995) has not shown a comparable decline (Institute of Medicine 1985, USDHHS 1984). Over 60 percent of the mortality of infants without structural or chromosomal congenital defects can be attributed to low birth weight (Shapiro et al. 1980).

Mechanisms of Action

Periodontal disease may contribute to adverse outcomes of pregnancy as a consequence of a chronic oral inflammatory bacterial infection. Toxins or other products generated by periodontal bacteria in the mother may reach the general circulation, cross the placenta, and harm the fetus. In addition, the response of the maternal immune system to the infection elicits the continued release of inflammatory mediators, growth factors, and other potent cytokines, which may directly or indirectly interfere with fetal growth and delivery.

Evidence of increased rates of amniotic fluid infection, chorioamnion infection, and histologic chorioamnionitis supports an association between preterm birth, low birth weight, and general infection during pregnancy. It is noteworthy that the largest proportion of such infections occurred during the pregnancies of the most premature births (Hillier et al. 1988, 1995). The biological mechanisms involve bacteria-induced activation of cell-mediated immunity leading to cytokine production and the synthesis

and release of prostaglandins, which may trigger preterm labor (Hillier et al. 1988). Elevated levels of prostaglandin as well as cytokines (interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor alpha (TNF-α)) have been found in the amniotic fluid of patients in preterm labor with amniotic fluid infection (Romero et al. 1993), compared with levels in patients with preterm labor without infection.

Animal Models

A variety of studies have used the pregnant hamster model. Some investigators have examined the effects of lipopolysaccharide, produced by oral gram-negative pathogens, on cytokine production (Collins et al. 1994a). In other studies, hamsters have been infected with *P. gingivalis*, with or without prior immunization. Collins et al. (1994b) challenged the animals with nondisseminating, low levels of *P. gingivalis*, introduced in a subcutaneous chamber at a dorsolumbar site. Although the doses were insufficient to induce fever or wasting, the hamster litters of the infected animals showed a significant reduction in fetal weight (24 percent) in comparison with control animals ($P < 0.0001$). This suppressive effect on fetal weight was accompanied by a proportional intrachamber rise in tumor necrosis factor alpha (TNF-α) and prostaglandin E2 (PGE_2) ($P < 0.0001$). Immunization prior to mating did not provide protection from a challenge during pregnancy, but rather potentiated the effects, indicating the potential strength of a chronic infection.

In another series of hamster studies, researchers observed the effects of experimental periodontitis on pregnancy outcomes and amniotic fluid mediators (Offenbacher et al. 1998). The investigators noted a 20 percent decrease in fetal weight ($P = 0.002$). Periodontal infection in the pregnant hamster also was associated with a significant rise in intra-amniotic PGE_2 from 3.31 ± 1.1 to 13.5 ± 4.1 micrograms per milliliter ($P = 0.03$). These data suggest a link between oral infection and changes in the fetal environment.

Epidemiologic Studies

Human case-control studies have demonstrated that mothers of low-birth-weight infants born as a result of either preterm labor or premature rupture of membranes tend to have more severe periodontal disease than mothers with normal-birth-weight infants (Offenbacher et al. 1996, 1998). A case was defined as a mother whose baby weighed less than 2,500 grams and who had one or more of the following factors: gestational age of infant of less than 37 weeks; preterm labor; or preterm, premature rupture of membranes. Controls were all normal-birth-weight, full-term infants. In a case-control study of 124 subjects, the mean clinical periodontal attachment level for the mothers of low-birth-weight babies was 3.10 + 0.74 (SD) millimeters (mm) per site (93 subjects) versus 2.80 + 0.61 (SD) mm per site (31 subjects) for mothers of normal-weight infants ($P = 0.038$ for all cases and controls). For a subset of mothers for whom this was the first child, the mean clinical periodontal attachment level for those with low-birth-weight babies was 2.98 + 0.84 (SD) mm per site (46 subjects) versus 2.56 + 0.54 (SD) mm per site for controls (20 subjects) at $P = 0.041$ (Offenbacher et al. 1996). This subset was analyzed separately to avoid the confounding effects of mothers with periodontal disease who had previously given birth to low-birth-weight infants but who later had normal-weight infants.

Logistic regression models demonstrated that severe periodontal disease was associated with a sevenfold increase in risk of low birth weight, after controlling for known risk factors such as smoking, race, alcohol use, age, nutrition, and genitourinary tract infection. This study suggests an association between periodontal disease and prematurity.

In a subsequent case-control study of 44 subjects, additional biochemical and microbial parameters of periodontal disease status were studied to assess the relationship of current periodontal status to current pregnancy outcome (Offenbacher et al. 1998). Results indicate that PGE_2 levels in gingival crevicular fluid were significantly higher in mothers of low-birth-weight infants than in controls (131.4 + 21.8 (SE) versus 62.6 + 10.3 (SE) nanograms per milliliter), respectively (at $P = 0.02$). Furthermore, within the group of mothers of low-birth-weight infants there was a significant inverse association between birth weight, gestational age, and gingival crevicular fluid PGE_2 levels (at $P = 0.023$ for current births). These data suggest that the level of PGE_2 in gingival crevicular fluid, serving as a marker of current periodontal disease activity, varies inversely with birth weight; that is, the higher the PGE_2 level, the lower the birth weights. In this study the periodontal disease was more severe in mothers with adverse pregnancy outcomes, as determined by biochemical and microbial biomarkers, but the difference in clinical attachment levels did not reach statistical significance ($P = 0.11$).

Studies also have been reported in other countries. In the United Kingdom a preliminary analysis of 167 cases and 323 controls did not show an association between periodontal disease and pregnancy

outcomes (Davenport et al. 1998); however, the investigators did not control for confounding factors. Dasayanake (1998) conducted a matched case-control study with 55 cases in Thailand. Gingivitis was associated with a higher risk of having a growth-restricted infant (odds ratio = 0.3; 95 percent CI, 0.12 to 0.72), controlling for mother's height, prenatal care, dental caries status, and the infant's gender. Smoking was not controlled for in this study.

Conclusion

As a remote gram-negative infection, periodontal disease may have the potential to affect pregnancy outcome. Not all the obstetric risk factors that result in babies being born too soon and too small have been fully identified (Gibbs et al. 1992, McCormick 1985). Oral infections have been investigated as a potential risk factor for preterm labor or premature rupture of membranes, which are major obstetric antecedents to spontaneous preterm births. Although the findings from animal research and case-control studies are promising, additional work, including longitudinal studies, research on mechanisms, and intervention trials, is needed to determine whether periodontitis is a risk factor and what the mechanisms of action may be for adverse pregnancy outcomes. In the United States, longitudinal and intervention studies are under way.

Conclusion

This critical look at the emerging associations among oral infections and specific conditions establishes the need for an aggressive research agenda to better understand the specific aspects of these associations and the underlying mechanisms. Prospective and intervention studies are under way and should provide additional and stronger evidence of the presence and direction of an association. It is essential for such studies to include populations at known risk for the underlying conditions as well as the general population. Of the conditions reviewed, the relationship of periodontal disease and diabetes has the strongest evidence, demonstrating that the risk of periodontitis is higher in individuals with diabetes. However, the effect of periodontitis on glycemic control is less clear, a reflection of the difficulty of controlling for the effect of systemic antibiotic treatments used to manage periodontal disease in diabetic patients in clinical trials.

IMPLICATIONS OF THE LINKAGES

This review of oral health linkages with general health reveals implications for the clinical practice of both medicine and dentistry. The recognition of well-known and established signs and symptoms of oral diseases may assist in the early diagnosis and prompt treatment of some systemic diseases and disorders. The presence of these signs also may lead to the institution of enhanced disease prevention and health promotion procedures. All health professionals, and the public, should be aware of these signs and symptoms. Individuals, practitioners, and community programs may also benefit from the accelerated development and testing of readily accessible, acceptable, and simple oral-based diagnostics.

A better understanding of the role of the oral cavity and its components in protecting against infection is needed. This information should permit the development of interventions to enhance these components. For example, research is under way investigating how to augment some of the natural antimicrobial molecules that are present in saliva and how to use oral and nasal vaccination routes to enhance immunity. Also, host susceptibility factors contributing to the dissemination of oral infections to other parts of the body should be investigated, especially in populations at high risk for disease and infection. In addition, further studies are needed to elucidate the role of the mouth as a means of transmitting infectious microbes. This in turn will allow the development of interventions to prevent transmission and curb the progression of infections once established.

The associations between oral infections and diabetes, heart disease and stroke, and adverse pregnancy outcomes warrant a comprehensive and targeted research effort. If any of these associations prove to be causal, major changes in care delivery and in the training of health professionals will be needed.

Awareness of the oral complications of medications and other therapies for disease management and for health promotion needs to be enhanced among health care professionals, the public, drug manufacturers, and the research community. For some of these therapies, known interventions exist and should be followed before initiating the therapy to minimize or modulate its side effects. To prevent the oral complications of other therapies, new approaches are needed. Ultimately, and ideally, the side effects of therapies should be considered in the development of new drugs and biologics.

FINDINGS

- Many systemic diseases and conditions have oral manifestations. These manifestations may be the initial sign of clinical disease and as such serve to inform clinicians and individuals of the need for further assessment.
- The oral cavity is a portal of entry as well as the site of disease for microbial infections that affect general health status.
- The oral cavity and its functions can be adversely affected by many pharmaceuticals and other therapies commonly used in treating systemic conditions. The oral complications of these therapies can compromise patient compliance with treatment.
- Individuals such as immunocompromised and hospitalized patients are at greater risk for general morbidity due to oral infections.
- Individuals with diabetes are at greater risk for periodontal diseases.
- Animal and population-based studies have demonstrated an association between periodontal diseases and diabetes, cardiovascular disease, stroke, and adverse pregnancy outcomes. Further research is needed to determine the extent to which these associations are causal or coincidental.

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