Informational Paper

The Pathogenesis of Periodontal Diseases

This informational paper was prepared by the Research, Science, and Therapy Committee of The American Academy of Periodontology, and is intended for the information of the dental profession. The purpose of the paper is to provide an overview of current knowledge relating to the pathogenesis of periodontal diseases. The paper will review biological processes thought to provide protection against periodontal infections. It will further discuss the mechanisms thought to be responsible for both overcoming and subverting such protective mechanisms and those that lead to destruction of periodontal tissues. Since an understanding of pathogenic mechanisms of disease is one foundation upon which new diagnostic and therapeutic modalities are based, the practitioner can use this information to help make decisions regarding the appropriate application of such new modalities in patient care settings. *J Periodontol 1999;70:457-470.*

Pathogenesis deals with the mode of origin or development of disease. In this paper, currently accepted concepts of the origin and progression of gingivitis and periodontitis are discussed. Since nearly all of the periodontal diseases are associated with and thought to be caused by microorganisms, some references to etiologic agents are of necessity utilized, particularly when certain disease processes are clarified by example.

Periodontal diseases comprise a variety of conditions affecting the health of the periodontium. Although the classification scheme defined at the 1989 World Workshop in Clinical Periodontics subdivided these diseases into a number of clinically defined subforms,[1] subsequent attempts to categorize patients according to the defined criteria have demonstrated the considerable problem of overlap in the disease definitions.[2] Furthermore, many of the microbiological and host response features of these diseases are common to several of the subforms of periodontitis. It has been the consensus of several groups, including the 1996 World Workshop in Periodontics,[3] that the current classification scheme requires revision. Such a revision could lead to considerably improved diagnostic categories if the disease definitions were dependent upon knowledge of the etiology and pathogenesis of the various disease subforms as well as upon more traditional parameters such as signs of inflammation, probing depths, clinical attachment loss, and age of onset.

Thus, although considerable progress has been made in defining both etiologic agents and pathways of pathogenesis in various forms of periodontal diseases, insufficient information exists to definitively recategorize these diseases. The approach to describing pathogenic mechanisms in this paper will, therefore, be in part generic and thus refer to "gingivitis" and "periodontitis" rather than to specific disease subforms. Where appropriate, descriptions of evidence for specific or unique pathways associated with specific forms of disease (as defined at the 1989 World Workshop in Clinical Periodontics) will be presented.

PATHOGENESIS OF GINGIVITIS

Chronic marginal gingivitis is characterized clinically by gingival redness, edema, bleeding, changes in contour, loss of tissue adaptation to the teeth, and increased flow of gingival crevicular fluid (GCF).[4,5] Development of gingivitis requires the presence of plaque bacteria[6,7] which are thought to induce pathological changes in the tissues by both direct and indirect means.[8] Histopathologic observations have led to the subdivision of gingivitis into 3 stages.[8-10] The initial lesion appears as an acute inflammatory response with characteristic infiltration with neutrophils. Vascular changes, epithelial cell changes, and collagen degradation are apparent. These initial changes are likely due to chemotac-

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tic attraction of neutrophils by bacterial constituents and direct vasodilatory effects of bacterial products, as well as activation of host systems such as the complement and kinin systems and arachidonic acid pathways.[11,12]

The early lesion is characterized by a lymphoid cell infiltrate dominated by T lymphocytes, with extension of collagen loss, while the established lesion is dominated by B lymphocytes and plasma cells. Although direct evidence for specific mechanisms explaining the appearance and progression of gingivitis lesions is not available, the chronic inflammatory infiltrate characteristic of the early and established lesions, as well as the proliferation of the junctional epithelium and destruction of collagen, are consistent with the activation of mononuclear phagocytes and fibroblasts by bacterial products with the recruitment and activation of the local immune system and cytokine pathways. The progression of the lesion from acute inflammation through T cell and then B cell predominance is likely orchestrated by a progression of cytokines (dealt with in more detail below) which are responsible for recruitment, differentiation, and growth of the characteristic cell types with progressive chronicity of the lesion. Importantly, meticulous removal of plaque will usually result in resolution of the chronic gingivitis lesion without residual tissue destruction.

Acute necrotizing ulcerative gingivitis (ANUG), an acute infection of the gingiva characterized by interdental soft tissue necrosis and ulceration, pain, and bleeding,[13] is characterized histologically by frank invasion of the gingival connective tissues by spirochetes and a predominance of *Prevotella intermedia* and *Fusobacterium nucleatum* in the non-spirochetal flora.[13] The association of ANUG with recent episodes of stress, or with other conditions of impaired host defense such as malnutrition, immunosuppression, and systemic diseases, implicates any of a number of possible environmental and systemic stressors as pathogenic factors leading to the expression of the same syndrome.[14-20] A common feature of nearly all cases is very poor oral hygiene, and nearly all cases can be managed with local debridement, improved plaque control, and judicious use of antibiotics.

Pathologic changes in the gingival tissues consistent with clinically chronic or acute gingivitis have been noted in a number of systemic conditions.[21-23] Some of these conditions may mimic the vascular alterations seen in plaque-induced gingivitis or result in cellular infiltration by aberrant leukocytes or other vascular elements. These include acute leukemia, hemophilia, Sturge-Weber syndrome, and Wegener's granulomatosis. In other cases a defective host response to bacterial infection may be manifested as an overexpression of gingival inflammation or caused by an alteration in the usual bacterial microflora. Such conditions include Addison's disease, diabetes mellitus, thrombocytopenia, combined immunodeficiency diseases, and HIV infection. A third group of these conditions is related to hormonal changes manifested as an exaggerated inflammatory response to plaque as well as an alteration in the subgingival microflora. These include changes associated with pregnancy, puberty, steroid therapy, and use of birth control medications.[24-27] Finally, a large number of drugs, many of which are associated with therapy for seizure disorders, hypertension, or transplant rejection, cause gingival enlargement in the presence of bacterial plaque.[28-33]

PATHOGENESIS OF PERIODONTITIS

Periodontitis is clinically differentiated from gingivitis by the loss of the connective tissue attachment to the teeth in the presence of concurrent gingival inflammation.[34] Loss of the periodontal ligament and disruption of its attachment to cementum, as well as resorption of alveolar bone occurs. Together with loss of attachment, there is migration of the epithelial attachment along the root surface and resorption of bone.[9] The histopathology of the periodontitis lesion is in many ways similar to that of the established lesion of gingivitis, with a predominance of plasma cells, loss of soft connective tissue elements, and, in addition, bone resorption.

Despite the histopathologic similarities between gingivitis and periodontitis, evidence is lacking that would indicate that periodontitis is an inevitable consequence of gingivitis. Furthermore, the pathogenic mechanisms explaining the progression of gingivitis lesions to periodontitis lesions are not clear, and the factors that lead to the initiation of periodontitis lesions are unknown. Clinical models of disease activity in periodontitis range from a continuous progression of disease during which loss of attachment occurs at a slow rate over long periods of time to

an episodic burst model in which loss of attachment occurs relatively rapidly during short periods of disease activity.[35-37] Clinical data indicate that either mechanism could be operant in different patients or at different sites or at different times within the same patient, implying that the pathogenesis of periodontal attachment loss could differ between patients and sites and times. Understanding the pathologic mechanisms involved still awaits measurement methods that clearly differentiate between active and quiescent disease.

Bacterial Virulence

It is widely accepted that the initiation and progression of periodontitis are dependent upon the presence of microorganisms capable of causing disease. Although more than 300 species of microorganisms have been isolated from periodontal pockets, it is likely that only a small percentage of these are etiologic agents.[38] Among the characteristics that implicate an organism or group of organisms as etiologic agents are bacterial virulence factors. These are bacterial constituents or metabolites capable of either causing disruption of homeostatic or protective host mechanisms or causing the progression or initiation of the disease. If such bacterial virulence characteristics are truly contributing to disease pathogenesis, modification of such virulence factors should result in an improvement in clinical condition. Thus, the pathogenesis of periodontal disease lesions is in part dependent upon the virulence as well as the presence and concentrations of microorganisms capable of producing disease.

At least 3 characteristics of periodontal microorganisms have been identified that can contribute to their ability to act as pathogens: the capacity to colonize, the ability to evade antibacterial host defense mechanisms, and the ability to produce substances that can directly initiate tissue destruction. It is now apparent that within a given pathogenic species, such as *Actinobacilius actinomycetemcomitans* or *Porphyromonas gingivalis,* only a subset of bacterial types or clonal or genetic subtypes may be pathogenic.[39,40] Thus the presence of a pathogenic bacterial species in the subgingival plaque may not by itself imply that a pathogen is present with virulence characteristics necessary to initiate or propagate periodontitis lesions. For example, recent data indicate that strains of *A. actinomycetemcomitans* in young patients with localized juvenile periodontitis differ from those in older patients with previously active disease in their ability to produce a leukotoxin that is thought to be an important virulence characteristic of this species.[39]

Bacteria need to possess the ability to survive and propagate in periodontal pockets in the complex ecosystem of the biofilm. Some examples of factors that have been identified as promoting virulence of important periodontal pathogens follow. Virulent organisms can express appendages such as fimbriae or molecules such as adhesins which promote association with tissues or other bacteria.[41,42] Furthermore, virulence can be enhanced via the presence of a capsular polysaccharide (as in the case of *P. gingivalis)* which provides resistance to host defenses such as antibody and complement. Some organisms are able to invade into or through host tissues, thereby creating a sequestered environment for their protection and gaining more direct access to susceptible host tissues. Two major periodontal disease pathogens, *A. actinomycetemcomitans* and *P. gingivalis,* are able to invade into the tissues. *A. actinomycetemcomitans* can pass through epithelial cells into the underlying connective tissues,[43] while *P. gingivalis* can invade and persist in epithelial cells.[44,45] It is likely that tissue invasiveness of these organisms may explain the difficulty in eradicating *A. actinomycetemcomitans* by mechanical root debridement, and could also explain the relatively high concentrations of serum antibody reactive with these two species in comparison with other bacteria in dental plaque.

An important feature of nearly all pathogenic microorganisms is the ability to evade the host defense mechanisms that would ordinarily control such infections and prevent disease. Foremost among these defense mechanisms in the periodontium is clearance of bacteria by neutrophils with the assistance of antibodies and complement proteins.[46,47] In health, neutrophils appear to form a barrier at the plaque-tissue interface, controlling bacterial numbers and preventing ingress of bacteria or their products to the tissue surface. The immune system typically assists the neutrophil by producing antibody molecules that opsonize bacteria; such opsonic antibodies, alone or in concert with the comple-

ment system, allow the neutrophil to recognize, ingest, and degrade bacteria. The local repository of such antibody molecules is the gingival crevicular fluid (GCF), a modified inflammatory exudate which flows through the junctional and sulcular epithelium into the gingival crevice or pocket. Amongst a large variety of other molecules, the GCF contains serum components such as antibody molecules,[48] locally produced antibody molecules[49] and other substances, such as neutrophil granule constituents,[50,51] that can be reflective of local immunology and inflammatory processes. Antibacterial antibodies can provide many protective functions. Opsonic antibodies promote phagocytosis via interactions with phagocyte Fc receptors.[52-54] In some cases, antibodies can activate the complement system, an antibacterial cascade of naturally occurring proteins, which can deposit additional opsonins on the bacterial surface, release chemical mediators that recruit additional neutrophils, and deposit macromolecular complexes into the bacterial surface that will lyse and kill certain bacteria. Antibodies may also be produced that will specifically neutralize bacterial toxins and enzymes,[48,55] or that will disrupt bacterial colonization by preventing adherence to the tooth or epithelial surface or to other bacteria.[56]

Little is known about the sequence of events leading to the initial breakdown of this barrier and subsequent initiation of periodontitis. A great deal is known, however, about the mechanisms evolved by some periodontal bacteria to overcome this protective mechanism, and some examples of this are given below. Some organisms, such as strains of *A. actinomycetemcomitans* [57] or *Campylobacter rectus*,[58] produce leukotoxins that can kill neutrophils directly, thus disrupting the primary antibacterial defense mechanism in the gingival crevice. Secondly, some bacteria, such as *P. gingivalis,* produce proteolytic enzymes that either directly degrade antibody and complement proteins in the surrounding serum or GCF or prevent the accumulation of these molecules on the bacterial surface.[55,59] This activity would prevent accumulation of complement-derived chemotactic factors which would ordinarily recruit many additional neutrophils to the site of infection, as well as retard the phagocytosis of both the proteolytic bacteria themselves and other bacteria that are in close proximity. Third, some bacteria such as *A. actinomycetemcomitans* produce factors that suppress the immune response to itself and other bacteria,[60, 61] thereby diminishing the production of otherwise protective antibodies. Finally, as mentioned above, some bacteria can invade tissue cells and avoid contact with neutrophils and molecules of the immune system. Thus, pathogenic bacteria appear to have devised a number of means by which they can evade control by neutrophils, either by directly decreasing their numbers or by destroying host mechanisms meant to promote opsonization, phagocytosis, and bacterial killing.

The interaction between neutrophils, antibody, and complement provides primary protection against the deleterious effects of periodontal pathogens. In general, high levels of antibody do not appear in a patient's serum or GCF until some time after the disease process has initiated. High levels of antibodies reactive with bacterial virulence factors such as *A. actinomycetemcomitans* leukotoxin or *P. gingivalis* proteases, or with whole bacterial antigen preparations, do not occur until relatively late in the disease process and probably do not play an important role in prevention of disease initiation.[48,62] However, it appears that in the case of the antibody response to *A. actinomycetemcomitans* and *P. gingivalis* in early-onset periodontitis patients the extent and severity of disease is the least in patients with the highest titers; thus, some antibody responses to periodontal disease pathogens may ultimately prevent or delay progression of existing disease.[63,64]

Destruction of Periodontal Tissues

The protective responses to periodontal pathogens may be overcome in a number of ways as outlined above, and the concentration of pathogens in subgingival plaque may reach a critical level required for initiation or progression of tissue destruction. Although at least two pathogenic bacteria have been shown to invade the superficial layers of the periodontal tissues, it is readily apparent from histologic observation that pathologic effects on connective tissue and alveolar bone occur at sites deep to the subgingival plaque and invading microorganisms. For this reason, in addition to the possible direct pathologic effects of bacteria on the periodontal tissues, it is clear that damage to the periodontium must also occur by indirect means. Bacterial

products must gain access to the cellular constituents of the gingival tissues and activate cellular processes that are destructive to collagenous connective tissue and bone.

Direct effects of bacteria. It is likely that direct pathological effects of bacteria and their products on the periodontium are significant during early stages of disease. Analysis of plaque samples from patients with increasingly severe levels of gingival inflammation reveals a succession of bacterial species with increased capacity to directly induce an inflammatory response. For example, increased and persistent levels of *Fusobacterium nucleatum* in sites of mild gingivitis and the consequent production of its metabolic by-products may directly affect the gingival vasculature. The resulting edema and increase in production of GCF may provide the environment and nutrients that allow putative pathogens to flourish.[38] Although it is unknown whether or not gingivitis is a prerequisite to development of a periodontitis lesion, it is reasonable that the alteration of the gingival environment by toxic or pro-inflammatory by-products of the gingivitis flora can set the stage for increased concentrations of more virulent microorganisms within the plaque mass.

It is also likely that bacteria can contribute to the pathogenesis of periodontal diseases directly by many other means. *P. gingivalis,* for example, is known to produce enzymes (proteases, collagenase, fibrinolysin, phospholipase A) that could directly degrade surrounding tissues in the superficial layers of the periodontium. In addition it produces metabolic by-products such as H_2S, NH_3, and fatty acids that are toxic to surrounding cells.[45,65-67] Furthermore, bacterial constituents such as lipopolysaccharide (LPS) are capable of inducing bone resorption in vitro.[68]

Indirect effects of bacteria. Once the major protective elements in the periodontium have been overwhelmed by bacterial virulence mechanisms, a number of host-mediated destructive processes are initiated. Polymorphonuclear leukocytes (PMNs), which normally provide protection, can themselves contribute to tissue pathology. During the process of phagocytosis, these cells typically "spill" some of their enzyme content extracellularly during a process known as degranulation; some of these enzymes are capable of degrading the surrounding host tissues, namely collagen and basement membrane constituents, contributing to tissue damage.

There is increasing evidence that the bulk of tissue destruction in established periodontitis lesions is a result of the mobilization of the host tissues via activation of monocytes, lymphocytes, fibroblasts, and other host cells. Engagement of these cellular elements by bacterial factors, in particular bacterial lipopolysaccharide (LPS), is thought to stimulate production of both catabolic cytokines and inflammatory mediators including arachidonic acid metabolites such as prostaglandin E_2 (PGE_2). Such cytokines and inflammatory mediators in turn promote the release of tissue-derived enzymes, the matrix metalloproteinases, which are destructive to the extracellular matrix and bone.[69,70]

Once defensive mechanisms have been averted, the subgingival bacterial microflora has established itself as a predominantly anaerobic, Gram-negative infection. The pathologic appearance of the periodontitis lesion and the mediators, mediator precursors, and mRNA protein templates recognizable either in the GCF or within cellular elements of the gingival tissues are consistent with the expected outcome of a local infection with Gram-negative bacteria. Cytokines, molecules which are released by host cells into the local environment, provide molecular signals to other cells thereby affecting their function. Many cytokines are produced by cells in periodontitis lesions. Among the cytokines and inflammatory mediators most consistently found to be associated with periodontitis are the following:

1. Interleukin 1 (IL-1)[71] is a pro-inflammatory, multifunctional cytokine, which among its many biological activities enables ingress of inflammatory cells into sites of infection, promotes bone resorption, stimulates eicosanoid (specifically, PGE_2) release by monocytes and fibroblasts, stimulates release of matrix metalloproteinases that degrade proteins of the extracellular matrix, and participates in many aspects of the immune response. IL-1 levels in general are elevated in both tissues[72,73] and GCF[74-77] from diseased, inflamed periodontal tissues compared to healthier sites, and elevated levels have been shown to be associated with active disease in animal models.[78] The predominant form in the periodontal tissues is IL-1α, which is produced primarily by macrophages.[79,80]

2. Interleukin 6 (IL-6)[81] is a cytokine that stimulates plasma cell proliferation and therefore

antibody production and is produced by lymphocytes, monocytes, and fibroblasts.[80] Levels of IL-6 have been shown to be elevated in inflamed tissues, higher in periodontitis than in gingivitis tissues, and higher in GCF from refractory periodontitis patients.[82-84] IL-6 has also been shown to stimulate osteoclast formation. Thus, this cytokine may in large part account for both the predominance of plasma cells in periodontitis lesions as well as bone resorption.

3. Interleukin 8 (IL-8)[85] is a chemoattractant that is mainly produced by monocytes in response to LPS, IL-1, or tumor necrosis factor alpha (TNF-α). It is present at high levels in periodontitis lesions, mainly associated with the junctional epithelium and macrophages,[86,87] and its levels in GCF are higher in periodontitis patients than in healthy controls.[88] In addition to serving as a chemoattractant for neutrophils, it appears to selectively stimulate matrix metalloproteinase (MMP) activity from these cells, thus in part accounting for collagen destruction within periodontitis lesions.

4. Tumor necrosis factor alpha (TNF-α)[89,90] shares many of its biological activities (pro-inflammatory properties, matrix metalloproteinase [MMP] stimulation, eiscosanoid production, and bone resorption) with IL-1. In addition, its secretion by monocytes and fibroblasts is stimulated by bacterial LPS.

5. Prostaglandin E_2 (PGE_2),[91,92] a vasoactive eicosanoid produced by monocytes and fibroblasts, induces bone resorption and MMP secretion. Many studies have shown the association of elevated levels of PGE_2 in tissues and GCF with periodontal inflammation, progressive periodontitis, and high-risk periodontitis patients (e.g., early-onset periodontitis, refractory periodontitis, diabetes mellitus).[93-100] The likely importance of eicosanoids in periodontal disease pathogenesis is underscored in several studies demonstrating the beneficial effects of both systemic and topical non-steroidal anti-inflammatory drugs on periodontitis in both animal models and in humans.[91,101-105]

In summary, a simplified model for pathogenesis of periodontitis within the local lesion is the following: virulent microorganisms capable of initiating or propagating periodontal attachment loss must be present in the local lesion at a critical minimal infective dose. In susceptible individuals, or in susceptible periodontal sites within susceptible individuals, protective mechanisms are breached exposing the underlying tissues and cells to bacterial components. Consequently, cellular components, including monocytes and fibroblasts, are stimulated by bacterial components such as LPS to produce many or all of the cytokines described above. These cytokines are capable of acting alone, or in concert, to stimulate inflammatory responses and catabolic processes such as bone resorption and collagen destruction via the MMPs.

Genetic Factors Promoting Periodontitis

As in any infectious disease, host susceptibility plays a major role in determining whether or not the presence of an infectious agent will ultimately lead to expression of disease or progression of preexisting disease. Genetic risk, one aspect of such host susceptibility, has been and is being examined. A summary of these data for specific periodontal diseases, appears below.

Adult periodontitis. Studies of adult periodontitis and periodontal health in twins have demonstrated that heredity accounts for a significant proportion of the population variance in various measures of periodontal diseases, such as gingival inflammation, probing depth, and radiographic bone levels.[106-108] Recent data indicate that a genetic variation or polymorphism in the gene encoding IL-1 (see above) is associated with severity of, and likely susceptibility to, periodontitis.[109] These polymorphisms are variations in the DNA sequence of genes coding for IL-1α (the IL-1A gene) and IL-1ß (the IL-1B gene). In a population of adult, non-smoking subjects of Caucasian Northern European heritage, a higher percentage of individuals with severe periodontal destruction tested positive for one of the genetic forms (alleles) of the IL-1A gene plus one of the Il-1B alleles more frequently than did subjects with less severe disease. Furthermore, one of the two alleles associated with risk for periodontitis is also known to be associated with elevated production of IL-1ß, thus providing a possible biological explanation for the enhanced susceptibility of patient with this genotype for periodontitis.

Early-onset periodontitis: localized juvenile periodontitis (LJP), generalized juvenile periodontitis (GJP), rapidly progressive periodontitis (RPP). These diseases are characterized by their age of onset (usually post-pubertal), by the extent and severity of disease, by their oftentimes characteristic bacterial microflora, and to a

lesser extent by associated pathological and immunological characteristics.[110] These post-pubertal forms of EOP have a familial distribution,[111-114] and a number of clinical and biological characteristics of EOP, including the epidemiology and immunologic responses, appear to be strongly influenced by race.[115-117] These data imply that it is possible that risk for EOP may be genetic. Although a number of genetic models have been tested using genetic segregation analysis, no consistent mode of inheritance for all forms of EOP has been observed.[118-124] One study has demonstrated genetic linkage of LJP with the Gc locus on chromosome 4 in one extended family, but this finding may not be generalizable to all families with EOP.[118,125]

A number of hypotheses have been proposed implicating candidates for genetic risk factors. The observation that many patients with EOP, particularly LJP, have neutrophil chemotactic defects, point to factors related to neutrophil function such as receptors for chemotactic agents or molecules participating in signal transduction.[126-128] Associations of EOP with some antigens of the major histocompatibility complex (HLA) region have been demonstrated, indicating that heritable factors related to immunologic responsiveness may be associated with risk for EOP.[129] Additionally, poorly functional heritable forms of monocyte FcγRII, the receptor for human IgG_2 antibodies, have been shown to be disproportionately present in patients with LJP. Such receptors cause monocytes to function poorly in phagocytosis of periodontal pathogens such as *A. actinomycetemcomitans,* because most of the antibody produced against this bacterium is of the IgG_2 subclass.[130] Finally, studies have demonstrated hyperresponsiveness of monocytes from EOP patients with respect to their production of PGE_2 in response to LPS. This hyper-responsive phenotype could lead to increased connective tissue or bone loss due to inappropriately excessive production of these catabolic factors.[131,132]

It is noteworthy that transmission of EOP in families, and many of the biologic characteristics of these diseases, may be explained by environmental factors as well as genetic factors, and some could be consequences of bacterial infection rather than the cause of such infections.

Pre-pubertal periodontitis. Prepubertal forms of periodontitis are usually subcategorized into a localized form (L-PP) and a generalized form (G-PP). L-PP is most commonly found in patients with no obvious health problems. Some, but not all, patients with L-PP display relative defects in neutrophil function and such patients can be frequently members of families in which other individuals have EOP. Additionally, it has been proposed that defects in cementum formation may predispose to L-PP.[133] In contrast, G-PP is frequently associated with systemic disorders that affect neutrophil function (chemotaxis, phagocytosis) or numbers. Among the disorders that can predispose to G-PP are leukocyte adhesion deficiencies (LAD),[134,135] a group of genetic disorders resulting in impaired adherence-dependent functions, as well as a number of other inherited phagocyte disorders (Chediak-Higashi syndrome,[136] cyclic neutropenia,[137] and Papillon-Lefevre syndrome[138-140]), collagen defects (Ehler-Danlos syndrome type VIII[141]), and enzyme defects (acatalasia and hypophosphatasia[129,142-144]). G-PP can, however, occur in patients with no such discernible defect; frequently, these patients are found in families of patients with other forms of early-onset periodontitis and thus may share common etiologic and pathogenic mechanisms with EOP.

Refractory periodontitis. This form of periodontitis is characterized by its relative resistance to repeated routine therapeutic attempts to control the progression of periodontal attachment loss. Studies have demonstrated that such patients, as seen in patients with EOP, can demonstrate hyperresponsive monocytic responses to bacterial LPS and produce high levels of PGE_2.[145,146] Some of these responses may be genetically determined in these patients.

SMOKING AND PATHOGENESIS OF PERIODONTAL DISEASE

It has been demonstrated that smoking is a risk factor for periodontitis in adults. The number of pack-years of exposure to tobacco smoke is associated with increased risk for adult periodontitis and increased disease severity in smokers compared to non-smokers.[147,148] Additionally, smoking has been shown to be associated with increased disease severity for the generalized forms of EOP (GJP, RPP).[149] The pathologic mechanisms proposed for the deleterious effects

of smoking on the periodontium include alterations of the periodontal tissue vasculature, direct alterative effects on the bacterial microflora, and inhibitory effects on immunoglobulin levels and antibody responses to plaque bacteria.

PERIODONTITIS ASSOCIATED WITH SYSTEMIC DISEASES

Many of the systemic conditions associated with or predisposing to periodontal attachment loss have as a common attribute defective neutrophil function. Severe periodontitis has been observed in primary neutrophil disorders including agranulocytosis,[150,151] cyclic neutropenia,[152,153] Chediak-Higashi syndrome,[136] and lazy leukocyte syndrome.[154] In addition, more frequent and severe periodontitis can be observed in many patients with diabetes mellitus,[148,155,156] Down's syndrome,[157,158] Papillon-Lefevre syndrome,[138-140] and inflammatory bowel disease,[128,159] which exhibit secondary neutrophil impairment. These disorders underscore the importance of the neutrophil in protection of the periodontium. It is assumed, though in nearly all cases not proven, that the pathogenic mechanisms leading to tissue destruction in patients with these diseases are similar to those in other forms of periodontitis as described above.

Unusual and severe forms of periodontitis can be more frequent in patients with certain severe combined and acquired immunodeficiency diseases. Furthermore, some patients with HIV infections develop necrotizing ulcerative periodontitis (NUP), in which acute destruction of the periodontium with bleeding, tissue necrosis, and pain can be observed.[18,20,160,161] It is important to note that this condition also occurs in the absence of HIV infection, and that its occurrence may be no more common than in the general population.[162] The pathogenesis of NUP associated with HIV infection is not clear; the subgingival bacterial flora in patients with HIV infections are not substantially different from that in other patients with periodontitis, with the exception that Candida and enteric pathogens can sometimes be found in some patients. Although it has been hypothesized that the dysregulation and suppression of the systemic and local immune response results in hyperresponsiveness of neutrophils in local lesions and exacerbation of the usual acute inflammatory response,[18,162] there are no definitive data to indicate that the pathogenesis of periodontal diseases in HIV-positive patients is different from that in HIV-negative patients.

A number of studies have demonstrated that there is a higher prevalence of periodontitis amongst patients with diabetes mellitus, and that diabetic patients have more severe periodontitis than do non-diabetic individuals.[148,156,163,164] Importantly, the degree of diabetic control and the duration of the disease are thought to be important factors contributing to the expression of periodontitis in diabetics. Additionally, the degree of control of periodontitis may influence metabolic control of diabetes mellitus.[165,166] Although the precise pathogenesis of periodontitis in such diabetic patients is not known, a number of pathologic features of this disease are consistent with increased risk for periodontitis. Factors such as impaired neutrophil function; microvascular alterations that could lead to impaired access of leukocytes and plasma proteins to the periodontium; and altered collagen metabolism reflective of increased collagenase activity, decreased collagen synthesis, and reduced bone matrix formation, all may contribute to the increased susceptibility of diabetics to periodontal breakdown.

SUMMARY

1. The initiation and propagation of most forms of gingivitis are dependent upon the presence and persistence of bacterial plaque. The histopathology of the gingivitis lesion and its stages are consistent with the following pathogenic mechanisms. Plaque bacteria contain or produce substances capable of causing inflammation. Such substances can have direct effects on the vasculature and on leukocytes, inducing vasodilatation, increased GCF flow, and emigration of neutrophils. Substances in bacterial plaque may also interact with host systems involved in inflammatory responses and thereby exacerbate clinical and histological parameters of inflammation. In more advanced stages of disease it is likely that bacterial antigens, via their ability to gain ingress to the periodontal tissues, activate host cells such as monocytes, lymphocytes, and fibroblasts, and thereby induce pathological changes that are consistent with a chronic inflammatory response.

2. Although a high proportion of sites that experience periodontal attachment loss display signs of gingival inflammation, there is little evidence demonstrating that gingivitis lesions will

always progress to become destructive periodontitis lesions. Furthermore, the pathologic processes that are operant during the initiation of attachment loss, whether alterations in the bacterial flora, fluctuations in host defense mechanisms, or other factors, are not well defined.

3. The pathology of periodontitis lesions are characteristic of, and consistent with, a subversion of host defenses against bacterial plaque pathogens and subsequent activation of bacterially-induced host-mediated processes that destroy periodontal tissues. Data indicate that pathogenic plaque bacteria have virulence characteristics that can prevent their efficient detection and elimination by the host, disable host cells and humoral factors, and directly adversely affect the tissues. The predominance of a Gram-negative bacterial flora, in combination with the cellular and cytokine profiles of the lesions, indicate the likelihood that bacterial LPS activation of monocytes and subsequent production of tissue-destructive cytokines is likely a major pathway for connective tissue attachment loss and bone loss in most forms of periodontitis. Such cytokines can cause tissue destruction via mobilization of tissue metalloproteinases, a major pathway for destruction of soft and hard connective tissues.

4. Emerging data indicate that individual susceptibility to some forms of periodontal disease may be heritable. However, no definitive data in this regard are available. On the other hand, many inherited and acquired diseases characterized by diminished protective function of inflammatory and immunologic pathways are associated with more severe periodontal disease.

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