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Environmental and other modifying factors of the periodontal diseases

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The aim of this review is to address how environmental factors modify periodontal disease. Our current understanding is that the environment and genetics govern whether an individual develops periodontitis. Innate genetic differences are revealed following plaque accumulation, resulting in inflammation that may manifest and remain as gingivitis or go on to form periodontitis in certain subjects. This chronic inflammatory condition is modified by smoking, hormones, diabetes, drugs and in rare cases by systemic diseases with periodontal manifestations, i.e. by environmental factors. Thus the environment influences healthy and diseased periodontal tissues and may modify preexisting gingival inflammation and result in more or less severe gingivitis responses or altered periodontitis.

Chronic gingivitis is seen commonly in individuals who stop toothbrushing for between 10 and 20 days (43). The clinical signs are exaggerated and the gingiva is more edematous and inflamed in individuals undergoing hormonal disturbance, such as children during puberty and females during pregnancy. Certain drug therapies such as nifedipine (a calcium channel blocker used in hypertensive patients), phenytoin (used to control epilepsy) and cyclosporine (an immunosuppressive drug) can result in gingival overgrowth in approximately 30% of individuals taking these medications. The gingival overgrowth is an exaggerated response to microbial plaque. Gingivitis is also affected by smoking. Smoking tends to reduce gingival inflammation, possibly by the effect of nicotine in causing vascular constriction and thus reduced tissue edema and reduced gingival crevicular fluid flow.

Periodontitis, in contrast to gingivitis, is seen in only a subset of the population (10–15%). It is variable in that it does not affect all teeth evenly, but has both a subject and site predilection. Recent epidemiologic studies of periodontal disease suggest that relatively few subjects in each age group suffer from advanced periodontal destruction and only specific sites in these individuals are affected (65, 89, 106). When considering changes in attachment level over time, it is also peculiar that only relatively few sites actually undergo extensive periodontal destruction during any given observation period. Studies (65, 84, 85) have found that 70% of the sites deteriorated by 3 mm or more during a 2-year monitoring period, but this occurred in only 12% of the subjects examined.

Periodontal disease is considered to have multiple risk factors. The term 'risk factor' refers to 'an aspect of personal behavior or lifestyle, an environmental exposure, or an inherited characteristic, which on the basis of epidemiologic evidence is known to be associated with a health related condition' (80). Risk factors are part of the causal chain for a particular disease or can lead to the exposure of the host to a disease (15). The presence of a risk factor implies a direct increase in the probability of a disease occurring. Although specific microorganisms have been considered as potential periodontal pathogens, it has become apparent that pathogens are necessary but not sufficient for disease activity to occur (128). Destructive periodontal disease is a consequence of the interaction of genetic, environmental, host and microbial factors (154). The presence of microorganisms is a crucial factor in inflammatory periodontal disease, but the progression of the disease is related to host based risk factors such as genetics, age, gender, smoking, socioeconomic factors, and certain systemic diseases. Examples of microbes implicated as risk factors in periodontitis are numerous. Carlos et al. (25) found that the presence of *Prevotella intermedia*, along with gingival bleeding

and calculus, was correlated with attachment loss in a group of Navajo adolescents aged 14–19. Grossi et al. (50) found that *Porphyromonas gingivalis* and *Tannerella forsythia* were associated with increased risk for attachment loss as a measure of periodontal disease after adjustment for age, plaque, smoking, and diabetes. Susceptibility to periodontitis will undoubtedly have both genetic and environmental components and these modifying factors will be addressed in this review.

The microbial plaque biofilm

Short-term clinical studies have shown that microorganisms quickly colonize tooth surfaces when an individual stops oral hygiene procedures; within a few days, microscopic and clinical signs of gingivitis become apparent. The inflammatory changes can be resolved when adequate oral hygiene is resumed (89, 145). Microorganisms which form dental plaque and cause gingivitis do so by various means including the release of bacterial products that induce tissue inflammation. Clinical trials emphasize the need to remove supra- and subgingival microbial plaque in the treatment of gingivitis and periodontitis. Furthermore, animal experiments have indicated that gingivitis only develops in animals that accumulate bacterial deposits. Clearly, gingivitis is a prerequisite for the development of periodontitis and thus prevention of gingivitis is also a primary preventive measure for periodontitis. As stated earlier, not all patients develop periodontitis and for those who do, it is due to a mixture of environmental and genetic factors which affect their host response to microbial plaque. This provides a research challenge for those interested in the pathogenesis of this multifactorial disease. The site specificity and predilection in periodontitis and gingivitis probably relate to the retention of plaque in specific areas such as restoration overhangs, poor crown margins, etc. The type of plaque, i.e. the specific organisms present, and its quantity, may be a crucial environmental influence in periodontal disease, but at the same time it could be the individual host response or most likely a combination of the two, but the weight of these predisposing and modifying factors needs to be tested experimentally.

Systemic modifiers of periodontitis

Microbial dental plaque is the initiator of periodontal disease but whether it affects a particular subject, what form the disease takes, and how it progresses are all dependent on the host defenses to this challenge. Systemic factors modify all forms of periodontitis principally through their effects on the normal immune and inflammatory defenses. Some good examples of this effect are when a reduction in number or function of polymorphonuclear leukocytes occurs; this may result in an increased rate and severity of periodontal destruction. Many other systemic factors are much less clear cut and are difficult to link causally to periodontitis. In many cases the literature is insufficient to make definitive statements on links between systemic factors and periodontitis. It is also at times difficult to be precise regarding the causative agent in systemic exposures such as smoking and even pharmaceutically with prescribed drug therapy.

The possible role of systemic diseases and systemic exposures in initiating or modifying the progress of periodontal disease is clearly a complex issue. It is, however, generally agreed that several conditions may give rise to an increased prevalence, incidence, or severity of gingivitis and periodontitis. The categorization of the systemic modifying factors causing periodontitis and the evidence to support the role of these factors are the focus of this review. An attempt has been made to consider the conditions under broad headings, but it will be clear that many conditions fall within more than one category and that for several conditions, only case reports exist, whereas in other areas an extensive literature is present.

Diabetes mellitus

Periodontal disease has been characterized as the sixth complication of diabetes (88), a view supported by several reviews which conclude that the bulk of evidence indicates a direct relationship between diabetes mellitus and periodontal disease (73, 111). Another report (102) concluded that the preponderance of evidence from studies conducted throughout the world suggests that some diabetics are at increased risk of periodontitis.

In a cross-sectional study of 1426 subjects (50), diabetes mellitus was the only systemic disease positively associated with attachment loss, with an odds ratio of 2.32. The relationship appears to be very strong within special populations; in a 6-year longitudinal study in Pima Indians, the age- and sex-adjusted incidence of periodontal disease, as measured by alveolar bone levels, was 2.6 times higher in noninsulin dependent diabetic (NIDDM) subjects

than in those without NIDDM. However, some caution has to be adopted in this interpretation, as there are numerous conflicting studies which do not support this association between periodontal disease and diabetes (129), suggesting that that there are differences in susceptibility to periodontitis among populations of diabetics. Insulin (IDDM) and noninsulin dependent diabetics appear to be equally at risk of periodontitis (138), and, with effective maintenance, their response to surgical and nonsurgical periodontal treatment is as favorable as in nondiabetics (149).

A study (138) involving 75 diabetic patients (IDDM and NIDDM) aimed to determine the association between long-term control of diabetes, as evaluated by glycosylated hemoglobin levels, and periodontitis. In that study, the prevalence, severity, and extent of periodontitis increased with poor control of diabetes when calculus was present; in the absence of calculus, however, the level of control did not affect the severity of periodontitis. A 1995 report (4) confirmed that metabolic control may be the most important factor between periodontal health and IDDM. These data support the hypothesis that diabetes and the level of metabolic control are important modifiers of periodontitis.

Thorstensson & Hugoson (140) compared periodontal disease status, as measured by alveolar bone levels, in 83 adult long-duration IDDM patients and 99 age- and sex- matched controls. They concluded that diabetics aged 40–49 years had more extensive bone loss and suggested that the age of onset was an important risk factor for future periodontal destruction. A more recent review (129), however, concluded that the duration of diabetes does not influence periodontal severity, a view supported by a 5-year longitudinal study (149), as well as others that failed to show an association between the duration of IDDM and NIDDM and the severity of periodontitis (138).

Thus it would appear that diabetes (IDDM and NIDDM) is associated with an increased risk of periodontitis and that the association may vary depending on differences in susceptibility to periodontitis among populations; that the level of diabetic control is an important factor in this relationship and may modify the response to dental plaque; that the duration of diabetes *per se* does not appear to be important; and that diabetics with periodontitis can be successfully treated, surgically or nonsurgically, and maintained. Further studies have suggested that periodontal treatment influences diabetic control positively and that diabetics with severe periodontal disease were much more at risk of renal and cardiovascular complications (139).

Medications

Phenytoin is an anticonvulsant drug strongly associated with gingival overgrowth. The onset of gingival overgrowth is generally 3 months after the commencement of phenytoin therapy (37) and approximately 50% of patients on phenytoin develop some degree of overgrowth (139), although this incidence is higher in institutionalized epileptics (59). It occurs primarily in young individuals and is reported to be seen rarely in persons over 40 years of age (1, 70), and it appears to affect the anterior teeth more severely than the posterior teeth (127, 139). More recent studies have implicated alternative antiepileptic drugs, such as valproic acid (7) and vigabatrin (71), as also causing gingival overgrowth.

Calcium channel blockers are drugs that block the slow calcium channels in human cell membranes and are used in the management of arrhythmias, the treatment of angina and the control of hypertension. They clearly affect gingival overgrowth; however, the prevalence of gingival overgrowth related to calcium channel blockers is relatively low. In a study in 911 English patients medicated with nifedipine, amlodipine or diltiazem for more than 6 months, only nifedipine was associated with significant gingival overgrowth, with a prevalence greater than 6% (38). The overgrowth associated with nifedipine is clinically and histopathologically similar to phenytoin-induced overgrowth and is considered to be due to an increase in ground substance secreted by gingival fibroblasts when stimulated by gingival inflammation following plaque accumulation (38). Although it could be argued that gingival overgrowth and pseudo-pocketing may be plaque retentive and thus might be local modifiers of periodontitis, this has not been shown in the literature. Thus, although there is evidence supporting the effects of these drugs on gingival overgrowth, there is currently no evidence of an association between calcium channel blockers and periodontitis.

Cyclosporine is an immunosuppressant which acts solely on the cell-mediated immune responses (21) and is used in post-transplant patients. Gingival overgrowth is a widely recognized side-effect of cyclosporine (16, 115) and it resembles phenytoin-induced overgrowth clinically and histopathologically. It tends to appear within 3 months of commencing the therapy, occurs in approximately 30% of individuals (122), although an incidence as

high as 77% has been reported (107), and the extent of the overgrowth is related to the serum concentration of the drug as well as the presence of plaque. Other immunosuppressants, such as azathioprine, have been shown to exhibit a lower risk for gingival overgrowth (107, 122).

Although it could be argued that gingival overgrowth and pseudo-pocketing may be plaque retentive and thus might act as local modifiers of periodontitis, this has not been shown in the literature. Thus, although there is evidence supporting the effects of these drugs on gingival overgrowth, there is currently no evidence of an association between anticonvulsants, calcium channel blockers, or immunosuppressants and periodontitis.

Studies associating steroid therapy with periodontal disease and alveolar bone loss are conflicting. Animal studies in rats have shown that hydrocortisone acetate significantly decreased the gingival concentrations of hyaluronic acid, chondroitin sulfate, and heparin (75) and induced periodontal breakdown by impairing collagen and mucopolysaccharide synthesis in bone (86). In contrast, clinical studies have failed to show any association between steroid treatment and periodontal disease. One study reported that, although long-term prednisone therapy may predispose to osteoporosis, no loss of alveolar bone was observed (72). In another study, a group of patients receiving prednisone for the treatment of multiple sclerosis for up to 4 years was compared with a group of patients on nonsteroidal therapy and a group of healthy controls; no differences in either the frequency or severity of periodontal disease were shown, indicating the lack of influence of steroids on periodontal disease (116).

Sex hormones

Elevations in plasma levels of sex hormones during pregnancy cause a modification in the host's response to dental plaque but this is largely confined to the soft tissues and manifests as an increase in inflammation severity in chronic gingivitis. Several studies have shown that the incidence and severity of gingival redness, edema, bleeding, and exudation increase from the second month of gestation to the eighth month and then decrease (30, 63, 87). These changes do not appear to be due to an increase in plaque but rather to an increase in the anaerobe to aerobe ratio and more specifically in *P. intermedia*. In a control study of 20 pregnant and 11 nonpregnant women, bleeding on probing and gingival indices peaked between 21 and 24 weeks of gestation and this correlated with an increase in the anaerobe to aerobe ratio (76). In the same study there was a positive correlation between *P. intermedia* and estradiol and progesterone levels at 21–24 and 25–28 weeks, respectively. Fluctuations in gingivitis with phases of the menstrual cycle and the effects of oral contraceptives on the gingiva further document the effect of sex hormones on the periodontal tissues (61, 69, 83). Moreover, puberty is often accompanied by increased gingival inflammation and this increased response to plaque has been attributed to the concentration of sex hormones in the plasma (134). An alternative explanation for gingivitis observed during puberty is that this is a period of mixed dentition, where erupting and exfoliating teeth present many sites for plaque retention. The decrease in gingivitis after puberty may reflect the fact that adolescents have improved dexterity and also become more aware of oral hygiene.

There is strong evidence that sex hormone levels may alter the inflammatory response to plaque and, although this predominantly results in gingivitis alone, an increased risk of periodontitis in these patients cannot be ignored (101, 146). However, to date, there are no published studies which implicate periodontitis as a sequelae to sex hormone-induced chronic gingivitis.

Osteoporosis

Several recent papers have drawn attention to a possible link between osteoporosis and periodontal disease (64). An animal study in sheep with estrogen deficiency suggests that reduced estrogen levels may influence periodontal disease progression (68) although an earlier study (90) in hamsters showed that hormones did not influence alveolar bone loss in this model. In a cross-sectional study of 28 women aged between 23 and 78 years of age, subjects were divided into two groups, an older postmenopausal group on estrogen replacement therapy and a younger premenopausal group (133). The older group had reduced alveolar bone density, from which the authors concluded that menopause may cause reductions in alveolar bone density. Age was not controlled for in this study and since aging could clearly influence the results, the choice of the control group is highly questionable. Another study of human subjects with osteopenia and osteoporosis has suggested that the severity of osteopenia is related to loss of alveolar crestal height and tooth loss in postmenopausal women (147). Large and, ideally, longitudinal studies or carefully controlled cross-sectional studies

are needed to elucidate the possible relationship between chronic periodontitis and osteoporosis.

Immunosuppression

The role of immunologic processes in the pathogenesis of chronic periodontal disease is illustrated by studies involving individuals with primary immunodeficiencies or those receiving immunosuppressive therapy. Cross-sectional studies on patients receiving immunosuppressive therapy (135, 142) failed to show differences between these patients and healthy controls in the prevalence or severity of periodontitis. These reports suggest that immunologic deficiencies do not predispose to periodontal disease, but it must be remembered that patients on immunosuppressive therapy often take repeated and intensive antimicrobial therapy, which may compensate for the reduced immune response.

HIV infection

Although many HIV-infected individuals do not have any form of periodontitis, they may frequently present with oral manifestations, several of which are found in the periodontium. Periodontal findings in HIV-positive patients include linear gingival erythema, necrotizing ulcerative gingivitis, severe localized periodontitis and severe destructive necrotizing stomatitis affecting the gingiva and bone (similar to noma or cancrum oris) (119, 150, 152, 153). It is possible that these lesions are not HIV or AIDS specific, but that they are necrotizing or complicated forms of periodontal disease which may be more exaggerated in immunosuppressed patients. Interestingly, HIV-infected individuals with $CD4^+$ cell counts < 200 cells$/mm^3$ present with more severe and extensive chronic periodontitis-related attachment loss (14, 113). This suggests that in immunocompromised HIV patients, preexisting periodontitis may be exacerbated. Thus HIV infection can be considered a modifier of periodontitis.

Smoking

The relationship between smoking and periodontal diseases has been studied extensively over the past 15 years and both cross-sectional and longitudinal studies provide strong epidemiologic evidence of a positive association between smoking and clinical and radiographic signs of periodontitis, as well as an increased risk of periodontitis in smokers (2, 17, 51–53, 62, 109).

In a 10-year longitudinal radiographic study of alveolar bone loss, smoking was a significant predictor of future bone loss in those subjects who had at least 20 teeth at the beginning of the study (22). In a 5-year study of attachment loss in 800 community dwelling adults, smokers were found to be at an increased risk of attachment loss. In a further 12-month longitudinal study, smokers exhibited both greater attachment loss and bone loss when compared with their nonsmoking counterparts. Smokers were shown to be at significantly greater risk for further attachment loss when compared to nonsmokers, the odds ratio being quoted as 5.4 (94).

In one of the largest studies of risk factors for periodontal disease with 1361 subjects from Erie County, NY, aged 25–74 years, it was shown that smokers were at greater risk of experiencing severe bone loss than nonsmokers, with odds ratios ranging from 3.25 to 7.28 for light and heavy smokers, respectively (49). In a study of 155 Swedish patients with periodontal disease, a significantly higher percentage were found to be smokers than in the population at large and the risk ratio was reported as 2.5 (17). Another study of 540 Swedish adults 20–70 years of age has revealed that three variables – smoking, greater age and higher mean plaque levels – were potential risk factors for severe periodontitis (100).

The risk for periodontitis is considerably greater for tobacco users, with estimated ratios in the range of 2.5–7.0 or even higher for smokers as compared with nonsmokers (118). Even when the levels of plaque accumulation and gingival inflammation were not significantly different between smokers and nonsmokers, smokers exhibited an increase in prevalence as well as severity of destructive disease (17, 53). A case-control study of the relationship between life-events and periodontitis has shown smoking to be statistically associated with periodontal disease, after controlling for oral health behavior and sociodemographic variables (53).

The relationship between smoking and periodontitis appears to be dose-dependent; the odds for more severe attachment loss range from 2.05 for light smokers to 4.75 in heavy smokers (50), and there is a significant correlation between probing depth and smoking pack-years (5). Furthermore, years of exposure to tobacco products have been shown to be a statistically significant risk factor for periodontal disease in 1156 community dwelling New England elders, regardless of other social and behavioral factors (66).

In a study of 889 Spanish patients, gingival recession, probing depth, and clinical attachment level were significantly associated with smoking

status. It was further noted that smoking one cigarette per day, up to 10, and up to 20, increased clinical attachment loss by 0.5%, 5% and 10%, respectively. However, only in the last group did loss of attachment differ significantly from that of nonsmokers. The authors concluded that tobacco use increases disease severity, and that this effect is clinically evident above a certain threshold (95). These data support those of Wouters et al. (155), who found significantly less alveolar bone in individuals smoking more than 5 g of tobacco per day than in those smoking between 1 and 5 g of tobacco per day, as well as those of Norderyd & Hugoson (100), who examined 547 Swedish adults and found that moderate to heavy smoking (greater than or equal to 10 cigarettes per day) was associated with severe periodontitis but that light smoking (less than 10 cigarettes per day) was not.

The response to surgical and nonsurgical periodontal treatment has been shown to be less favorable in smokers compared to nonsmokers in terms of probing depth reduction and clinical attachment gain, even in the presence of ongoing, effective supportive therapy (2, 109). Furthermore, in a group of refractory periodontitis patients, 90% of the subjects reported to be smokers (92).

The mechanisms by which smoking leads to loss of attachment are not well-understood (51). It has been noted that the occurrence, relative frequency, or combinations of microorganisms associated with periodontitis were not different between smokers and nonsmokers (110). It has been suggested that smoking affects the vasculature, the humoral immune system, the cellular immune and inflammatory system and has effects throughout the cytokine and adhesion molecule network.

Smokers with periodontal disease present with reduced signs of clinical inflammation (41) and bleeding on probing (18) compared with nonsmokers. Although in the past it was hypothesized that this is due to the property of nicotine to exert local vasoconstriction reducing blood flow, research results have been contradictory. Recent studies suggest that inflamed sites in smokers have reduced vascular density and angiogenesis compared to inflamed sites in nonsmokers, thus impairing inflammatory response and wound healing (19, 108, 112).

Emotional stress

The incidence of necrotizing ulcerative gingivitis increases during periods of physiologic (39) and emotional stress (46) and, as a result, stress has long been recognized as one of the contributing factors for necrotizing ulcerative gingivitis. The negative effect of stress on the periodontium can be due either to altered behaviors, such as poor oral hygiene and smoking, and/or to impaired immune function, leading to increased susceptibility to infection (124). Another mechanism through which stress may affect the periodontium is an increase in levels of circulating corticosteroids (114). Although stress is not an easily measured factor, corticosteroid levels in urine can be measured and were found to be higher in necrotizing ulcerative gingivitis patients (32). Maupin & Bell (96) found a significant elevation of 17-hydroxycorticosteroids in necrotizing ulcerative gingivitis patients and a significant decrease when the disease was resolved.

Recent studies suggest that there is also an association between emotional stress, usually measured as negative life events, and chronic periodontitis. Green et al. (48) studied individual 'life events' such as divorce and bereavement and concluded that increased stressful events led to a greater prevalence of periodontal disease. These conclusions are supported by a more recent study (33) which looked at the relationship between life events and chronic periodontitis and found that both negative life events and oral health risk behaviors, such as poor oral hygiene and smoking, clustered together as important determinants of periodontitis. Genco et al. (44) evaluated the association of stress, distress, and coping behaviors with periodontal disease in 1426 subjects, aged 25–74. They found that psychosocial measures of stress associated with financial strain are significant risk indicators for periodontal disease in adults.

Psychologically depressed human subjects who smoked and had high titers of IgG against *T. forsythia* were found to have more severe and extensive chronic periodontitis; the authors explained this by the negative influence of depression on the immune system (99). Another study of chronic periodontitis patients found that those resistant to therapy were more stressed than those who responded to therapy (10). Further studies on experimental gingivitis volunteers also suggested that proinflammatory cytokine levels are increased in stressed subjects (36).

These data strongly suggest that stress may be a contributing factor not only for necrotizing ulcerative gingivitis, but also for other periodontal diseases, such as gingivitis and chronic periodontitis, and may also modify the response to periodontal treatment. The intervening physiologic mechanisms between stress and increased susceptibility to periodontal disease are not well documented but are probably

related to impaired immune function and altered oral health behaviors.

Hematologic disorders

The linkage between periodontal disease and hematologic disorders is variable depending upon the nature of the disorder. For example, in a series of 50 patients with histiocytosis syndromes, 36% had oral involvement; 16% of these patients were first diagnosed by a dentist (125). Adults, children, and infants can all be affected by histiocytosis syndromes, which are characterized clinically by punched out necrotic ulcers with granulation tissue, tissue necrosis and significant bone loss. Because the lesions may clinically mimic necrotizing ulcerative periodontitis lesions, definitive diagnosis must be confirmed by biopsy of the granulation tissue. Familial erythrophagocytic lymphohistiocytosis is the only form that appears to have a genetic component. Early hematologic and immunologic investigations, along with possible biopsy of the associated granulation tissue, should be initiated at an early stage to facilitate sound diagnostic management (24, 123). The extent of the disease may also be determined with chest radiographs and skeletal surveys.

Although it has been demonstrated that polymorphonuclear leukocytes may cause tissue damage in periodontal disease (42, 79), there is a growing body of evidence that polymorphonuclear leukocytes actually play a protective role in hematologic diseases where there is a greater susceptibility to periodontitis. To be effective in this role, polymorphonuclear leukocytes are integrated in chemotaxis, phagocytosis, and destruction of the ingested organism or substance. Individuals exhibiting polymorphonuclear leukocyte deficiencies, either quantitative (neutropenia or agranulocytosis) or qualitative (chemotactic or phagocytic), exhibit severe destruction of the periodontal tissues.

Quantitative polymorphonuclear leukocyte deficiencies are generally accompanied by destruction of the periodontium. Patients with neutropenia present with a variety of periodontal manifestations such as the malignant form, where there is ulceration and necrosis of the marginal gingiva with associated bleeding and occasional involvement of the attached gingival (9). More protracted forms of the disease such as cyclic, chronic, and familial benign neutropenia exhibit lesions that are frequently severe, with deep periodontal pockets and extensive, generalized bone loss involving the permanent dentition (12, 81, 126). The primary dentition may in some cases be characterized by bone resorption (29, 78). Periodontitis does not always occur in familial benign chronic neutropenia (35) and not all subjects are affected by either recurrent infections or by periodontal disease. Variable expression of the disorder between siblings or the impact of the environment (e.g. oral hygiene) on this disorder may help explain these findings.

Leukemia is another quantitative polymorphonuclear leukocyte deficiency where affected individuals often exhibit periodontal lesions. Acute forms of leukemia are associated with more severe periodontal lesions; 36% of individuals with acute and 10% of those with chronic forms (91) of leukemia exhibited generalized gingival enlargement due to infiltration by leukemic cells. This phenomenon is usually a feature of acute monocytic leukemia, although it has been reported as a feature of other forms, including chronic lymphocytic leukemia (136). Thrombocytopenia has been linked with gingival bleeding in both acute and chronic leukemia because gingival bleeding is a common occurrence in both forms (131).

Qualitative polymorphonuclear leukocyte deficiencies associated with neutrophil function are also associated with severe forms of periodontal destruction. Qualitative defects are often associated with localized destruction affecting only the periodontium of certain teeth (151). Chediak–Higashi syndrome is a rare genetic disease transmitted as an autosomal recessive trait. Generalized, severe gingivitis, extensive loss of alveolar bone and premature loss of teeth (137) characterize affected individuals due to an extreme susceptibility to bacterial infections that appears to be related to alterations in the functional capacity of the neutrophil. Chediak–Higashi syndrome, Chronic granulomatous disease and Leukocyte adhesion deficiency syndrome are other functional deficiencies of leukocytes and are discussed within the genetic diseases section of this review.

Other blood disorders such as those involving red blood cells, platelets and clotting disorders also influence the management of periodontal disease; however, there is no evidence that these conditions increase susceptibility to periodontal disease (72).

Genetic disorders

A number of genetic disorders increase susceptibility to chronic periodontitis. Microbial plaque, modified by levels and duration of accumulation, environmental factors (e.g. smoking), diabetes, systemic health, and individual genetic make-up all contribute to susceptibility. Genetic aspects are covered elsewhere in this volume.

Down's syndrome is characterized by a generalized early periodontitis that manifests itself in the primary dentition (31, 34, 67) and continues into adulthood. The prevalence and severity of periodontal disease in individuals with Down's syndrome is extremely high when compared to either their siblings (103) or other mentally handicapped individuals (67, 120). Early onset periodontitis is evidenced by pocket formation in 36% of Down's syndrome children less than 6 years of age (67, 120). Older age groups are characterized by an increased prevalence and severity of periodontal disease (31, 34, 67) as reported in cross-sectional studies. Longitudinal studies indicate that the progression of periodontal disease is very rapid (98). The most frequent sites of periodontal destruction are the incisor and molar areas (31, 121). Premature loss of the mandibular incisors is associated with short roots (23) and loss of bone in this area (67). One study calculated a mean annual incidence which predicted that the entire dentition would be lost 9 years after the onset of periodontal disease.

Leukocyte adhesion deficiency syndrome is a rare autosomal recessive disease characterized by neutrophils with defects in several cell-cell adhesion receptors. Defects in these receptors may lead to increased susceptibility to infectious diseases such as periodontitis (6). Two studies that describe severe inflammatory periodontal disease in young patients with the Leukocyte adhesion deficiency syndrome (105) indicate that the disease is often fatal. Children with deficiencies in expression of the lymphocyte function-associated antigen (LFA) family of adhesions have been reported as suffering from severe periodontal infections (6), but data relating adult periodontitis to this condition are not available. The importance of the adhesion molecules to the function of the immune and inflammatory systems is nevertheless fundamental and even small variations or deficiencies could contribute to a depressed host response and an increased risk of periodontitis.

Chronic granulomatous disease is a rare condition that manifests as either autosomal recessive or x-linked recessive. Phagocytic cells (both polymorphonuclear leukocytes and monocytes) are unable to kill through utilizing the oxidative pathway after ingestion. Kinane & Davies (74) described a family with the X-linked recessive form of Chronic granulomatous disease where the female carriers suffered from photosensitivity dermatoses and had severely lower nitroblue tetrazolium reducing ability within their phagocytes. All female carriers in this series were examined for oral and periodontal lesions and no periodontal manifestations were attributed to this condition, although gingival erythema and occasional ulceration were noted.

Papillon–Lefèvre syndrome is a disease exhibiting autosomal recessive inheritance (97) and characterized by the presence of hyperkeratotic skin lesions. Individuals with this disease exhibit diffuse palmar-plantar keratosis associated with a severe generalized periodontitis that commonly occurs before puberty and is characterized by early loss of primary and permanent teeth (13, 23, 28, 40, 47, 55, 148). Teeth are generally lost in the order of eruption (55) and as yet there is no general agreement on the success of dental therapy. The general population frequency of this disease is reported as 1 in 4 million (13), with 25% having an increased susceptibility to infection. A history of consanguinity is also noted in 33% of those affected (55). Another related disease characterized by palmar-plantar keratosis and severe early onset periodontitis is Haim Munk syndrome. Preliminary genetic studies of these two diseases suggests that the gene defect in Haim Munk syndrome is not genetically linked to the other more common forms of palmar-plantar keratosis (57). It does appear that there is a high degree of consanguinity in these families and that they are probably part of the same syndrome (130), although this work has been questioned.

Hypophosphatasia is a condition in which patients exhibit a decreased serum alkaline phosphatase level. Affected individuals exhibit a severe loss of alveolar bone and premature loss of the primary teeth (11, 20, 26, 141).

Chediak–Higashi syndrome is inherited as an autosomal recessive trait associated with severe periodontitis (27, 45, 54, 104, 137). Affected patients exhibit defective neutrophil chemotaxis and abnormal bactericidal functions.

The Ehlers–Danlos syndrome encompasses a group of autosomal dominant connective tissue disorders that is characterized by defective collagen synthesis. The disorders are classified into 10 types on the basis of inheritance and clinical symptoms. The joints and skin are the most affected sites. Patients with Types IV and VIII have an increased susceptibility to periodontitis (58). Type VIII is particularly associated with fragile oral mucosa and blood vessels along with severe generalized periodontitis that has the clinical appearance of generalized early onset periodontitis (82). The Ehlers–Danlos syndrome type VIII was first recognized by McKusick (97) in a family with skin fragility, abnormal scarring, early tooth loss and severe periodontitis. Another family with the Ehlers–Danlos syndrome type VIII exhibited joint laxity, skin fragility and extensive periodontal destruction (8). It

appears that there is considerable interfamilial variability in the Ehlers–Danlos syndrome type VIII but the distinguishing finding is periodontitis clinically resembling the early onset form and leading to premature loss of permanent teeth (132).

There are other rare genetic disorders that deserve mention here. Glycogen storage disease 1b is an autosomal recessive condition in which there is faulty carbohydrate metabolism and an association with low neutrophil numbers, impaired neutrophil function and periodontal disease (56, 104). Infantile genetic agranulocytosis is an extremely rare autosomal recessive disorder that features severe neutropenia and an associated periodontitis resembling the early onset form (77, 117). Cohen's syndrome is an autosomal recessive disease characterized by nonprogressive mental and motor retardation, obesity, dysmorphia and neutropenia (3). Individuals with Cohen's syndrome manifest more frequent and extensive alveolar bone loss than matched mentally retarded controls (3).

Age

The prevalence of periodontal disease increases with age. However, it is not clear if becoming older is related to an increased susceptibility to periodontal disease; that is, if it changes our host response capability, or if the cumulative effects of disease over a lifetime explain the increased prevalence of disease in older people. Horning et al. (62) stated that age is a risk factor for periodontitis, although loss of attachment and alveolar bone with age is dependent on the presence of plaque and calculus. Holm-Pederson et al. (60) and Machtei et al. (93) suggest that, up until the age of 70, the rate of periodontal destruction is the same throughout adulthood and that age *per se* is not a risk factor, at least for those under the age of 70 (43).

Summary

Microbial dental plaque initiates periodontal disease but the form and severity of the disease is dependent on the environmental, genetic and host defenses to this challenge. Systemic disorders or variations and environmental exposures may modify the normal defenses and influence the resultant periodontal disease. A reduction in number or function of polymorphonuclear leukocytes results in increased severity of periodontal destruction. Many drugs such as phenytoin, nifedipine, and cyclosporine predispose to gingival overgrowth in conjunction with microbial plaque and host response characteristics and thus may modify pre-existing periodontitis. Changes in circulating hormone levels may result in an increased severity of plaque-induced gingival inflammation but not typically in any increased susceptibility to periodontal attachment or bone loss. Hormonal changes as seen during and after menopause have been associated with osteoporosis but there is a lack of studies linking menopause or an estrogen-deficient state to a higher susceptibility to periodontal disease. Immunosuppressive drug therapy and any disease resulting in suppression of the normal inflammatory and immune processes, such as HIV infection, may predispose the individual to periodontal destruction. It is difficult, however, to determine the precise causative agent in these conditions and it is particularly complex when immunosuppressive drugs are prescribed together with antibiotics for variable periods of time. The evidence for smoking having a deleterious influence on periodontal health is convincing. Nutritional deficiencies in animals have been shown to affect the periodontal tissues but epidemiologic data do not support the suggestion that such deficiencies play an important role in chronic periodontal disease. Gingival bleeding is the most consistent oral feature of vitamin C deficiency, or scurvy, but there is also some evidence to suggest that avitaminosis-C may aggravate established chronic periodontitis (143, 144). Stress and other psychosomatic conditions which may have direct anti-immune effects or indirect, behavior-mediated effects on the body's defenses may prove to be important in the etiology of periodontitis and necrotizing ulcerative gingivitis and periodontitis. The role or relative importance of these mechanisms has yet to be fully elucidated but the evidence that stress, neural factors, and depression can influence the immune system is increasing. Many genetic disorders have numerous host response modifications, which may render the individual susceptible to periodontal disease. Many genetic conditions influence the periodontium during childhood and the periodontal manifestations of the disease may resemble the early onset forms of periodontitis; the effects of such diseases may persist into adulthood. Although systemic diseases such as diabetes will aggravate all forms of periodontitis, chronic or adult periodontitis is the most prevalent and thus will be the most common form presenting with diabetes-induced modifications. Currently, numerous genetic polymorphisms relevant to inflammatory and immune processes have been suggested and are being investigated for their modifying effects on periodontal disease. The literature on how periodontitis is modified by systemic factors, with the

exception of the link with diabetes, HIV infection, and smoking, is as yet sparse and clearly well controlled cross-sectional and longitudinal studies are needed to fully elucidate the relationship between environmental modifiers and genetic influences and periodontitis.

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