CHAPTER 5. ETIOLOGY AND CONTRIBUTING FACTORS

Section 1. Microbiology

DEFINITIONS (Newman and Nisengard, 1988)

Cell Types

Prokaryote: A cell which lacks both a nuclear membrane and a large number of membrane-limited organelles. Prokaryotes are represented by bacteria. Size ranges from 1 to 1.5 μm wide and 2 to 6 μm long.

Eukaryote: A cell which has a nuclear membrane and large numbers of membrane-limited organelles. Algae, fungi, protozoa, plant, and animal cells are in this group.

Bacterial Structures

Capsule: An outermost layer composed of either carbohydrate or protein which provides bacteria with a means of evading certain host defense mechanisms and is involved in the expression of virulence. The capsule also provides for immunologic specificity.

Cell Wall: A rigid limiting layer which is responsible for cell shape and resistance to changes in environmental osmotic pressure. Gram's stain is directed to the cell. Gram-positive cells retain the blue crystal violet and stain blue while the Gram-negative bacteria do not retain the dye and thus stain red with safarin after alcohol treatment. The cell wall of Gram-positive bacteria is thicker (15 to 50 nm) than found in Gram-negative forms (7.5 to 10 nm). About 30% of the outer membrane of the cell wall of Gram-negative bacteria is made up of glycolipid, lipopolysaccharide (LPS).

Flagella: Organelles adapted for motility. A flagellum consists of three regions: a basal body, a hook region, and a distal filament. Unipolarly flagellated cells are termed monotrichous while cells which have flagella distributed over the entire cell surface are termed as peritrichous.

Pili: Cell surface filaments which play a role in bacterial adherence and transfer of genetic material between bacteria (the F or sex pili). Pili are straight and about one-half the length of flagellum.

Fimbriae: Pili which are specific for bacterial adherence. In several Gram-negative bacteria, virulence in a host is regulated by the presence or absence of fimbriae.

Oxygen Requirements

Aerobic: Organisms which grow very well at normal room atmosphere.

Microaerophilic: Organisms which grow best in an atmosphere of reduced oxygen.

Anaerobic: Growth in the absence of oxygen.

Facultative Anaerobic: Growth in either an aerobic or anaerobic environment.

Canophilic: Organisms which require greater concentrations of carbon dioxide.

INTRODUCTION

Robert Koch's postulates for bacterial specificity follow: 1) a bacteria should be able to be isolated from diseased tissues; 2) pure cultures of that bacteria can be obtained; 3) bacteria inoculated in experimental animals should cause the disease; 4) the bacteria should then be isolated in the diseased tissues of the animal.

Efforts to apply Koch's postulates to periodontal disease have been largely unsuccessful. Because of this, Socransky (1977) proposed alternative criteria to identify key bacteria in periodontal infections which included:

- the presence of the putative pathogen in proximity to the periodontal lesions and in high numbers compared to either the absence of the bacteria or presence in much smaller numbers in healthy subjects;
- patients infected with these periodontal pathogens often develop high levels of antibody in serum, saliva, and gingival crevicular fluid and may also develop a cell-mediated immune response to the putative pathogen;
- these bacteria can often demonstrate in vivo production of virulence factors that can be correlated with clinical histopathology;
- experimental implantation of the organism into an animal model should lead to at least some characteristics of naturally occurring periodontal disease; and
- clinical treatment that eliminates these bacteria from periodontal lesions should result in clinical improvement.

Loesche (1975) described the non-specific plaque hypothesis (NSPH) and the specific plaque hypothesis (SPH). According to the NSPH, caries and periodontal disease result from the elaboration of noxious substance by the entire plaque flora, while SPH suggests that only certain plaque cause infections because of the presence of a pathogen(s) and/or a relative increase in the levels of certain indigenous plaque organisms.

Theilade (1986) described destructive periodontitis as the result of subgingival colonization, which is favored by such ecological changes as plaque accumulation, gingivitis, and gingival exudate. These changes increase the numbers of microorganisms and alter their proportions, but no single species appears in active sites which is not also commonly present in inactive sites. The subgingival microorganisms have several virulence factors that promote colonization of

the pockets, destroy host defense mechanisms, and provoke inflammation. It appears that different combinations of indigenous bacteria, rather than just a single species, can produce the pathogenic potential necessary to cause progression from gingivitis to destructive periodontitis.

Slots (1986) studied 196 adults with advanced periodontitis and reported *Actinobacillus actinomycetemcomitans* in 50% of progressing lesions and in only 6% of non-progressing sites, and *Porphyromonas gingivalis* in 42 to 52% of progressing lesions and 14% of non-progressing ones. The median *P. gingivalis* recovery in culture-positive sites was more than 10-fold higher in progressing than in non-progressing sites. *Prevotella intermedia* was recovered from 59 to 89% of progressing lesions and from 36 to 53% of non-progressing sites. *P. intermedia* averaged 5 to 10 higher recovery in infected progressing lesions than in infected non-progressing ones. Only one progressing lesion failed to produce any of the above organisms.

REVIEWS OF PUTATIVE PERIODONTAL PATHOGENS

Spirochetes

Loesche (1981) reviewed the role of spirochetes in periodontal disease and concluded that spirochetes are at least diagnostic of periodontal status if not overly pathogenic. Spirochetes have been categorized based on cellular diameter (small, medium, or large) and by the number of axial filaments. All of the cultivable oral isolates are classified in the genus *Treponema*. Spirochetes comprise 30% of the microscopic count in ANUG with evidence of tissue invasion by the organisms reported.

Actinobacillus actinomycetemcomitans (Aa)

Zambon (1985) reviewed the relationship of Aa to periodontal disease. Aa is an anaerobic, non-motile, coccobacillus for which 3 serotypes have been described. Serotypes a and b are most common, with serotype b being elevated in localized juvenile periodontitis (LJP). Evidence for Aa involvement in the pathogenesis of LJP includes the following: 1) almost all cases of LJP harbor large numbers of Aa; 2) successful treatment of LJP has been correlated with eradication of Aa from the pocket; 3) histopathologic findings have provided evidence for Aa penetration of the crevicular tissues in LJP; 4) immunological studies have demonstrated elevated antibody titers to Aa in LJP; and 5) Aa produces a leukotoxin which may be a major virulence factor.

Bacteroides Species

Van Winkelhoff et al. (1988) reviewed the significance of black-pigmented *Bacteroides* (BPB) in oral infections. BPB are anaerobic, Gram-negative, non-motile, rod-shaped cells which produce brown or black-pigmented colonies when grown on blood-containing media. The BPB have been categorized based on fermentation. *P. gingivalis, B. asaccharolyticus*, and *B. endodontalis* are non-fermentative whereas *P. intermedia* is saccharolytic. The BPB are found in small numbers in the healthy gingival sulcus. Correlations have been found between the degree of clinical inflammation and percentage of *P. gingivalis* recovered. The other BPB are not frequently isolated from periodontal pockets although *P. intermedia* has been found in higher levels in acute necrotizing ulcerative gingivitis. Localized juvenile periodontitis lesion have been shown to harbor *P. gingivalis, P. intermedia*, and *B. endodontalis.*

Known virulence factors of BPB include pili or fimbriae, capsules and vesicles which aid in attachment. The BPB can release non-chemotactic factors which compete for chemotactic receptors and inhibit neutrophil chemotaxis. Among the BPB, *P. gingivalis* is the most virulent species. The lipopolysaccharide of *P. gingivalis* is not inhibited in human serum and can induce production of interleukin-1 by macrophages and monocytes. In short, the BPB possess properties which help explain their pathogenic nature in oral infections.

Wilton et al. (1993) found that patients with a history of destructive periodontitis have a higher level of serum opsonins to *P. gingivalis* than matched controls with no periodontal destruction.

Wolff et al. (1993) determined the distribution and prevalence of 5 bacterial pathogens in subgingival plaque, their relationship with each other, and with probing depth. Plaque was collected from 6,905 sites in 938 subjects. A bacterial concentration fluorescence immunoassay and bacterial specific monoclonal antibodies were used to determine the presence and level of *P. gingivalis* (Pg), *A. actinomycetemcomitans* (Aa), *P. intermedia* (Pi), *E. corrodens* (Ec), and *F. nucleatum* (Fn) in each plaque sample. The prevalence in subjects was lowest for Pg (32%) and highest for Ec (49%). The site-based frequency distribution of these bacterial species ranged from 10.3% for Pg to 18.7% for Ec. Pi and Ec were the bacterial combination most often found together in a subject (27.2%). While 64.0% of the sites were without any of the 5 bacterial species evaluated, 20.2% had only 1 of the 5 bacteria species evaluated. The remaining 15.8% of sites had at least 2 bacteria species present. There was a general linear association of the detection level of the bacterial species and probing depth. The odds ratios were 3.9 (Pg), 3.0 (Aa), 4.0 (Pi), 2.7 (Ec), and 2.8 (Fn) of finding high levels of these bacterial pathogens at >5 mm probing depth ($P = 0.01$) in subjects with a specific bacterium compared to molar sites in subjects without the bacteria. The observation that these 5 bacterial species frequently inhabit the subgingival environment, yet are not associated with advanced disease, suggest that a susceptible host is required, in addition to a "pathogenic bacteria," before disease progression may occur.

VIRULENCE FACTORS OF PUTATIVE PERIODONTAL PATHOGENS

General Considerations

Socransky and Haffajee (1991) critically assessed the microbial mechanisms related to the pathogenesis of periodontitis. Virulence factors were defined as the unique properties which permit a bacterial species to colonize a target organ, defend itself from the host, and cause tissue damage. Virulence factors were divided into those properties which favor bacterial adherence and colonization, and those which mediate host tissue destruction. In regard to adherence, subgingival species have adhesions which include fimbriae and cell-associated proteins. After adherence, colony growth depends on environmental factors such as temperature, pH, oxidation-reduction potential, and available nutrients. Competition among different bacterial species can favor or oppose colonization.

Host defense mechanisms which must be overcome include salivary and gingival crevicular fluid flow, mechanical displacement (e.g., tissue desquamation), specific antibodies, host products (e.g., glycoproteins that block bacterial cell binding), and cells of the immune system. Bacterial mechanisms which may mediate host tissue damage include invasion of the tissue by pathogens or diffusion of bacterial byproducts from the crevice into the gingival tissues. Identification of virulence factors requires studies to detect the appropriate bacterial strains, disclosure of possible virulence factors, confirmation in animal models, and confirmation of virulence in humans.

Endotoxin

Daly et al. (1980) reviewed the role of endotoxin or lipopolysaccharide (LPS) in periodontal disease. LPS is found in the outer membrane of Gram-negative bacteria and can be extracted for study by the hot phenol-water procedure of Westphal. Major portions of LPS include lipid A and heteropolysaccharide. Lipid A has been shown to be the toxic factor in Gram-negative sepsis and can activate the classical complement pathway. The polysaccharide component activates the alternate complement pathway. LPS is a potent B-cell mitogen and can stimulate macrophages to release collagenase and induce bone resorption in vitro. Studies have demonstrated the presence of LPS in the cementum of untreated periodontally involved teeth. The highest concentrations of LPS have been found within the loosely adherent subgingival plaque. A study in dogs demonstrated that tritiated LPS can pass through intact crevicular epithelium.

Bacterial Invasion

Listgarten (1965) described the superficial (250 μm) penetration of spirochetes in the ulcerated region of acute necrotizing ulcerative lesions. Spirochetes were found in the non-necrotic tissue before other bacteria and present in higher concentrations within the intercellular spaces of the epithelium adjacent to the ulcerated lesion, as well as within the connective tissue.

Frank and Voegel (1978) and Frank (1980) have reported the presence of filaments, rods, and coccoid organisms in the intercellular spaces of human pocket epithelium.

Using scanning electron microscopy, Saglie et al. (1982A) found bacteria invading the epithelial wall of deep periodontal pockets in 5 out of 8 cases. In one case the bacteria had traversed the basement lamina and reached the connective tissue. Bacterial morphotypes included cocci, short rods, filaments, and spirochetes.

Gillett and Johnson (1982) observed the bacterial invasion of the connective tissue in cases of juvenile periodontitis, using electron microscopy. The invading flora was described as mixed but composed mainly of Gram-negative bacteria, including cocci, rods, filaments, and spirochetes.

Saglie et al. (1982B) identified the following tissue-invading microorganisms in localized juvenile periodontitis: *A. actinomycetemcomitans, C. sputigena, Mycoplasma*, and spirochetes.

Saglie et al. (1985, 1986, and 1987) have also described the presence of bacteria in the oral epithelium in cases of advanced adult and juvenile periodontitis, and the increased numbers of Langerhans cells in relation to bacterial invasion. Pertuiset et al. (1987) found increased numbers of intragingival bacteria in recurrent sites.

Nisengard and Bascones (1987) published informational overviews from a workshop on bacterial invasion in periodontal disease. Studies on the virulence of *P. gingivalis* (Pg) suggest that invasive strains of Pg from subgingival plaque at periodontal disease sites tend to spread along tissue planes rather than grow in colonies, while non-invasive strains in dental plaque not from diseased sites exhibited a localized abscess formation. Evidence of bacterial invasion by viable *A. actinomycetemcomitans* in LJP has been identified by immunoperoxidase and immunofluorescent studies. The number of Gram-negative bacteria in connective tissue was significantly higher in sites with ongoing attachment loss than at inactive sites.

Sanavi et al. (1985) studied the morphologic features and pattern of bacterial invasion in immunosuppressed rats with ligature-induced gingival inflammation.The authors indicate that bacterial invasion, in which proliferating bacteria penetrate the tissues, should be differentiated from bacterial translocation, in which bacteria are passively transported into the tissues by mechanical means such as biopsy or histological processing.

Sandros et al. (1993) confirmed that *P. gingivalis* (Pg) is capable of adhering and entering into oral epithelial cells in vitro. The presence of coated pits in the epithelial cell surfaces suggested that internalization of Pg was associated with receptor-mediated endocytosis. Formation of outer membrane vesicles (blebs) by intracellular bacteria indicated that

internalized Pg was able to retain its viability. *E. coli* strain HB 101 neither adhered to nor invaded epithelial cells.

CLINICAL STUDIES

Technical Problems

Socransky et al. (1987) reviewed the difficulties encountered in the search for specific bacteria in periodontal disease. Conceptual problems include the complexity of the microbiota, with approximately 300 bacterial species present in plaque. If combinations of species are involved in active disease, the complexity increases dramatically. Another difficulty is the inability to accurately define the disease status at a given site at the time of sample collection. Current methods of disease detection only allow for detection of sites which have recently lost attachment over a period of time. Technical difficulties are present at the time of collection of the bacterial sample, cultivation, and characterization of the bacteria. The small diameter of the sulcus and the lack of a "gold standard" makes it impossible to determine if a representative sample has been collected. The dispersion process following collection of the sample tends to create error by selecting more robust microbes which survive the dispersion process. In the culture process, it is impossible to determine if all bacteria originally sampled grow out. Furthermore, cultured bacteria cannot always be characterized and identified, leading to further error.

In an in vitro study of bacterial sampling by absorbent paper points, Baker et al. (1991) reported that the sample obtained misrepresents the bacterial species actually present. By layering 2 bacterial species in a specific way and then reversing the order, the authors noted that the top layer of bacteria accounted for 90% or more of the colony forming units (CFU). When the bacteria were mixed, equal numbers of CFU were detected. From a practical standpoint, it is likely that few of the bacteria from the apical portion of the pocket are detected, leading to error in the bacteriologic assay.

Associated Studies

Genco et al. (1988) reviewed the source of bacteria in periodontal infections. Indigenous organisms are constant members of the microbiota while exogenous organisms are transient. Opportunistic organisms overgrow as a result of environmental changes or alteration of the host resistance.

Technical advances in anaerobic culturing have allowed the identification of specific bacteria associated with health and periodontal disease. Healthy sites harbored a sparse plaque, mostly Gram-positive cocci like *Actinomyces* and *Streptococci.* Gingivitis harbored increased *Actinomyces* and reduced *Streptococci. A. odontolyticus, A. naeslundii, Fusobacterium nucleatum, Lactobacillus, Veillonella,* and *Treponema* species were the mostly likely etiologic agents in experimental gingivitis. It has been noted that increased *P. intermedia* levels were observed in experimental gingivitis. Severe adult periodontitis was associated with *P. gingivalis.* Other organisms prominent in periodontitis include *F. nucleatum* and *Eubacterium timidium.* In localized juvenile periodontitis, *A. actinomycetemcomitans* is predominant. Acute necrotizing ulcerative gingivitis harbors Pi and intermediate spirochetes. Genco et al. indicate that indigenous organisms play a key role in gingivitis while exogenous organisms seem to be implicated in periodontitis. It must be remembered that if the causative agents are indigenous, they will be difficult to eradicate. In contrast, exogenous pathogens may be more easily eliminated.

In the experimental gingivitis study by Löe et al. (1965), 12 subjects ceased all oral hygiene efforts and were monitored clinically and microbiologically. They found that gingivitis began in 10 to 21 days and resolved within 1 week of renewed oral hygiene efforts. Three phases of plaque morphogenesis were described based on time (days).

Phase 1 (day 1 to 2) was characterized by a sparse flora to a dense mat of Gram-positive cocci and short rods; desquamated epithelial cells; and small accumulations of PMNs along the gingival margin.

During phase 2 (days 2 to 4), filamentous forms and rods increased, although cocci were still present in large numbers. The PMN concentration continued to increase.

Phase 3 (days 6 to 10) was associated with a gradual shift to vibrios and spirochetes. Gram-positive cocci and short rods still constituted 45 to 60% of flora, and PMN concentrations were great.

When the oral hygiene was resumed and healthy gingival conditions re-established, the gingival flora returned to one of predominantly Gram-positive cocci and short rods. No vibrios or spirochetes were observed in health.

Savitt and Socransky (1984) attempted to differentiate the composition of bacterial plaque in health, gingivitis, or adult and juvenile periodontitis. Thirty-six (36) patients were sampled by syringe and curet for culture (with selective media) and darkfield microscopy, respectively. No attempt was made to sample sites with active attachment loss. Generally, Gram-negative and motile forms were less common and coccal forms were elevated at healthy sites. Black-pigmented *Bacteroides* species were detected in 20% of the healthy, 42% of gingivitis, 61% of adult periodontitis, and 73% of juvenile periodontitis sites.

Tanner et al. (1984) studied the microbiota of sites which had lost crestal alveolar bone. In 3 subjects, the percentage of small spirochetes was positively related to sites with recent attachment loss while *P. gingivalis,* "fusiform" *Bacteroides* (*B. forsythus*), medium spirochetes, and curved motile rods were also isolated in higher proportions in sites with recent bone loss. *Streptococcus intermedius* and *Fusobacterium nucleatum* made up a higher proportion of the microbiota in inactive sites. Cluster 1 (Pg, Fn, and "fusiform" *Bacteroides*) corresponded to sites with recent bone loss. Cluster 2 (Pg, Fn, and Gram-positive rod type A) was associated with inactive sites. Gingival swelling and bleed-

TABLE 1. SUMMARY OF PUTATIVE PERIODONTAL PATHOGENS

	Characteristics					Socransky's Alternative Criteria to Identify Pathogens				
Species	Cell Morph	Gram Stain	Motility	Oxygen Requirement	Colony Morph	Periodontal Disease Association	Presence in Disease	Increased Ab Titer	Virulence Factors	Implantation Studies
Actinobacillus actinomycetemcomitans	Coccobacillus	negative	nonmotile	Capnophilic (anaerobic)	star-shaped internal morphology	localized juvenile periodontitis	LJP lesion high in Aa	in LJP, high Ab titer to Aa	leukotoxin tissue invasion	
Prevotella intermedia	Bacillus	negative	nonmotile	anaerobic	brown black	acute necrotizing ulcerative gingivitis	*Pi* cultured ANUG		pili and fimbriae capsule LPS	
Porphyromonas gingivalis	Bacillus	negative	nonmotile	anaerobic	brown black	adult periodontitis	*Pg* from advanced sites		collagenase LPS	
Campylobacter recta	helical to straight rod 2 to 6 μm by .5 to 1 μm	negative	motile (single flagella)	anaerobic	yellow to grey pitting of surface	adult periodontitis				
Spirochetes	sprilla 5 to 20 μm by 0.1 to 0.5 μm	negative	motile	strict anaerobes	no colonies "just haze"	acute necrotizing ulcerative gingivitis			tissue invasion	
Eikenella corrodens	Bacillus	negative	trans locating twitching	facultative anaerobe	pitting, corrosion of agar surface	adult periodontitis				
Fusobacterium nucleatum	Bacillus long, tapered	negative	nonmotile	strict anaerobe		adult periodontitis				
Bacteroides forsythus	Bacillus tapered ends	negative	nonmotile	anaerobe	black brown	adult periodontitis				

Sources: Loesche and Laughon (1981); Zambon (1985 and 1990); Theilade (1986); Genco et al. (1988); Van Winkelhoff et al. (1988); Chen and Wilson (1992).

ing on probing distinguished the sites with recent bone loss from the inactive sites. The clusters formed were independent of the depth of the sample within the pocket. Significantly, no single microorganism was found to predict recent bone loss.

Dzink et al. (1985) compared the cultivable Gram-negative species associated with active sites (as determined by the tolerance method which looked for differences between the means of repeated attachment loss measurements greater than 2 mm) versus inactive (control) sites in the same subject. They determined that higher proportions of Gram-negative rods were present at active sites. *Wolinella recta, P. intermedia,* "fusiform" *Bacteroides,* and *A. actinomycetemcomitans* were the 4 species which were elevated only at the active sites.

Bowden (1990) reviewed the microflora associated with root caries. Early research in the 1970s using animal models emphasized the role of *Actinomyces viscosus* and *Actinomyces naeslundii.* More recently, studies have implicated *Streptococcus mutans* and *Lactobacillus* in the prediction of root caries risk. Table 1 is a summary of the characteristics of the putative periodontal pathogens and selected studies which fulfill Socransky's alternative criteria for bacterial specificity in periodontal disease.

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Section 2. Accretions

DEFINITIONS

Plaque: An organized mass, consisting mainly of microorganisms, that adheres to teeth, prostheses, and oral surfaces and is found in the gingival crevice and periodontal pockets. In addition to microorganisms, plaque consists of an organic, polysaccharide-protein matrix consisting of bacterial by-products such as enzymes, food debris, des-

quamated cells, and inorganic components such as calcium and phosphate.

Pellicle: Tooth- or mucosal-adherent salivary proteins.

Calculus: A hard concretion that forms on teeth or dental prostheses through calcification of bacterial plaque.

Subgingival (Seruminal) Calculus: Calculus formed apical to the gingival margin; often brown or black, hard and tenacious.

Supragingival (Salivary) Calculus: Calculus formed coronal to the gingival margin; usually formed more recently than subgingival calculus.

BASIC CHARACTERISTICS OF PLAQUE

Plaque consists of approximately 80% water and 20% solid material, the latter consisting (dry weight) of 35% cellular (primarily bacteria) and 65% extracellular constituency (e.g., polysaccharides). These polysaccharides include dextrans (95%) that facilitate adhesion, and levans (approximately 5%) which may serve as a hydrolyzable energy source.

An acquired pellicle, derived from salivary glycoproteins, provides a scaffold for progressive and dynamic plaque formation (Genco et al., 1990). Van Houte (1982A, 1982B) notes that Van der Waals forces, glycocalyx, and lectin-like receptors (carbohydrate binding proteins) help mediate bacterial attachments during plaque development. Such adherence also depends on attachment forces, numbers of bacteria, host flora and respective oxidation-reduction potentials, and aforementioned salivary (or gingival fluid) proteins. Lipoteichoic acid from Gram-positive bacteria may aid plaque accumulation by increasing the overall negative charge. The presence of fissures, roughened areas, and gingival areas sheltered from oral forces also influence this process. The author noted that the oral cavity is sterile at birth. The initial sources of floral transmission include the mother and other immediate environmental contacts. Anaerobic bacteria are not established until the teeth erupt, with *S. salivarius* and *A. naeslundii* predominating to this point. Following tooth eruption, *S. sanguis, S. mutans, A. viscosus*, and lactobacilli are present. Black-pigmented *Bacteroides* (BPB) and spirochetes are not consistently isolated until late adolescence or adulthood. Selected BPB are purportedly facilitated by selected nutritional factors (hemin, vitamin K, and estrogen), altered redoxpotential and attachment to certain Gram-positive bacteria (e.g., *Actinomyces*). As subgingival niches develop and bacterial successions are influenced by plaque thickness, a more anaerobic flora develops. Subgingival growth primarily represents an extension from the supragingival plaque. Its formation is facilitated by the presence of gingival crevicular fluid.

PLAQUE MORPHOLOGY

Listgarten (1976) examined the structure of the microbial flora on natural tooth surfaces in periodontal health and disease (53 teeth and suggested 5 categories of disease based on gingival inflammation, probing depth, and amount/pattern of radiographic bone loss). He reported that:

1. Normal samples presented a thin layer of adherent bacterial cells—predominantly Gram-positive cocci (GP), lower numbers of Gram-negative organisms (GN), and no spirochetes (S) or flagellated bacteria (FB)—and ranged from a few cells to 60 μm thick.

2. Gingivitis samples consisted of densely packed cells 0.4 mm thicker than normal. "Corncob" formations (central filament, *Bacterionema matruchotii*, covered by streptococci) were present in supragingival plaque. Flagellated bacteria and spirochetes were found in apical plaque sites, covering underlying bacteria in some areas.

3. In periodontitis, dense supragingival plaque mimicked that of gingivitis. Increasing numbers of flagellated bacteria and fewer large filaments comprised a transitional zone between the supragingival and largely motile subgingival plaque. Distinct features of the subgingival plaque included thin layers of smaller cells adhering to the root which contained "bristle-brush" and "test-tube brush" formations (Gram-negative filament, *Leptotrichia buccalis*, surrounded by flagellated rods and short filaments aligned perpendicular to axial surface). Tissue associated flora included spirochetes, FB, cocci, and GN rods.

4. The flora associated with juvenile periodontitis was sparse and simple. Small clumps of GN cocci and thin layers of GN filamentous bacteria were present.

5. Post-juvenile periodontitis was characterized by a flora similar to periodontitis.

Vrahopoulos et al. (1992) examined the ultrastructural morphology of subgingival plaque from patients with chronic adult periodontitis. In the plaque just coronal to the apical plaque border, they described 3 to 4 distinct morphologic layers. The plaque nearest the cementum was densely-packed Gram-positive coccoid cells aligned perpendicular to the root surfaces. The superficial layer (nearest the tissue) was mainly Gram-negative rods and cocci. The two layers between the cemental and superficial layers consisted of a mixture of Gram-positive and Gram-negative bacteria with spirochetes randomly distributed among the other forms. In the superficial layer, "corncob," "rosettes," and "test-tube brush" configurations were identified. They also noted that the most apical organisms were almost always lysed, and bacterial cell-ghosts extended apically for a variable distance from the actual apical plaque border into the so-called plaque-free zone.

Corbet and Davies (1993) reported that levels of supragingival plaque and calculus have been related to progressive periodontal disease. They also noted that control of supragingival plaque in conjunction with professional subgingival tooth cleaning forms the basis for the management of periodontal disease. However, the contribution of supragingival plaque control alone in managing progressive periodontal disease is not clear. There are studies which address, directly or indirectly, the contribution of supragin-

gival plaque control alone in the management of progressive periodontal disease. The effects of supragingival plaque control alone have been evaluated clinically, histologically, and microbiologically. Collectively, these effects may not be as marked as when professional subgingival tooth cleaning is also performed. However, given the patterns of periodontal disease found in adults in many communities, these studies can form the basis for advocating high individual levels of supragingival plaque control as a community measure in the management of periodontal disease. Further long-term investigations into this approach appear warranted.

CALCULUS

Composition

The inorganic constituents of calculus include calcium, phosphorus, carbonate, sodium, magnesium, potassium, and trace elements (fluoride, zinc) (Genco et al., 1990). The major crystalline form in mature calculus is hydroxyapatite; lesser amounts of octacalcium phosphate ($Ca_8[HPO_4]_4$), whitlockite (a magnesium containing tricalcium phosphate), and brushite are present. Subgingival calculus contains greater concentrations of calcium, magnesium, and fluoride compared to supragingival calculus (relates to greater concentrations of these ions in gingival crevicular fluid [GCF] versus saliva). In maturing calculus (< 3 months), brushite may account for 50% of the crystalline forms. Developmentally, crystalline forms appear in the following order: brushite, octacalcium phosphate, whitlockite, and hydroxyapatite.

Organic constituents account for approximately 15 to 20% of the dry weight of mature supragingival plaque (protein, 50 to 60%; carbohydrate, 12 to 20%; lipids, 10 to 15%).

Formation

Calculus formation may begin in as little as 4 to 8 hours and calcifying plaques may become 50% mineralized in 48 hours (Carranza, 1979). Unmineralized plaque is always present on the mineralized surface. The genesis of calculus formation parallels that of plaque, as previously described. The principal mineral source for supragingival and subgingival calculus respectively is saliva and GCF (Genco et al., 1990).

Genco et al. (1990) describes the formation of calculus and the presentation of incremental lines relating to calculus formation. The lines are oriented horizontally in supragingival calculus and vertically in subgingival calculus. The stratifications suggest that calculus deposits increase by apposition of new layers of calcifying plaque. Anerud et al. (1991) longitudinally (15 years) examined calculus formation in Sri Lankan tea laborers who had no professional dental care. They reported that subgingival calculus formation began 6 to 8 years after eruption, continuing to approximately 30 years of age, at which time it leveled off. Teeth with calculus showed a significantly higher rate of attachment loss than teeth without calculus. Subgingival calculus was found to form first on the mandibular incisors and maxillary molars, suggesting that the initial deposits in a supragingival location might have created conditions facilitating subgingival calculus formation.

Mineralization

Genco et al. (1990) reviews 4 theories of mineralization of calculus: 1) The Booster mechanism in which high pH, calcium, and phosphorus concentrations allow precipitation of calcium phosphate. Loss of CO_2, NH_3 production, acid/alkaline phosphatase activity, and calcium liberation are influencing factors. 2) The epitaxic concept suggests that calcium and phosphorus levels are inadequate for spontaneous precipitation but great enough to support growth of hydroxyapatite crystals about "nuclei/seed" sites. Crystal growth proceeds in the presence of metastable ionic solutions. "Nucleators" may include Ca-phospholipid-PO_4 complexes, collagen molecules, and proteoglycans. This theory is widely held. 3) The inhibition theory is based on alteration of the inhibition mechanism which maintains certain sites as noncalcifying. Calcification occurs when this mechanism is disrupted by a number of possible agents (e.g., pyrophosphate degradation by alkaline phosphatase, yielding PO_4). 4) The transformation theory suggests that amorphous, noncrystalline deposits (and brushite) may be transformed to octacalcium PO_4 and hydroxyapatite. Pyrophosphate may play a role in this process.

Attachment

Zander (1953) described 4 modes of calculus attachment in 50 teeth using light microscopy (LM): 1) attachment by secondary cuticle; 2) microscopic irregularities in the cemental surface; 3) microbial penetration of cementum; and 4) cemental resorption bays. Subsequently, calculus attachment in areas of cemental separation (Moskow, 1969) and by direct contact of calcified matrix to tooth structure (Selvig, 1970) was reported.

Using light (LM), scanning electron (SEM), and transmission electron (TEM) microscopy, Canis et al. (1979) found no evidence of direct extension of microorganisms into cementum, and attributed Zander's observation by LM to artifact. Attachment in mechanical undercuts (e.g., resorption bays, cemental tears, and areas of root gouging/caries) was fairly common. Intimate adaptation of calculus to cementum mediated by an indistinguishable interface ("calculocementum") was frequently observed.

Morphology

Based on LM and TEM observations, Friskopp (1983) described morphological characteristics of supragingival and subgingival calculus. Supragingival calculus was heterogenous, presenting filamentous microorganisms, small needle-shaped crystals, and large ribbon-like crystals (islets of intermicrobial calcification). Distribution of the small

needle-like crystals (100 nm long) occurring near the inner bacterial membrane appeared influenced by microorganisms. Bundles/rosettes of large crystals (1 nm to 50 nm long) were associated primarily with the small crystals (versus microorganisms). Subgingival calculus was homogeneous at the LM level, containing microorganisms (cocci, filaments, and rods), but no calcified material. Only small crystals (< 50 nm) were present in the calculus itself, initially occurring within the microorganisms; a few noncalcified microorganisms were observed. The bacterial cell wall was the last structure calcified in supragingival and subgingival calculus.

CALCULUS AND PERIODONTAL DISEASE

Calculus and Inflammation

Mandel (1986) provided a detailed review of calculus and periodontal disease. The author discussed epidemiologic, clinical morphological, and experimental aspects. Salient points of this review are presented below, noting the original authors and publication dates.

Schroeder (1969) considered plaque the cause of inflammation and calculus the result of inflammation which in turn promotes chronic inflammation. While studying 200 dental students and 200 dental clinic patients, Alexander (1971) reported a closer match between the distributions of gingival indices and plaque than between gingival indices and calculus. Buckley (1980) examined 300 teenagers and reported a higher correlation between gingival indices and plaque than between gingival indices and calculus. In a national health examination survey, Douglas (1983) found that 51.4% of subjects were free of gingival disease in 1971-1974 compared to 26.1% in 1960-1962; the debris scores had improved significantly but not the calculus scores.

Calculus Toxicity

Supragingival calculus is completely permeated by dyes in 24 hours (Baumhammers and Rohrbaugh, 1970). It has a spongy appearance and contains empty spaces (Lustman, 1976). Calculus and cementum from periodontally diseased teeth have induced bone resorption in vitro (Patters, 1982).

Calculus and Attachment Loss

Lennon and Clerehugh (1984) determined that calculus was the best predictor of attachment loss epidemiologically. Tagge (1975) noted that removal of calculus resulted in statistically greater improvement in probing depths and soft tissue response than oral hygiene alone (22 patients). Chawla (1975) observed that scaling and oral hygiene correlated directly to improvement in clinical health; plaque control alone failed to result in such improvement (1,500 patients). Hughes and Caffesse (1978) found that plaque control had minimal influence on attachment levels and that root instrumentation was the primary contributor to positive gingival changes (15 patients). Cercek (1983) compared brushing and flossing in 7 patients to removal of only subgingival plaque or removal of subgingival plaque and calculus. He observed that removal of subgingival plaque only resulted in little reduction in bleeding scores or improvement in probing attachment levels (neither did supragingival plaque removal by brushing/flossing). Only the removal of both subgingival plaque and calculus resulted in clinical improvement. Ramfjord (1982) found that with professional tooth cleaning every 3 months, the level of oral hygiene was not critical for maintenance. (End of Mandel review.)

Calculus and Defect Depth

Richardson et al. (1990) evaluated the relationship between apical calculus position and defect depth and morphology in 260 intrabony defects in 39 patients. Using loops and fiberoptic lighting, the most apical level of calculus was grooved with a bur. Histologic evaluation of en bloc tissue specimens failed to reveal calculus apical to the groove in any specimen. Mean distance of apical calculus to defect base was significantly greater for 3-wall defects than for 1- and 2-wall defects and increased as intrabony defect depth increased. In most cases, the apical extent of calculus was found at mid-depth of intrabony defects. Reasons for absence of calculus at the base of the defect include: 1) the apical aspect of the defect is the area of most recent tissue destruction and organisms had not yet calcified; 2) the most apical portion of defect is not pathologically exposed but is the zone of cementum and Sharpey's fiber attachment; 3) defects may have been produced by traumatic occlusion, resulting in loss of bone height and volume but not attachment loss.

Calculus and Healing

In order to achieve faster healing post-mucoperiosteal flap reflection, instrumentation of the root surface is required. Fujikawa et al. (1988) showed that it took dogs 120 days in non-instrumented areas (where calculus was not disturbed) to achieve the same healing that occurred sooner (in about 30 days) on instrumented root surfaces. Calculus retained after instrumentation is associated with increased inflammatory infiltrate in the connective tissue.

Interruption of Calculus Formation

Suomi (1974) observed that dentifrices containing calculus-reducing agents had no significant effect on gingivitis.

Zacherl et al. (1985) and Lobene (1986), each using slightly different formulations of a dentifrice containing 3.3% pyrophosphate and 0.24% sodium fluoride, were able to show reductions of 37% and 44% in supragingival calculus in 6 months and 3 months respectively. The pyrophosphate is believed to inhibit calcification by preventing the initial calcification nucleus from growing, possibly by "poisoning" the growth centers of the crystal.

Rosling and Lindhe (1987) compared the relative efficacy of calculus inhibition of 2 commercial tartar control

toothpastes, (CR) and (CO), to a placebo dentifrice in 161 adults with history of supragingival calculus buildup. At baseline and after 3 months (brushing twice a day), there was no significant difference in calculus formation among the 3 groups. At 6 months, calculus in CR and CO relative to placebo was reduced by 9% and 42.2%, respectively. At both 3- and 6-month exams, the CO group demonstrated significantly more calculus-free surfaces than the placebo group. CO provided a statistically significant reduction in supragingival calculus after 6 months when compared to CR or placebo. CO and CR both contain 0.243% sodium fluoride and 3.3% soluble pyrophosphate in a silica abrasive system. The soluble pyrophosphate in CO is from a mixture of 1.5% tetrasodium and 4.5% tetrapotassium pyrophosphates whereas that in CR is from tetrasodium and disodium dihydrogen pyrophosphates.

Radiographic Detection

Buchanan et al. (1987) quantified the sensitivity and specificity associated with radiographic calculus detection on proximal surfaces of teeth with severe periodontitis. Periapical radiographs were taken on 18 patients using a paralleling device, with standardized kVp, mA, exposure time, and processing. Extracted teeth were stained with methylene blue and the percentage of proximal root surface area occupied by calculus was calculated. Calculus detection on radiographic surfaces as compared with visual assessment of the same tooth surface demonstrated a sensitivity of 43.8% (only 43.8% of surfaces with visual calculus were detected radiographically) and specificity of 92.5% (92.5% of surfaces visually free of calculus showed no calculus radiographically). Sensitivity was unaffected by tooth type, but specificity decreased from anterior teeth to posterior teeth. In the majority of surfaces with thin or moderate calculus deposits, radiographic evaluation was not effective as a diagnostic method. Conventional oral radiography predicted calculus on less than half of the proximal surfaces where calculus was present visually.

Subgingival calculus appears to contribute significantly to the chronicity and progression of periodontal disease. Calculus may be analogous to a ligature (Friskopp, 1984); i.e., it may extend the sphere of influence of microbial plaque's bone resorptive activity, limit self-cleansing mechanisms, and promote new plaque formation.

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Section 3. Immunology

DEFINITIONS

Antibody: A class of serum proteins that are induced following interaction with an antigen. They bind specifically to the antigen that induced their formation.

Antigen: Any foreign material that is specifically bound by antibody.

Cell-mediated immunity: An immune reaction mediated by T-cells (activated lymphocytes release biologic response modifiers [lymphokines] on exposure to antigen).

Chemotaxis: The migration of cells along a concentration gradient of an attractant.

Complement: A group of serum proteins involved in the control of inflammation, the activation of phagocytes, and the lytic attack on cell membranes. The system can be activated by interaction with antigen-antibody complexes or by bacterial substances.

Immunoglobulin: A glycoprotein composed of "heavy" and "light" peptide chains; functions as antibody

in serum and secretions. There are five major classes abbreviated as IgG, IgA, IgM, IgD, and IgE, each with specialized functions. The classes are described below:

IgG: Most abundant immunoglobulin (Ig) of internal body fluids, particularly extravascular, where it combats microorganisms and their toxins. Fixes complement through the classical pathway. Crosses the placental barrier to provide defense against infection during babies' first weeks of life. Binds to macrophages and polymorphonuclear cells.

IgA: Major Ig in sero-mucous secretions where it defends external body surfaces. Aggregated IgA binds to polymorphonuclear leukocytes and can also activate the alternative complement pathway.

IgM: Very effective agglutinator; produced early in the immune response. Largely confined to the bloodstream where it plays an important role against bacteremia. Fixes complement through the classical pathway.

IgD: Present primarily on the on surface of B lymphocytes.

IgE: Contact with antigen leads to degranulation of mast cells with release of vasoactive amines. Responsible for symptoms of atopic allergy. The main physiologic role of IgE is protection of external mucosal surfaces of the body where an acute inflammatory reaction is triggered, thereby recruiting plasma factors and effector cells.

Lymphocyte: A spherical cell of the lymphoid series (7 to 20 μm in diameter) with a large, round nucleus and scant cytoplasm. It is the principal cell involved in the immune response. There are two major populations, T- (or thymus-dependent) lymphocytes and B- (or bursa-equivalent) lymphocytes. B-lymphocytes differentiate and become antibody-producing plasma cells, while T-lymphocytes are involved in a variety of cell-mediated immune reactions.

Lymphokine: Soluble factors released from lymphocytes that transmit signals for growth and differentiations of various cell types.

Macrophage: A large phagocytic cell of the monocyte series. Important as an antigen-presenting cell and as a producer of certain cytokines such as interleukin-1 and gamma interferon.

Mitogen: A substance that causes DNA synthesis, blast transformation, and mitosis in lymphocytes.

Neutrophil: The predominant polymorphonuclear leukocyte comprising up to 70% of the peripheral white blood cells that is important in infection and injury repair. May have impaired function in some forms of early onset periodontitis.

Opsonin: A substance (e.g., antibody, complement) capable of enhancing phagocytosis.

INTRODUCTION

Schonfeld and Checchi (1985) further defined complement as a multicomponent system which has several important functions. It can be activated by the complex or "classical" pathway (initiated by antigen bound to IgG or IgM which in turn is bound to the first component of complement) and the properdin or "alternate" pathway (activated by bacterial endotoxins and certain other substances). An activated complement complex may lyse cells on which the antigen-antibody complexes are found, stimulate the release of histamine and thromboxanes from mast cells, increase vascular permeability and smooth muscle contraction, effect chemotaxis for PMNs and macrophages, and account for the symptoms of immediate hypersensitivity. The anaphylatoxic and chemotactic factors of activated complement (C3a and C5a) are produced in both pathways.

Immunological mechanisms which can protect the host against infectious organisms may also cause tissue destruction. These include: 1) type I anaphylaxis is mediated by IgE bound to mast cells or basophils, which may degranulate, resulting in possible anaphylactic reaction; 2) type II antibody-dependent cytotoxic (IgG or IgM mediated) autoimmunity; 3) type III immune complex mediated responses which activate complement; and 4) type IV cell mediated (delayed-type) responses which are slower than type I, II, or III reactions and involve activation of special T cells which release lymphokines or perform effector functions.

SELECTIVE IMMUNE SYSTEM RESPONSE

Specific lymphocytes capable of reacting to specific antigens undergo division to produce amplification of the cell clones which are reactive to respective antigens. An exception to this is polyclonal B cell activation in which certain substances activate B cells without regard to their antigenic specificity. Activated cells either differentiate into effector (or plasma) cells or become "memory" cells which can mount a much stronger second response to an antigen.

Host tissue damage can result from immune response when oral bacteria and their products gain access to the gingival connective tissue and react with specific T and B cells which release lymphokines. These can cause death of gingival fibroblasts, enhance osteoclastic bone resorption, and activate and attract PMNs and macrophages. The PMNs and macrophages, when activated, can contribute to tissue destruction through release of enzymes. Additionally, immunoglobulins produced by plasma cells can activate the complement system with potential destructive effects. When components of the immune system are activated, the ensuing inflammatory response is accompanied by some degree of tissue destruction.

Genco and Slots (1984) reviewed the host immune response in periodontal disease. The immune systems responding to bacterial infections include the mucosal or secretory immune system, neutrophil-antibody-complement system, lymphocyte-macrophage system, and immunoregulatory systems. While antibodies have the potential to inhibit mucosal bacterial adherence, their role in preventing coloni-

zation of periodontopathic organisms is unknown. This is also the case of the immune response's role relative to temperature, pH, oxidation-reduction potential, nutrition, bacterial antagonisms, and synergisms. Microbial killing may result from complement-dependent cytolysis/complement-antibody mediated cytolysis and phagocytes functioning independently or in combination with opsonic factors such as antibody and complement. Phagocytes can increase bactericidal activity through oxygen reduction, excitation mechanisms, or oxgyen independent mechanisms such as lysosome, lactoferrin, and azurophilic granules.

Serum antibody studies have shown correlations between predominant organisms in several forms of periodontal disease and antibody titers. These include *Porphymonas gingivalis* (Pg) and severe adult periodontitis, *Actinobacillus actinomycetemcomitans* (Aa), and localized juvenile periodontitis (LJP), and intermediate-sized spirochetes, and *Prevotella intermedia* (Pi) with acute necrotizing ulcerative gingivitis.

Complement plays an extensive role in periodontal disease through its effects on phagocytosis, chemotaxis, alteration of vascular permeability, killing of cells, lymphokine production, antibody synthesis, lysosomal enzyme release, and bone resorption. Complement proteins (or cleavage products) bind to receptors on neutrophils, platelets, mast cells, macrophages, erythrocytes, and specific target cells. Its activation in periodontal disease originates locally via the alternative pathway through C3 and Factor B cleavage in adult periodontitis and LJP and via the classical pathway in LJP as evidenced by the marked depression of C4 levels.

Depressed neutrophil chemotaxis and phagocytosis have been demonstrated in LJP. Approximately 75% of classic LJP patients suffer from a peripheral blood neutrophil chemotactic abnormality due to a reduced chemotactic gradient response. This is due to a reduced number of cell surface receptors for the synthetic peptide N-formyl-1-leucyl-1-phenylalanine (FMLP) and may be hereditary. LJP patients demonstrate antibodies to Aa and Aa antigen in cells. The containment of LJP to localized areas may be due to host antibodies that opsonize Aa leading to effective ingestion and killing by phagocytes.

Hypersensitivity to periodontopathic microbial antigens has been demonstrated using lymphokine production or the blastogenesis assay as in vitro indicators of cellular immunity. Three patterns of reactivity of peripheral blood monocytes following stimulation by oral organisms have been suggested: 1) specific or non-specific stimulation of lymphocyte blastogenesis by mitogenic or polyclonal activation of lymphocytes, regardless of disease activity level; 2) peripheral blood lymphoproliferative response, in a few individuals with non-categorized disease status; and 3) stimulation of more positive responses by Gram-negative anaerobic organisms (e.g., *P. gingivalis* and *Treponema denticola*) in patients with destructive disease as compared to subjects with gingivitis or healthy subjects.

The severity of periodontal disease may be a consequence of B-cell hyperactivity. The lymphoproliferative response results in a production of lymphokines, such as alpha-lymphotoxin and osteoclast activating factor, which may in turn produce tissue destruction. Lymphocytes can induce macrophage activation to produce tissue destructive factors such as collagenase and oxidizing agents. It has been observed that patients with deficient lymphocyte functions have less gingival disease than immunocompetent patients, but patients with reduced neutrophil numbers or function are very susceptible to disease.

Lymphocytes and macrophages also produce factors which recruit fibroblasts to areas of inflammation and lead to their proliferation. The latter results in increased collagen production for repair.

POLYMORPHONUCLEAR LEUKOCYTES (PMNS) AND PERIODONTAL DISEASE

Miller and Lamster (1984) reviewed the role of PMNs in periodontal diseases, comparing this relationship to a double-edged sword. On one edge, the primary role of PMNs is defensive, playing an essential role in containing gingival bacteria and their products. On the opposite edge, PMNs release extracellular lysosomal enzymes which may contribute to localized tissue destruction. PMN impairment or absence accompanying diseases such as Chédiak-Higashi syndrome, agranulocytosis, cyclic neutropenia, and diabetes mellitus have been associated with severe periodontal destruction. The presence of PMNs in the gingival crevicular fluid may have a future role as a clinical diagnostic test in the determination of disease activity pending development of an effective and predictive assay.

Miyasaki (1991) reviewed the role of the neutrophil in controlling periodontal bacteria. Neutrophils kill bacteria or influence bacterial growth by oxidative (cytosol, membrane granules) or non-oxidative mechanisms (azurophil granules, defensins). Delivery of antimicrobial substances by the neutrophil can occur by 4 mechanisms: 1) delivery of oxygen metabolites or so-called "respiratory burst" (this occurs as phagocytes consume and transfer dioxygen resulting in superoxide and hydrogen peroxide production); 2) secretion which involves release of cytoplasmic granule contents as a result of fusion of granules with the plasma membrane; 3) phagocytosis by engulfment of particles within a membrane bound structure called a phagosome; phagosomes fuse with lysosomes to form phagolysosomes, which effectively deliver high concentrations of granule contents; and 4) death as a result of injury or failed phagocytosis (cytolysis) or as a result of programmed cell death (apoptosis). Miyasaki also described the "order" of components of the host defenses in response to a bacterial challenge. Initially protection is afforded by serum complement; activation of complement produces an influx of neutrophils. As the reaction becomes more chronic, monocytes/ macrophages arrive. If the antigen is not destroyed at this point through

phagocytosis, the antigen is presented to T-lymphocytes which in turn activate B-lymphocytes resulting in maturation of immunoglobulin-producing plasma cells. All of these responses are an attempt of the body to contain the bacterial antigen.

Newman and Addison (1982) compared the functional activity of gingival crevicular PMNs in LJP patients with healthy controls. They observed that although 80% of the gingival crevicular PMNs were viable in both patient groups, 95% of those in LJP patients exhibited altered morphology and none phagocytized the test organism, *Candida guillermondiae*. Respective percentages for healthy controls were 10% and 25%. Seventy-five percent (75%) of LJP PMNs (versus 50% of controls) were able to phagocytize Gram-negative and Gram-positive organisms in vivo, but did not effectively lyse the cells once engulfed. The authors concluded that LJP-affected gingival crevicular PMNs showed reduced phagocytic function compared to normal or periodontitis-affected PMNs. The decreased functional behavior of these cells may relate to their life stage (i.e., functional end-stage) and not accurately reflect their original capabilities.

Clark et al. (1977) also assessed chemotactic activity levels of PMNs from patients with LJP, adult periodontitis, advanced generalized periodontitis and healthy controls. They reported that PMNs of 7 out of 9 LJP patients exhibited an impaired chemotactic level, approaching 62.3% of that noted in the normal controls. The serum from 5 out of 9 LJP patients inhibited chemotaxis by 68.0 to 80.2% versus 31.6% for normal controls. Three of 4 advanced generalized patients also demonstrated reduced cellular chemotactic responses and serum chemotaxis inhibition. None of the adult periodontitis patients had reduced PMN chemotactic levels and only 1 out of 5 had serum chemotaxis inhibition. The authors concluded that in LJP, PMNs may contribute to host destruction by failing to protect the host adequately and by releasing their toxic lysosomal or metabolic products into the adjacent tissues.

DeNardin and DeLuca (1990) utilized monoclonal antibodies (MOABs) specific for FMLP chemotactic peptide receptors, noting that 5 out of 7 reaction sites demonstrated reduced binding against PMNs from chemotaxis defective LJP donors. The decrease was possibly due to qualitative differences in the epitope, epitope masking, or reduced expression of FMLP receptors on the PMN surface.

Using beagle dogs, Wennstrom and Heijl (1980) found that extracts of *Actinomyces viscosus* derived from bacterial plaque (associated with gingivitis) exerted a greater chemotactic affect on leukocytes than extracts of *Capnocytophaga ochracea* (associated with periodontitis). Both were greater than saline control units. Complement activation appeared to be the dominant source of chemotaxis in this study.

CELL MEDIATED IMMUNITY

Seymour (1991) and Seymour and Powell (1979) reviewed the immune response as it relates to the pathogenesis of periodontal disease and hypothesized that periodontal disease in adults occurs in 2 forms, a stable lesion and a progressive lesion. Advanced (progressive) forms of periodontal disease are dominated by a B-lymphocyte/plasma cell lesion, while early and stable forms are dominated by T-lymphocytes. Based on these observations, the goal of therapy should be to convert B cell to T cell lesions. Depressed T-helper:T-suppressor ratios have been demonstrated in gingivitis and ligature-induced periodontitis suggesting that a local immunoregulatory imbalance is associated with disease. Disease susceptibility has been evaluated using the autologous mixed lymphocyte response (AMLR) as an in vitro measure of immunoregulation. A depressed AMLR has been demonstrated in some, but not all patients with severe periodontitis. A reduced AMLR has been demonstrated in generalized juvenile periodontitis versus LJP. This depressed AMLR may be either the result or cause of disease. PMNs have also had a protective role.

SYSTEMIC DISEASES

Systemic diseases associated with severe periodontitis (such as agranulocytosis, cyclic neutropenia, Chédiak-Higashi syndrome, and lazy leukocyte syndrome) have been shown to have qualitative and/or quantitative PMN deficiencies. In modeling genetic factors, immuno-responsive genes may divide the population into two groups consisting of susceptible and non-susceptible individuals. Susceptible individuals are in balance (or stable) with their oral flora until untoward shifts result in progressive lesions. Non-susceptible individuals may also experience environmental disruptions that precipitate shifts to progressive lesions.

NEUTROPENIA AND AGRANULOCYTOSIS

Neutropenia is the reduction in the number of PMNs in the peripheral blood to below 1,500 per mm^3. This condition may be transient and insignificant. When it is below 500 per mm^3 and predisposes to infection, it is called agranulocytosis. One of the known causes of agranulocytosis is drug idiosyncrasies (aminopyrine, chloramphenicol, sulfonamides, chlorpromazine, etc.). Agranulocytosis reduces the defense mechanisms and leads to infections, including ulcerative necrotizing lesions of the gingiva and other areas of the oral cavity. Less frequently, ulcers and infections occur in anal-genital areas, GI tract, skin, urinary tract.

Leukocyte Adhesion Deficiency

These patients have an inherited chemotactic defect of the adhesion glcoproteins. Infections occur early in life and include generalized prepubertal and postpubertal severe periodontal diseases (Waldrop et al., 1987).

Job's Syndrome (hyper-Immunoglobulinemia E)

This is a rare condition in which a complex autosomal recessive disorder induces a defect in neutrophil motility that leads to deficient chemotaxis and infection and "cold" abscesses in skin and respiratory tract. Severe periodontal disease has been described but studies are incomplete.

Chédiak-Higashi Syndrome

Neutrophils have decreased chemotaxis and bactericidal activity resulting in neutropenia, depressed inflammation, and severe periodontal destruction, and ulcerations. Lavine et al. (1976) described severe periodontal disease in mink and mice with this syndrome.

Papillon-Lefèvre Syndrome (PLS)

This syndrome represents rapid destruction of the periodontium and palmo-plantar hyperkeratotic lesions at an early age (prepubertal). PLS has been found to be associated with diminished neutrophil activity (Van Dyke et al., 1984) and an increase in circulating NK cells (Genco, 1992).

Chronic Granulomatous Diseases

This is another rare inherited disorder associated with severe, life-threatening, suppurative infections of skin, liver, lymph nodes, and other organs. Neutrophils and monocytes from these patients have a defective oxygen metabolism and are unable to kill many species of bacteria and fungi. Patients with CDG have oral ulcerations and gingivitis, but there is no correlation with severe periodontal destruction (Cohen et al., 1985).

Periodontal Diseases

Altman et al. (1985) studied PMN and monocyte (MN) chemotaxis in 7 patients with prepubertal, 37 with juvenile, 35 with rapidly progressive, and 8 patients with adult type periodontitis. In the prepubertal groups, 5 patients had abnormal PMN chemotaxis, 5 had depressed MN chemotaxis, and 1 had reduced serum chemotactic activity. All patients in this group had at least 1 form of reduced leukocyte chemotactic activity. In the juvenile periodontitis group, 17 patients had abnormal PMN responses: 16 were depressed and 1 was enhanced. MN chemotaxis was depressed in 4 of these patients and elevated in 2. Five patients had reduced serum chemotactic activity and 1 manifested a serum chemotactic inhibitor. In total, 65% of juvenile periodontal patients had some form of abnormality. In the rapidly progressive group, 15 had abnormal PMN chemotaxis, 7 had aberrant MN chemotaxis, 4 had reduced serum chemotactic activity, and 8 had a serum inhibitor of chemotaxis. No abnormalities were found in the PMNs or sera of the adult periodontitis patients. Overall, 66% of the early-onset patients manifested some form of cell or serum-related leukocyte chemotactic abnormality.

Reinhardt et al. (1988) evaluated lymphocyte subset densities and distributions in gingival biopsies from active, stable, or healthy sites. Sections were labeled with monoclonal antibodies for 1) pan T cells, 2) T-suppressor (Ts) cells, 3) T-helper (Th) cells, and 4) pan B cells. Lymphocyte populations were identified from the sulcular, middle, and oral one-third of each section. Relative proportions of lymphocyte subsets were also analyzed in peripheral blood samples using direct immunofluorescence. Pan B cells were significantly more prevalent in infiltrates from active sites than stable or healthy sites. The T/B cell ratio was significantly lower in active versus stable sites or blood. The Th/Ts cell ratio did not vary significantly between groups, but a trend toward lower relative numbers of Th cells in sulcular infiltrates of active sites was noted. These results support the premise that active periodontal sites display elevated B cell populations and abnormal immune regulation possibly involving the Th cell subset.

Donaldson and Ranney (1982) compared the blastogenic response of periodontally healthy subjects with matched groups of subjects having either LJP, severe periodontitis, or moderate periodontitis. Bacterial stimulants of known pathogens to these disease entities were utilized. Peripheral blood lymphocytes (PBL) were harvested after a 4-hour pulse with tritiated thymidine on days 4 and 6 of culture. The healthy subjects responded as frequently as those in all the diseased groups. The dose-response distributions of these groups were indistinguishable and the magnitude of the responses was not substantially different between groups. These results suggest a nonspecific activation of blastogenic response to antigenic stimulation rather than specific sensitization occurring during initiation or progression of periodontitis.

Using mitogens and hemogenates of periodontopathogens, Osterberg and Page (1983) evaluated the blastogenic responsiveness of peripheral blood monocytes (PBM) obtained from LJP, rapidly progressive periodontitis (RPP), adult periodontitis (AP), and healthy control subjects. Blastogenic responsiveness to unstimulated cell cultures, putative periodontal pathogens *Bacteroides melaninogenicus*, *Capnocytophaga*, *Fusobacterium nucleatum*, *Actinomyces viscosus*, and to mitogens phytohemaglutinin and pokeweed mitogen was assessed by tritiated thymidine uptake after 3 days (mitogens) and 5 days (bacterial). They found that since PBMs from periodontally diseased subjects respond to plaque and bacteria by undergoing blastogenesis, measurement of lymphoid cell responsiveness could help establish diagnosis, prognosis, and recall intervals. Results indicated that the AP and healthy groups differed with regard to spontaneous blastogenic activity in unstimulated cultures. This reflects different proliferation rates of T-lymphocyte subsets which respond to the presence of autologous non-T cells and ultimately to a different immune response. Patients with chronic periodontitis may have basic abnormalities in mechanisms of immune regulation. Results also demonstrated marked increases in unstimulated and bacterially stimulated PBM responsiveness during ther-

apy, with decreased responsiveness to the mitogens and autologous plaque. This enhanced immune responsiveness may be a consequence of a developing immune response accompanying inoculation of bacterial-substances into the blood and lymph during periodontal treatment. Protective immunity could be a beneficial effect of treatment.

Tew and Miller (1981) compared the cellular response of young adults with severe periodontitis (SP) to those with a healthy periodontium (HP). They evaluated T-cell and B-cell levels, blast transformation, production of leukocyte inhibitory factor (LIF), and phagocytosis and killing by peripheral PMNs. They found that PMNs and B-cell levels were virtually identical. While blastogenesis was not statistically significantly different, SP subjects tended to respond to bacterial extracts more frequently. Responses to bacterial extracts were higher in female SP and lower in male SP patients when compared to the HP group. No differences existed in group responses to phytohemaglutinin (PHA). Thymidine uptake in unstimulated control cultures of SP subjects was significantly lower than the average background in cultures from HP subjects. Production of LIF was not different in the SP and HP groups, nor was the phagocytosis or killing of *Streptococcus sanguis* by PMNs.

O'Neill and Woodson (1982) evaluated lymphoid cells from human gingival tissues classified as normal, periodontal inflammation without pocket formation (group 1) or periodontal inflammation with pocket formation (group 2). These cells were assessed for their ability to kill gingival fibroblasts in vitro and to produce lymphotoxin without in vitro stimulation. No cytotoxic activity was exhibited by normal cells while activity increased from group 1 to group 2. The cells from the latter group were very active. Lymphotoxin production followed a similar pattern. The authors concluded that chronically inflamed gingiva exhibited a localized hyperimmune response in which gingival lymphocytes were activated, with potential tissue destruction accompanying lymphotoxin production.

Celenligil and Kansu (1990) evaluated the phenotypic properties of gingival lymphocytes in adult periodontitis using immunohistological analysis. Gingival tissue lymphocytes were identified using monoclonal and polyclonal antibodies. All specimens revealed a significant degree of CD3+ (mature) cell infiltration beneath the pocket epithelium compared to the oral epithelial side. CD4+ (T-helper) cells and CD8+ (T-suppressor) cells were evenly distributed. Numerous HLA-DR+ cells were also noted. There was a predominance of IgG-bearing plasma cells identified in the lamina propria, followed by IgA-positive cells and a few IgM-positive cells. These findings suggest that T-cell mediated regulatory mechanisms play an important role in the pathogenesis of adult periodontitis.

Using a rat model, Yamashita and Ohfuji (1991) transferred a single *Actinobacillus actinomycetemcomitans* (Aa) T-helper (Th) cell specific clone to a group of heterozygous rats (Aa+Th+). A second (Aa+Th-) and third group (Aa-Th-) received no T cells. Beginning 1 day after transfer, the first and second groups were infected orally with Aa for 5 consecutive days. A significantly higher number of lymphocytes were recovered from the gingival tissues of the Aa+Th+ group than either of the other groups. The Aa-Th- group exhibited significantly elevated serum IgG and IgM to Aa compared to the other groups. Bone loss was significantly reduced in the Aa+Th+ group compared to the Aa-Th- group and was approximately equal to the third uninfected group. This experiment supports the hypothesis that T-cell regulation can affect periodontal disease with Th cells apparently interfering with periodontal bone loss.

Okata and Ito (1987) evaluated the effect of T-cell influence on IgG synthesis in T-cell independent polyclonal B cell activation. Results supported the hypothesis that T-helper cells become activated and introduce signals to B cells. T-helper cells could not respond to antigens from *Actinomyces viscosus* or bacterial lipopolysaccharide from *E. coli* but could recognize the "self" major histocompatibility complex class II antigen expressed on the surface of B cells. These cells subsequently activated and participated in T independent B cell activation. The results suggest that T cells may regulate polyclonal B cell activation by oral bacteria in periodontal inflammation and thereby participate in the development of IgG-rich periodontal lesions.

Ito and Harada (1988) continued the investigation related to the previous study by in vitro examination of the effect of autoreactive T cells on T-independent polyclonal B cell activation (PBA) IgG synthesis in a mouse model. Th cells were activated by interaction with Ia antigens expressed on B cells. Activated T cells enhanced IgG synthesis in the PBA reactions. Ia antigen expression on B cells was increased when stimulated by polyclonal B-cell activators. The supernatant from an autoreactive T cell line also enhanced IgG synthesis in PBA. The results suggest that autoreactive T cells may play a role in the establishment of the IgG plasma cell-rich periodontal lesion.

Ranney and Zander (1970) demonstrated that hypersensitivity reactions of antibody to bacterially-produced antigens may be important in periodontal disease. Reactions ranged from inflammation upon initial challenge with antigen to an acute destructive lesion characterized by many of the features of human periodontal disease. These changes were observed after 3 months of repeated challenges.

HUMORAL IMMUNITY

Tew and Engel (1989) reviewed polyclonal B cell activation (PBA) in periodontitis. Both antigen-specific and polyclonal activation of lymphocytes may occur in periodontally diseased tissues. The B-cell life cycle consists of 4 stages: resting, activation, proliferation, and differentiation. Differentiation is influenced by certain substances or events resulting in either immunoglobulin secreting cells (plasma cells) or memory (memory B cells). Activation occurs pri-

marily through antigen interaction with cell surface immunoglobulin receptors. Other factors such as lipopolysaccharide (LPS) and pokeweed mitogen may also induce B cell activation. These PBA factors may stimulate 30% of B cells, with different factors apparently affecting selected subpopulations or clones of B cells. B-cell growth is influenced by substances which provide competence signals (e.g., interleukin-4) that enhance major histocompatibility class II molecules (HLA-DR) and prompt phase entry of resting B cells upon LPS stimulation. Progression signals such as B cell growth factor also promote DNA synthesis. Activated B cells produce effector molecules which may also play a role in the progression of periodontal disease. These effectors include immunoglobulin, interleukin 1, interleukin 2, interferon, and tumor necrosis factor. Antibodies produced by PBA factors are not highly avid or specific; however, the high numbers of clones activated make it likely that reaction with a given microbial invader may occur. Resulting antibodies may participate in blocking adhesion, thereby increasing opsonization and enhancing complement-lysis. B cells and plasma cells are the predominant inflammatory cells in the established and advanced periodontal lesions.

Studies suggest that patients with B cells which are more responsive to B cell mitogens may be most susceptible to periodontal destruction. Inherited hyper-responsiveness to B cell mitogens may explain the familial tendency observed in early-onset periodontitis. The amount of specific antibody stimulated by antigen alone or PBA factors alone is small compared with the level of specific antibody obtained by the combination of specific antigen plus non-specific activator. Human serum immunoglobulin levels are only modestly elevated in patients with periodontal disease because of the localization of the lesion and the concentration of locally-produced immunoglobulin in GCF (versus the blood vascular system). Bacterial-derived PBA factors are linked with many periodontitis-associated Gram-negative bacteria and several Gram-positive species. Bacterial components which may elicit PBA include LPS, peptidoglycan from the cell envelope, and extracts of bacterial products. Activated B cells and plasma cells may form antibodies which react with bacteria or host tissues to form immune complexes, leading to complement activation and complement mediated toxicity reactions. Antibody-dependent, cell-mediated cytotoxicity may also occur. Serum levels of autoantibody (produced by PBA factors) to type 1 collagen may be higher in periodontitis patients than normal controls. Polyclonally activated B cells also produce IL-1 which demonstrates bone-resorbing activity as well as numerous other effects on connective tissue and the immune and inflammatory systems.

Klausen and Houghen (1989) evaluated the role of T-lymphocytes and B-lymphocytes in the development of marginal periodontitis using a rat model consisting of nude (congenitally T-lymphocyte deficient), thymus-grafted nude (lymphocyte reconstituted), anti-u treated (temporarily T-lymphocyte deficient) and normal rats. A group of rats were inoculated with Aa, Pg, and a strain of oral spirochetes. Ninety-five percent (95%) of the inoculated rats had increased serum levels of IgG or IgM against one or more of the test microorganisms, with nude mice having the lowest. Inoculated rats had significantly less periodontal bone support than the controls. A temporary deficiency led to significantly less periodontal bone support than the congenital T-lymphocyte deficiency or normal rats. No difference was found between normal, congenital, or temporary deficiencies. The authors concluded that congenital T-lymphocyte deficiency did not interfere with the development of periodontal diseases in this model, whereas a temporary and moderate reduction in B-lymphocyte numbers seemed to predispose periodontal bone loss.

Ebersole and Frey (1987) investigated the relationship between local and systemic host antibody responses, colonization of subgingival plaque by periodontal disease-associated microorganisms and the progression of periodontal disease in 61 patients. They reported 54 to 78% agreement between the distribution of elevated static crevicular fluid antibody and presence of corresponding microorganisms for most periodontopathogens. Data showed that antibody was produced locally since local levels were greater than serum levels.

Turner and Dai (1989) evaluated serum and gingival tissue antibody levels to 8 oral microbial antigens in adult periodontitis and healthy patients. Using an enzyme-linked immunosorbent assay (ELISA), they found that antibody levels of diseased serum samples were significantly higher than those of healthy serum samples. Serum antibodies against Pg antigens were significantly higher than all others except Pi and *B. asaccharolyticus*, while gingival tissue antibody levels against Pg antigens were significantly higher than all other antigens. The results suggest selective, specific, and localized antibody production during or following the establishment of chronic adult periodontitis.

Using serum samples, Vincent and Falkler (1987) evaluated the effect of clinically successful periodontal therapy in LJP, rapidly progressive (RPP), and periodontally healthy subjects. They evaluated antibody levels of Pg, *B. ochraceus*, *Fusobacterium nucleatum*, and Aa using an ELISA. LJP patients showed an initial rise in antibody levels immediately following therapy and a significant decrease in antibody levels 3 to 4 years later. The RPP patients demonstrated only a significant decrease at 3 to 4 years. The antibody levels of both LJP and RPP patients remained significantly higher than healthy subjects at all time points.

Using direct immunofluorescence, histologic sections, and gingival eluates, Okada and Kida (1982) studied the cell types involved with advanced periodontitis in humans.

In lamina propria, 65% of the mononuclear cells were plasma cells that produced predominantly IgG. Cells producing IgA represented 11.2% and those producing IgM, 1.3%. In the sulcular areas, many of the Ig negative cells were T-lymphocytes, accounting for about 30% of the infiltrated cells. Only a few T cells were found in the lamina propria. Macrophages and monocytes were detected in and subjacent to the pocket epithelium. When all cells with Fc receptors were examined, 30% consisted of macrophages and monocytes. Two types of T cells with Fc receptors were delineated. One type had Fc receptors for IgG (T-gamma) and the other, Fc receptors for IgM (T-mu). When comparing these "T cell families" it was noted that the T-mu cell quantities were equivalent in peripheral blood and gingival tissues. T-gamma cells, however, were less numerous in local gingival tissues than in the peripheral blood. This may represent an imbalance in the T-gamma cells and may be part of a local immunological imbalance accounting for progression of periodontal disease.

Daly and Cripps (1983) investigated immunoglobulin production in vitro for lymphocytes recovered from gingival tissue of patients with chronic marginal gingivitis. The authors assessed IgG production over 7 days, reporting that 56% of the IgG was present by 24 hours, 80% by day 3, and 86% by day 5. IgG production by gingival lymphocytes was higher than that of optimally stimulated peripheral blood lymphocytes, while IgA levels were similar. The results indicated that lymphocytes recovered from chronically-inflamed gingival tissue secreted immunoglobulin progressively throughout a 7-day culture period. Gingival B-lymphocytes appeared to have been highly stimulated in vivo and were actively secreting immunoglobulin at the time of recovery from tissue.

Yamashita and Ohfuji (1988) evaluated the blastogenic response and immunoglobulin production (IgG, IgM) by lymphocytes (GL) obtained from the inflamed gingiva of dogs. The responses of GLs were compared to those of peripheral blood lymphocytes (PBL) and submandibular lymph node cells (SNL) following stimulation with 3 mitogens. The responses of PBLs and SNLs were substantial while GL response levels remained at the level of unstimulated lymphocytes. GLs did produce and secrete IgG and IgM, with IgG production elevated above that of PBLs and SNLs. IgM production was less than PBLs and SNLs. The local response of GLs is apparently different from the systemic response of PBLs and SNLs.

Reinhardt and McDonald (1989) investigated IgG subclasses in the gingival crevicular fluid (GCF) of periodontally active and clinically similar, but stable or healthy sites. Using an ELISA (monoclonal antibodies), IgG subclass and albumin concentrations in serum and interproximal GCF samples were quantified. Despite variability, mean IgG1 and IgG4 concentrations were higher in GCF from active periodontitis areas than from stable sites. Mean adjusted concentrations in GCF were generally greater than in serum, especially for IgG4. This increased level of IgG4 may be a useful indicator of the immunological changes which take place in active periodontitis.

Hall and Falkler (1990) evaluated the local production of immunoglobulins in diseased tissue from LJP patients. IgG was the major immunoglobulin present in the first-day tissue culture medium in 92% of the LJP tissue explant cultures. This figure decreased to 43% in day 4 supernatants. IgA was present in 15% of the cultures, with no evidence of IgM in any tissue culture specimen. This study further supports the protective or destructive involvement of local immune processes in the pathogenesis of disease.

Murray and Burstein (1989) examined the immune response to Pg in serum and GCF of patients with gingivitis, untreated adult periodontitis, and treated adult periodontitis. Using ELISA, untreated patients demonstrated a humoral immune response to Pg, producing significantly higher serum and local GCF levels of IgG than did treated patients. The ratio of GCF to serum antibody levels was not significantly different among any of the groups. The authors concluded that the GCF levels of antibody may be due to leakage of serum into the GCF rather than a site-specific response to infection.

Mackler and Waldrop (1978) investigated subclasses of IgG-bearing cells in gingival biopsies in order to further define inflammatory cell infiltrates and correlate findings with different stages of human periodontal disease. Mild gingivitis was characterized by lymphocytes which lacked surface IgG and Fc receptors suggestive of thymus dependent cells. In severe gingivitis the localized cellular infiltrate changed, with increasing numbers of IgG1 (22%) and IgG3 (17%) labeled lymphocytes, and with lower numbers of IgG4 (7%) and IgG2 (1%). Destructive periodontitis was characterized by high numbers of plasma cells (57%) distributed throughout the gingiva. The subclass distribution was IgG1 (25%), IgG4 (19%), IgG3 (18%), and IgG2 (1%). This distribution did not reflect normal serum concentrations. These findings support the concept that a shift from a T cell to a B cell dominated lesion occurs in advancing periodontal disease.

Ogawa and Tarkowski (1989) also analyzed the distribution of IgM, IgG, and IgA secreting cells isolated from gingiva at different stages of periodontal disease. The total number of plasma cells increased with the severity of disease. The majority were IgG isotypes with significant numbers of IgA+ cells also present. Few IgM+ cells were observed. Monoclonal antibodies were utilized to analyze IgG and IgA subclasses. Analysis of slight, moderate, and advanced stages of periodontal disease showed a progressive increase in spot-forming cell numbers. The major isotype was IgG followed by IgA. IgG1 was the major IgG subclass followed by IgG2. IgG3 and IgG4 subclass levels were found to be similar to each other. IgG4 levels in-

creased in more advanced disease, IgA1 predominated in moderate stages, and selective increases in IgA occurred in more advanced stages of disease. These gingival responses are similar to those found in synovia of rheumatoid arthritis subjects and in mitogen triggered spleen and peripheral blood mononuclear cells.

Hara and Maeda (1987) compared gingival tissue specimens from patients with chronic periodontitis with clinically healthy or gingivitis subjects to determine relative numbers of immunoglobulin-bearing cells. The authors reported a predominance of IgG-bearing cells, followed by IgA-bearing cells. IgM and IgE-bearing cells were present in small numbers. The latter cell types were elevated in moderately and severely infiltrated lesions relative to the total inflammatory cells present. Their findings support the concept that a hypersensitivity reaction mediated by IgE may play a role in periodontitis.

Nisengard (1977) has written an excellent review on the role of immunology in periodontal disease which discusses basic immunology, including information on immunoglobulins, complement, and hypersensitivity reactions.

Ebersole (1990) authored a comprehensive review detailing the systemic humoral immune responses in periodontal disease. Information includes: 1) general aspects of humoral immune responses to bacteria; 2) bacterial specificity of antibody responses in periodontal disease; 3) antigen specificity of antibody responses in periodontal disease; 4) longitudinal considerations in humoral immune responses in periodontitis; 5) function of humoral antibody responses in periodontal disease; 6) diagnostic potential of antibody responses in periodontal disease; and 7) future considerations of humoral responses in periodontal disease. This review is invaluable as a reference for immunology relative to periodontitis.

Lally and McArthur (1982) investigated the biosynthesis of complement components in chronically-inflamed gingiva. C3 and C5 synthesis was detected in 8 out of 10 individuals with periodontal disease, compared to none in normal controls. Results indicated that greater consumption of complement occurs in periodontal disease than previously predicted on the basis of serum studies. The local production of complement could play a role in modulating the inflammatory response in the gingiva. The macrophage is involved with extrahepatic synthesis of complement. C5 synthesis has been observed in a variety of sites but usually by monocytes. Both C3 and C5 synthesis can occur at mucosal sites as well. Complement may have a modulating effect on host defense and plaque organisms in the gingival crevice.

Anusaksathien and Dolby (1991) reviewed evidence for an autoimmune component in the host immune response of periodontal disease. They reported that the majority of studies address detection of antibodies (AB) to host components, especially collagen. ABs to DNA and aggregated IgG have also been reported, as have in vitro reports of killing of cells of the periodontium by mononuclear cells isolated from patients with periodontal disease. The presence of autoantibodies in periodontal disease may be explained by the following: 1) enhanced presentation of self antigens (Ag) through increased expression of the molecule associated with Ag presentation; 2) altered T-helper or T-suppressor cell function; 3) polyclonal activation of cells which have the ability to produce autoantibodies; 4) idiosyncrasies of the Ag-idiotype network; 5) bacterial or viral cross reactivity with self-antigen leading to the production of cross reactive ABs; and 6) genetic predisposing factors.

Autoantibodies detected in periodontal disease appear to be derived from pre-existing natural ABs and play a physiologic role in the elimination of dead cells and damaged tissue constitutents resulting from the tissue degradation associated with periodontal disease. The possibility remains that this system, established to deal with the consequences of tissue damage, may in certain circumstances become excessive and contribute to the progress of the disease.

PERIODONTAL STATUS IN IMMUNOSUPPRESSED PATIENTS

Schuller et al. (1973) investigated the severity of periodontal disease in 33 renal transplant patients receiving prednisone and azathioprine to suppress the immune responses and prevent rejection. The findings indicate that persons on immunosuppressive therapy show no correlation between age, plaque, and calculus. This implies inhibition of inflammation and/or the immune response.

Tollefsen et al. (1978) studied chronic gingival lesions in 4 categories of patients. One group of healthy subjects were kept plaque-free (CO), while in the second group (CP) moderate accumulations of plaque were permitted. The third group (UH) was comprised of patients with uremia and in hemodialysis. A fourth group (IS) had received renal allografts and were on an immunosuppressive regimen. Differential blood counts and serum immunoglobulin quantitation from the UH and the IS groups gave mean values within normal ranges. Gingival biopsies were obtained for each subject. The connective tissue inflammation (CTI) scores were compared between the groups. Despite abundant local plaque accumulations, the UH group displayed essentially the same CTI scores as plaque-free controls (CO), while the IS group showed a significantly lower CTI score than the 2 in question. The CTI scores of the CP group (controls with plaque) were significantly higher than those of the UH, IS, and CO groups.

Tollefsen et al. (1982) took gingival biopsies from 3 main categories of patients. One group (IS) consisted of 19 patients of whom 16 had received renal allografts. All were treated with immunosuppressive agents. A second group (UH) was comprised of 19 patients who suffered from chronic renal failure. Control specimens were obtained from 30 systemically healthy patients with plaque-free teeth

and healthy gingiva. Samples were also taken from 30 other systemically healthy persons with less efficient oral hygiene. All specimens were examined by light microscopy. In addition, 11 selected biopsies were processed for light microscopy. Beneath the dento-gingival epithelium, the control group with plaque had a significantly higher number of cells than the other groups. Residual cell infiltrates were always present in samples from the plaque-free healthy subjects and the uremic patients, whereas scaling and an adequate plaque control virtually eliminated inflammatory cells from the IS specimens. Lymphocytes predominated in the lesions of the UH and IS patients with clinical loss of attachment and persistent inadequate oral hygiene. The authors concluded that immunosuppression does not abolish the host reaction to dental plaque, but the inflammatory and/or immune responses are different from those in otherwise healthy subjects.

Been and Engel (1982) reported that the administration of immunosuppressive drugs significantly reduced the level of gingival inflammation in the presence of high levels of plaque.

Tollefsen and Johansen (1985) compared the periodontal condition of 33 prospective and 26 renal transplant recipients with systemically healthy patients, matched for age, teeth present, social status, and sex. Progressive uremia and immunosuppression by drug therapy resulted in less clinical gingivitis.

Novak and Polson (1989) studied the effects of levamisole on experimental periodontitis. The immunomodulating agent, levamisole hydrochloride, enhances PMN chemotaxis. Levamisole was administered by oro-gastric intubation to 4 squirrel monkeys (experimental) every 2 days for 18 days. After 2 doses of levamisole, marginal periodontitis was induced around several teeth. Similar periodontitis was induced in 4 control monkeys not receiving levamisole. All animals were killed 2 weeks after induction of periodontitis. Clinically, gingival inflammation was more pronounced in experimental animals at both 7 and 14 days after initiation of periodontitis. The enhancement of the inflammatory response by levamisole resulted in a denser band of inflammatory cells between plaque and gingival tissues, but this did not afford any additional protection against the initiation, progression, and extent of periodontal destruction.

Tolo (1991) reviewed periodontal diseases in immunocompromised patients and defined immune deficiency as either primary or secondary. Primary type deficiencies involve a total deficit of one portion of the immune system, with males affected most frequently. Affected individuals usually live for only a few years. Secondary type deficiencies represent substandard responses of the immune system to challenge. The prevalence of immune deficiency among patients with periodontal disease is unknown. Factors important to resisting infections include: circulating granulocytes above 500/mm^2, immediate granulocyte response to infection and leukocyte adhesion and locomotion. Expression of specific glycoproteins (Mac-1, LFA-1, and p150,95) stored intracellularly in secondary granules mediate adhesion and locomotion. In adhesion, Mac-1 or CR3 are the surface receptors for C3b. LFA-1 is important for adhesion, phagocytosis, and production of hydrogen peroxide. Granulocytes can move at 40 to 50 μm/hour and macrophages at 10 to 20 μm/hour. Total hereditary deficiencies of these glycoproteins lead to death by age 3. Moderate deficiencies result in gingivitis or periodontitis characterized by an absence of pus.

In LJP patients, defective neutrophil chemotaxis is present 70 to 80% of the time. Colonizing bacteria may interfere with defense mechanisms. Neutrophils and macrophages express Fc-receptors that moderate attachment to opsonins such as IgG, IgM, and C3b which stimulate the cells to phagocytize the antigen. Some organisms can produce Fc-binding proteins which interfere with complement activation.

Increased levels of autoantibody production by gingival plasma cells have been observed in patients with periodontal disease. Rheumatoid factor, another autoantibody, may also play a role in periodontal disease. The inflammatory infiltrate in the gingival sulcus may cause accumulation of lymphocytes and initiate the production of anti-IgG and anti-type I collagen antibodies by polyclonal B stimulation. In periodontal disease there is an increase in both IgG and IgA. Since monomeric IgA is present, it may block the opsonic effect of IgG in complement activation. IgG1 and IgG3 are the most effective C3 activating subclasses.

Tolo (1991) indicates that a compromised immune system may be an important factor in the progression of periodontal disease.

Dahlen et al. (1993) investigated the presence of caries and periodontal disease in 22 females and 3 males with primary hypogammaglobulinemia or IgG subclass deficiencies with or without comcomitant IgA deficiency. Only 1 patient showed more tooth loss than that found in the normal Swedish population. One patient demonstrated advanced periodontal disease. No patient exhibited more severe dental caries than that of comparable normal Swedes. Microbiological samples from periodontal pockets and saliva showed recovery of potential periodontopathic and cariogenic bacteria within normal ranges. This study could not support the notion that immunodeficient subjects exhibit an increased risk of developing periodontal disease or caries.

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Section 4. Furcation Anatomy and Furcation Invasion

DEFINITIONS

Furcation: The anatomic area of a multirooted tooth where the roots diverge.

Furcation Invasion: Pathologic resorption of bone within a furcation.

INTRODUCTION

Furcations may be divided into three parts on the basis of anatomy. 1) roof; 2) surface immediately coronal to root separation (flute); and 3) the area of root separation where the roots are separated by alveolar bone (root separation) (Grant et al., 1988) (Figure 1).

The etiology of furcation invasion has been attributed to the extension of periodontal inflammatory disease (Waerhaug, 1980), trauma from occlusion in the presence of inflammation (Glickman, 1963; Lindhe and Svanberg, 1974), pulpal disease (Bender and Seltzer, 1972), defective plaque-retentive restorations (Gilmore and Sheiham, 1971) or because of anatomic variations. Proximal furcae of maxillary molars and birooted first premolars tend to be invaded early in the progression of marginal periodontitis, with invasion of mandibular furcae occurring later due to inherent buccal and lingual positions (Schluger et al., 1990).

CLASSIFICATION

Many systems have been suggested for classifying furcation invasions. A brief review of 3 systems is presented below

Glickman (1958) divided furcation invasions into 4 grades:

Grade I: Pocket formation into the flute but intact interradicular bone;

Grade II: Loss of interradicular bone and pocket formation of varying depths into the furca but not completely through to the opposite side of the tooth;

Grade III: Through-and-through lesion;

Grade IV: Same as Grade III with gingival recession, rendering the furca clearly visible to clinical examination.

In 1975, Hamp et al. proposed 3 levels:

Degree I: Horizontal loss of periodontal tissue support < 3 mm;

Degree II: Horizontal loss of support > 3 mm but not encompassing the total width of the furcation;

Degree III: Horizontal through-and-through destruction of the periodontal tissue in the furcation.

Tarnow and Fletcher (1984) proposed the following classification based on the vertical component of bone loss in furcations:

Subclass A: 0 to 3 mm probeable depth;

Subclass B: 4 to 6 mm probeable depth;

Subclass C: > 7 mm probeable depth.

ANATOMICAL CONSIDERATIONS

Mardam-Bey et al. (1991) reviewed anatomical factors which may predispose the furcation to attachment loss. Studies included in their review and other investigations by others have identified furcation and root morphology, enamel pearls, certain enamel projections, and the existence of accessory pulp canals as factors of concern in furcation invasion:

Furcation Morphology

Bower (1979A) reported that 81% of all furcation entrance diameters measure < 1 mm, with 58% < 0.75 mm. Since commonly used curets have blade face widths ranging from 0.75 to 1.10 mm, it is unlikely that proper instrumentation of furcations can be achieved with curets alone. Similar findings were reported by Chiu et al. (1991) in maxillary and mandibular permanent first molars from Hong Kong Chinese. This study revealed 49% of furcation entrances to be < 0.75 mm in width, and the authors suggested that sharpening curets to narrow blade width or using an ultrasonic tip which has a 0.5 mm diameter at the terminal end may improve instrumentation of furcations. In a study of furcation root surface anatomy, Bower (1979B) also found that the furcal aspects of maxillary roots were concave in 94% of mesiobuccal roots, 31% of distobuccal roots, and 17% of palatal roots. Mean depths of these concavities were 0.3 mm, 0.1 mm, and 0.1 mm respectively. Mandibular molars presented concavities in 100% of the mesial roots and 99% of the distal roots, with mean depths of 0.7 mm and 0.5 mm, respectively.

Root Morphology

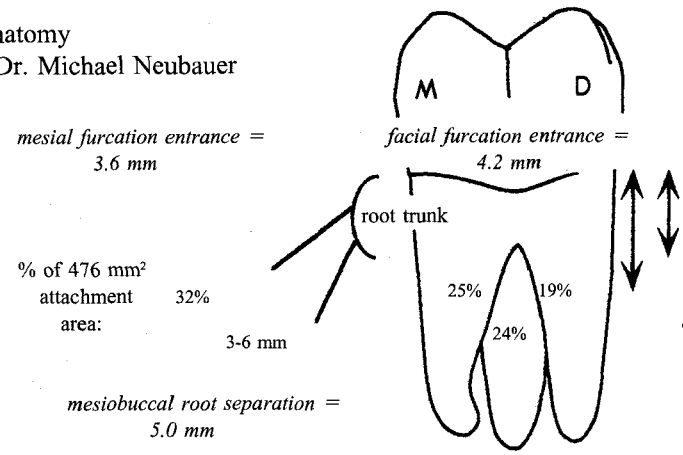
Booker and Loughlin (1985) found mesial concavities in 100% of 50 maxillary first premolars evaluated. The average CEJ to furcation distance was 7.9 mm. They reported that 100% of the two rooted maxillary first premolars examined had "developmental depressions" in the furcal aspect of the buccal root at the 9.4 mm level. Furcation entrances for maxillary molars are located 3.6 mm, 4.2 mm, and 4.8 mm apical to the CEJ on the mesial, facial and distal surfaces, respectively (Gher and Dunlap, 1985).

Gher and Vernino (1980) reported that 78% of maxillary first premolars have a developmental depression on the furcation surface of the buccal root (buccal furcation groove). The mesiobuccal root of the maxillary first molar presented a developmental depression on the distal surface, with other roots having concavities on furcal aspects. The surface area of the mesiobuccal root may be greater or equal to that of the palatal root. The distal and mesial roots of mandibular first molars had mesial and distal concavities.

Hermann et al. (1983) investigated the potential attachment area of the maxillary first molar noting that the surface area of the root trunk was significantly greater than any of the individual roots. The root trunk averaged 32% of total root surface area, the mesiobuccal 25%, the palatal 24%, and the distobuccal 19%. Horizontal attachment loss which extends to the level of the furcation involves the root trunk and results in a loss of one third of the total support of the tooth (Grant et al., 1988). Using the surface measurements reported by Dunlap and Gher (1985), the respective percentage of total root surface for mandibular first molars

Figure 1. Furcation Anatomy
Original drawings by Dr. Michael Neubauer

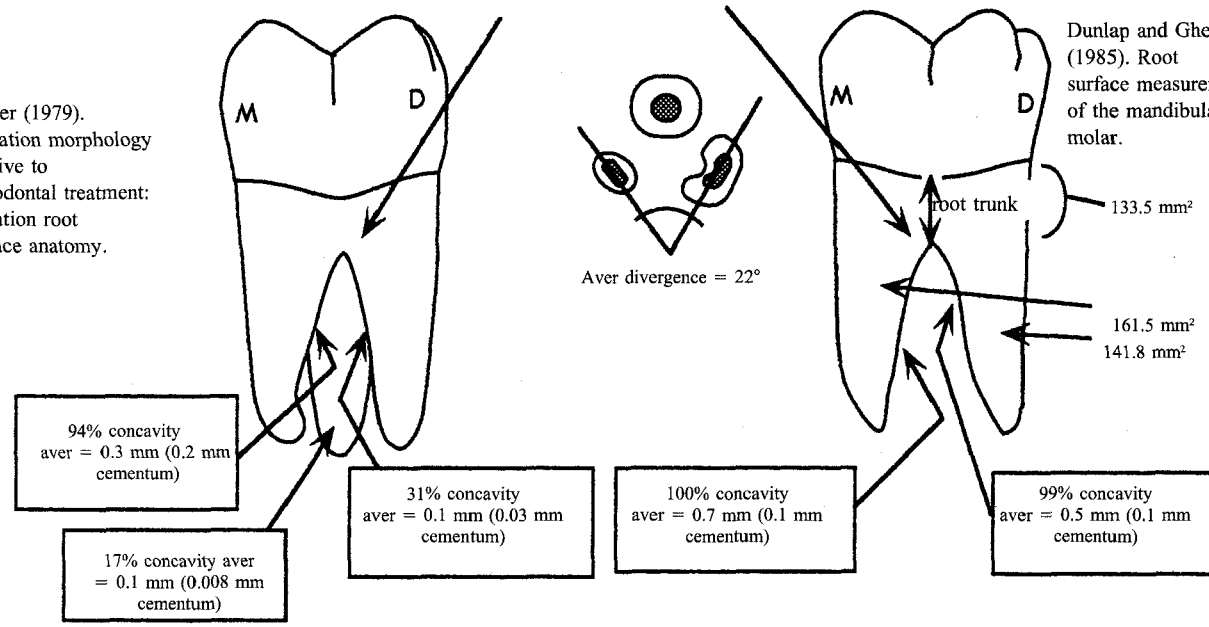
Hermann and Gher (1983). The potential attachment area of the maxillary first molar



Gher and Dunlap (1985). Linear variation of the root surface area of the maxillary first molar

Bower (1979). Furcation morphology relative to periodontal treatment—furcation entrance architecture
81% < 1.0 mm; 58% < 0.75 mm
(aver curet = 0.75–1.10 mm)

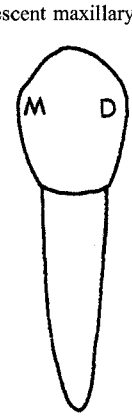
Bower (1979). Furcation morphology relative to periodontal treatment: furcation root surface anatomy.



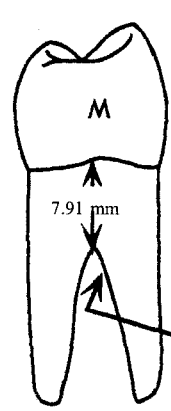
Dunlap and Gher (1985). Root surface measurements of the mandibular first molar.

Booker and Loughlin (1985). A morphologic study of the mesial root surface of the adolescent maxillary first premolar.

100% concavity
single rooted teeth: 0.35 mm deep increasing to 0.59 @ 4.7 mm
double rooted teeth:
0.44 mm deep increasing to 1.08 @ 4.7 mm



Most had concavities at or below 2.35 mm from CEJ > in furcated teeth and less deep than M



Increasing cemental thickness as proceed apically

"Buccal Furcation Groove" found at 9.4 mm level (in 100% of teeth)

37% for the mesial root; 32% for the distal root; and 31% for the root trunk.

Anderson et al. (1983) used stereophotogrammetry to confirm that the mesial root of the mandibular first molar had the greatest root surface area (average 251.9 mm^2). The distal root often appears larger radiographically and clinically.

Intermediate Bifurcation Ridges

Intermediate bifurcation ridges were first described by Everett et al. (1958) and were reported in 73% of the mandibular molars studied. These ridges were primarily cementum, originating on the mesial surface of the distal root, crossing the bifurcation and ending high on the mesial root. The type of surface in the bifurcation from which the intermediate bifurcation ridge originated was also studied. The ridge projected above a buccolingual concavity in 15% of the teeth examined, projected from a convex bifurcational surface in 39%, and in the remainder of the teeth the interradicular surface was flat. If the interradicular area was either concave or flat, it was delineated on its buccal and lingual borders by prominent line angles between the respective sides of the tooth and the bifurcational surface. These prominent borders were designated the buccal or lingual bifurcation ridges and consisted essentially of dentin formations covered with only a small amount of cementum. The intermediate bifurcation ridge was also studied by Burch and Hulen (1974) who reported an incidence of 76.8%. These studies underscore the deterrents that anatomical factors may pose during the performance of effective plaque control by the patient. These aberrations may also present complications for the therapist in root preparation during initial therapy.

Enamel Pearls and Projections

Enamel on the furcal area of the root surface may manifest as cervical enamel projections (CEPs) or enamel pearls. Connective tissue attachment is prevented by the presence of enamel, potentially predisposing the area to attachment loss.

In a review article, Moskow and Canut (1990) cited an incidence rate for enamel pearls ranging from 1.1 to 9.7% (mean 2.69%) with a predilection for maxillary third and second molars. According to Masters and Hoskins (1964), CEPs occur primarily on buccal surfaces of molars (28.6% mandibular, 17% maxillary) and may be classifed as: Grade I: distinct change in CEJ contour with enamel projecting toward the bifurcation; Grade II: CEP approaching the furcation, but not actually making contact with it; and Grade III: CEP extending into the furcation proper. Masters and Hoskins (1964) noted CEPs in $>$ 90% of isolated mandibular bifurcation involvement.

Bissada and Abdelmalek (1973) observed a 50% association between CEPs and furcation invasion. Swan and Hurt (1976) reported a statistically significant relationship between tooth surfaces with Grade II or III CEPs and furcation invasion and concluded that when sufficiently pronounced, CEPs may be an etiologic factor in tissue breakdown. However, Leib et al. (1967) found no relationship between CEPs and incidence of furcation invasion. Most authors agree that Grade I CEPs are most common and that buccal surfaces are most often affected. In decreasing order of incidence, CEPs occur in mandibular second molars, maxillary second molars, mandibular first molars, and maxillary first molars.

Accessory Pulp Canals (APCs)

Controversy exists regarding the role of pulpal disease in the etiology of furcation invasion. The prevalence of accessory canals in the furcal region have been reported by several authors. Bender and Seltzer (1972) noted APCs "in great numbers" in human, dog, and monkey teeth, concluding that the periodontal lesion can develop as a result of pulpal disease. Lowman et al. (1973) studied extracted teeth, reporting the incidence of accessory canals in the coronal and middle thirds of the root surface as 55% in maxillary molars and 63% in mandibular molars. They proposed that pulpal disease may influence the periodontium. Vertucci and Williams (1974) observed accessory canals in the furcation region in 46% of human lower first molars observed. They believed that the isolated periodontal lesion in the furcation area may be of pulpal origin. Burch and Hulen (1974) demonstrated openings in the furcation area in 76% of maxillary and mandibular molars. The authors felt that lesions within the furcation area may be associated with pulpal pathoses. Kirkham (1975) found no accessory canals in the furcation areas of 45 extracted maxillary and mandibular molars and premolars. According to Gutmann (1978), the incidence of accessory canals was 29.4% in mandibular molars and 27.4% in maxillary molars.

DIAGNOSIS

The diagnosis of furcation invasion is best determined by using a combination of radiographs, periodontal probing with a curved explorer or Nabers probe, and bone sounding (Kalkwarf and Reinhardt, 1988). Ross and Thompson (1980) evaluated 387 molars from 100 patients and reported a 90% incidence of furcation invasion in maxillary teeth and 35% incidence in mandibular teeth. Proximal surfaces of maxillary molars were twice as likely to be involved as buccal surfaces. The authors found that radiographs detected furcation invasion in 22% of maxillary and 8% of mandibular molars. Waerhaug (1980) reported greater attachment loss on furcal surfaces (62.8%) than outer surfaces (47.3%). The author suggested that attachment loss was related to the downgrowth of subgingival plaque, especially in furcations. Hardekopf et al. (1987) determined that the association of a radiographic furcation arrow with Degree II or III proximal furcation invasion was significant when compared with uninvolved furcations. The existence of a buccal furcation did not influence its appearance. While cautioning that radiographic and clinical evidence must be

correlated for proper diagnosis, the authors believe that the presence of the furcation arrow is a reliable diagnostic tool. The image at the mesial furcation was 19% for Degree 1; 44% for Degree 2; and 55% for Degree 3 furcation invasions. For the distal furcations, the "furcation arrow" incidence was 12% for Degree 1; 30% for Degree 2; and 52% for Degree 3.

Zappa et al. (1993) assessed the association between clinical depth of involved furcations and their bony defects. Six dentists evaluated furca lesions in 12 patients using the Ramfjord index and the Hamp index and their findings were compared with measurements during surgery. Findings indicated that clinical assessment overestimates the true defect depth.

THERAPY

Therapeutic options that may enhance adequate root preparation include finishing burs, modified curet tips, and ultrasonic instrumentation. Leon and Vogel (1987) reported that ultrasonic scalers were more effective than hand instruments in closed debridement of furcally invaded teeth. The prognosis of multirooted teeth with furcation invasion was once so poor that extraction was the treatment of choice. Treatment options may include: scaling and root planing; open flap debridement; gingivectomy/apically-positioned flaps; odontoplasty, ostectomy/osteoplasty-tunnel procedures; root amputation; tooth resection; and regeneration, including guided tissue regeneration.

Ross and Thompson (1978) reported that relatively conservative treatment of teeth with maxillary furcation involvement resulted in a long-term functional survival rate of 88% for a period of 5 to 24 years after treatment. Their approach to treatment involved combinations of the following procedures: scaling, curettage, comprehensive occlusal correction by coronal reshaping, periodontal surgery of soft tissue, and oral hygiene instruction. It is significant to note that no osseous surgery, root resections, hemisections, or tunneling procedures were performed.

Kalkwarf et al. (1988B) compared results following different therapies for teeth with maxillary and mandibular furcation involvement. Therapies included flap with osseous resectional surgery (FO), coronal scaling (CS), root planing (RP), and modified Widman surgery (MW). FO resulted in the most dramatic reductions in probing depth but also was responsible for a loss in clinical attachment level (CAL). All other groups showed a gain in CAL. However, FO treated teeth demonstrated a lower percentage of sites (2.6%) with significant CAL loss during 2 years of maintenance than CS (6.7%), RP (8.4%), and MW (5.9%).

Carranza and Jolkovsky (1991) noted that techniques developed in the last decade have greatly improved the diagnosis of Grade II furcation involvement. The recommended technique combines the principles of guided tissue regeneration using polytetrafluoroethylene membranes with grafting with porous hydroxyapatite or decalcified freeze-dried bone. Grade III and Grade IV furcation involvements still have a poor long-term prognosis because predictable reconstructive techniques for their treatment have not been demonstrated. When possible, a root resection approach may be advisable.

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Section 5. Additional Local and Anatomic Factors

INTRODUCTION

Numerous local anatomic factors have been allegedly associated with isolated periodontal destruction. Such factors include but are not limited to marginal ridge discrepancies, open contacts, food impaction, palato-gingival grooves, and cervical enamel projections. The rationale for implicating these factors with site-related periodontal destruction relates to plaque accumulation and an anatomic susceptibility to breakdown.

DEFINITION

Food Impaction: The forceful wedging of food into the interproximal space by chewing pressure (vertical impaction) or the forcing of food interproximally by tongue or cheek pressure (horizontal impaction).

FOOD IMPACTION—OPEN CONTACTS

Hirschfeld (1930) classified food impaction according to etiological factors as follows: Class I (occlusal wear); Class II (loss of support proximally); Class III (extrusion beyond occlusal plane); Class IV (congenital tooth abnormalities); and Class V (improper restorative design).

Food impaction may contribute to plaque-induced inflammation and root caries if oral hygiene is ineffective. Uneven marginal ridges, plunger cusps, overbite, open contacts, and defective restorations may also promote food impaction (Carranza, 1990).

Hancock et al. (1980) studied the influence of interdental contacts on periodontal status, assessing food impaction, gingival inflammation, plaque, caries, calculus, restorations, and overhangs. No significant relationship was noted between contact type and gingival index or pocket depth. Four percent (4%) of all interdental contacts exhibited food impaction and probing depths were greatest at open contacts. However, while open contacts were correlated with food impaction and food impaction was correlated with increased probing depth, there was no direct correlation between open/loose contacts and probing depth. The authors concluded that food impaction contributes to periodontal pathosis.

Koral et al. (1981) reviewed 90 patient records demonstrating radiographic evidence of open contacts on bitewing films, with no evidence of open contacts on the contralateral side. Periodontal disease severity was classified as Type I through IV based on record entries and radiographic bone loss. When compared by site, only the Type II group (incipient periodontitis) showed bone loss around the open contact site exceeding the bone loss around the control. With the possible exception of an association in incipient disease, results demonstrated that open contacts were not associated with a greater degree of bone loss than closed contacts.

Jernberg et al. (1983) compared periodontal status adjacent to unilateral open contacts and contralateral closed contacts in 104 patients. Seventy-five percent (75%) of these open contacts studied were in anterior teeth. Slight, but significantly greater, clinical attachment level (CAL) and probing depth (PD) were observed at open contact sites: 60.6% of patients had greater CAL at open contacts compared to 17.3% at closed contacts. Similarly, 49% of patients had deeper PD at open contacts compared to 22.1% at closed contacts. Mean CAL and PD were 2.80 mm and 3.04 mm for open contacts versus 2.32 mm and 2.77 mm for closed contacts, respectively. Significantly greater prevalence of food impaction and occlusal interference was found at open contacts. The significant trend toward increased PD and CAL suggests that closure of the open contact may be beneficial.

MARGINAL RIDGE RELATIONSHIPS

Kepic and O'Leary (1978) examined marginal ridge discrepancies (MRDs) in posterior teeth of 100 patients, cor-

relating PD, plaque (PLI), calculus (CI), gingival status (GI), and attachment loss (AL). Correlations between MRDs and PD, PLI, CI, GI, and AL were low. It was the authors' opinion that effective oral hygiene in the presence of gross MRDs could maintain papillary gingival health with little, if any, attachment loss. Pihlstrom et al. (1986) reported a correlation between attachment loss and uneven marginal ridges.

PALATO-GINGIVAL GROOVES

Palato-gingival grooves (PGG) are developmental anomalies of the maxillary incisor teeth which usually begin in the central fossa, cross the cingulum, and extend varying distances/directions apically. They are also termed palato-radicular, radicular-lingual, and disto-lingual grooves (Withers et al., 1981; Kogon, 1986).

Withers et al. (1981) examined 2,099 maxillary incisors in 531 patients noting the presence of PGGs and correlating them with health status of adjacent periodontal tissues. The authors reported PGGs in 8.5% of individuals examined and 2.33% of maxillary incisor teeth (4.4% in lateral incisors; 0.28% in central incisors). PGGs were associated with poorer periodontal health (GI, PDI) and greater plaque accumulation.

Kogon (1986) examined 3,168 extracted maxillary lateral and central incisors with a dissecting microscope, reporting palato-radicular grooves (PRGs) in 4.6% (5.6% in lateral incisors; 3.4% in central incisors); 54% of the PRGs terminated on the root and 58% of these extended ≥ 5 mm apical to the CEJ. Root involvement was more frequent and severe in central incisors; enamel rarely extended onto the root surface (4%).

In a similar study, Everett and Kramer (1972) examined 672 extracted lateral incisors, reporting an incidence of 1.9% PRGs. Extension to the affected root apex was observed in 0.5% of the teeth.

Hou and Tsai (1993) examined a total of 404 maxillary central and lateral incisors in 101 individuals for the presence of PRGs and correlated their presence with plaque index, gingival index, and probing depth in the area. They concluded that: 1) the proportional test showed statistical non-significance among the sexes; 2) PRGs were greatest in lateral compared to central incisors; 3) PRGs were most often located in the midpalatal part of the affected tooth as opposed to the mesial or distal area; however, more distal and mesial PRGs were associated with probing depths when compared to centrally located PRGs; and 4) a direct statistical relationship was established between the depth, location of PRGs, and the gingival and plaque indices and development of probing depths in affected teeth.

OTHER FACTORS

Tal (1984) investigated the correlations between interproximal distance and frequency of intrabony pockets (IBP). He reported a positive and statistically significant correlation between interproximal distances and the presence of IBP. The frequency of IBPs increased with increasing interdental distance and were frequently associated with interproximal distances > 2.6 mm, up to 4.6 mm. Two IBPs in the same interdental area were present only when these areas were > 3.1 mm.

Heins and Wieder (1986) investigated interproximal widths in 29 human (post mortem) specimens: 116 second premolar-first molar and first molar-second molar interproximal spaces. Inter-root distances ranged from 0.2 to 4.5 mm with the narrowest distance observed between the roots of the maxillary first and second molars. Bone did not exist between the roots of adjacent teeth when the inter-root distance was < 0.3 mm; rather, a continuous PDL space from root to root was present. Root proximity of 0.3 to 0.5 mm demonstrated cortical bone and PDL without cancellous bone. Cancellous bone was only observed between the laminae durae separating adjacent teeth when the inter-root distance was > 0.5 mm.

Kugelberg (1990) compared the periodontal status of second molars 2 and 4 years after surgical removal of impacted mandibular third molars in patients < 25 years and < 26 years of age. Two years after third molar removal, 16.7% of cases < 25 years had vertical defects > 4 mm compared to 40.7% in the > 26 year age group. At the 4-year examination, 4.2% of those < 25 years old and 44.4% of those > 26 years old had vertical defects > 4 mm. Vertical defects associated with the distal of second molars improved or were maintained in all subjects < 25 years old. Nearly 30% of the defects in individuals > 26 years old deteriorated further. The author concluded that age is an important factor in healing, and suggested that if the need for extraction can be anticipated, early removal of impacted third molars might have a beneficial effect on the periodontal health of the adjacent second molar.

Kugelberg et al. (1991) prospectively studied periodontal healing after removal of 176 mandibular third molars in patients < 20 or > 30 years of age. In the < 20 year group, initial probing depths were > 7 mm in 21.5% versus 45.8% of the > 30 year old group. At 1 year, 4.8% of the > 30 year old cases and no cases in the < 20 year old group had probing depths > 7 mm. Bone loss > 50% of the root surface was found initially in 18.3% of the < 20 year old group and 41% of the > 30 year old group. At 1 year, only 2.2% of patients < 20 years old had bone loss of > 50% compared to 37.3% of the > 30 year old patients. Intrabony defects > 4 mm were reduced from 32.3% to 14.0% in those < 20 years of age and from 59% to 47% in those > 30 years of age. Widened follicles did not appear to affect healing in the younger age group, whereas 78.3% of widened follicles in patients > 30 years old were associated with deep intrabony defects. A higher prevalence of intrabony defects was found in smokers > 30 years old. The authors concluded that periodontal healing was impaired after third molar removal in patients over 30 years old,

particularly when associated with an intrabony defect or widened follicle.

SUMMARY

All factors reviewed above should be considered as contributors or predisposing elements associated with adjacent periodontal destruction. As such, their role is absolutely secondary to the etiologic impact of bacterial plaque.

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Section 6. The Role of Occlusion in Periodontal Diseases

DEFINITIONS

Occlusal Trauma: An injury to the attachment apparatus as a result of excessive occlusal force.

Primary Occlusal Trauma: Injury resulting from excessive occlusal forces applied to a tooth or teeth with normal support.

Secondary Occlusal Trauma: Injury resulting from normal occlusal forces applied to a tooth or teeth with inadequate support.

Occlusion, Physiologic: Occlusion in harmony with the functions of the masticatory system.

Occlusal trauma as it relates to periodontal disease and therapy has been and remains a controversial issue. Research findings are based on human and various animal model systems.

HUMAN STUDIES

Glickman (1963) proposed the concept of co-destruction in an effort to clarify the role of occlusion in periodontal disease. Glickman stated that, while occlusion does not cause gingival inflammation or pocket formation, inflammation of the supporting tissues in the presence of occlusal trauma alters alignment of transseptal fibers allowing inflammation to spread into the periodontal ligament space with resultant intrabony pocket formation. Glickman defined a zone of irritation bound by the marginal gingiva and transseptal fibers (apically) and suggested a zone of co-destruction bound coronally by the transseptal and labially/lingually by alveolar crest fibers. He hypothesized that occlusal trauma does not affect the zone of irritation; however, inflammation and occlusal trauma become co-destructive in periodontitis.

In a study on human autopsy material, Glickman and Smulow (1965) corroborated the relationship between excessive occlusal forces and the pathway of gingival inflammation shown experimentally in animals. They opine that gingival inflammation and trauma from occlusion are different types of pathologic processes which participate in a single disease, periodontitis. Together they exert a combined co-destructive effect which produces angular bone defects and intrabony pockets.

Stahl (1968) studied 4 surgical human specimens and concluded that there was great variability in periodontal tissue responses to the combination of trauma from occlusion and marked gingival inflammation.

Waerhaug (1979) postulated that bacterial plaque in conjunction with variation in local anatomy was the primary cause of intrabony defect formation and not occlusal trauma. He examined 31 complete dentitions (106 interdental sites) from autopsy specimens, radiographs, occlusal analyses, and mobility assessment prior to jaw removal and preparation of specimens for histologic exam and found no evidence implicating traumatic occlusal forces as a co-factor in the formation of bony defects. In general, the shape of the interdental septum was dependent on the location of the cemento-enamel junctions of adjacent teeth. Loss of attachment was always associated with the apical growth of subgingival plaque located 0.2 to 1.8 mm (mean 0.96 mm) from areas of connective tissue lysis. The reduction in alveolar crestal height was also related to the presence of subgingival plaque, ranging from 0.5 to 2.7 mm (mean 1.63 mm) from the alveolar crest. (Note that a subsequent Waerhaug article [1979] using extracted teeth indicated that the range of bacterial plaque influence was 2.5 mm). The author indicated that angular defects resulted when subgingival plaque advanced to different levels on adjacent teeth

and circumferential defects formed when the alveolus was thicker than the range of bacterial influence.

Yuodelis and Mann (1965) reported a direct relationship between periodontal disease and molar non-working contacts in a retrospective study of charts, non-standardized radiographs and study models of 54 patients (413 molars) with periodontal disease. Fifty-three percent (53%) of molar teeth had non-working contacts and mobility. Bone loss (mean 0.4 mm) and probing depth associated with the latter teeth were significantly greater. No healthy controls were included, nor was there a clinical examination of these subjects to confirm non-standardized charted findings.

A subsequent study by Shefter and McFall (1984) reported no relationship between occlusal disharmonies (centric, balancing, or protrusive contacts) and pathoses associated with inflammatory periodontal disease in 66 patients 15 to 62 years of age (mean 30 years) with mild to moderate periodontitis. Seventy-eight percent (78%) had a deviation from centric relation (CR) to centric occlusion (CO). CR contacts occurred most commonly on first premolars. Bilateral group function was the most common excursive pattern (46%). Fifty-six percent (56%) had non-working contacts in lateral movements (33% in protrusive movements). Second molars exhibited the most non-functional contacts, followed by first molars, total of 75%.

Pihlstrom et al. (1986) examined maxillary first molars clinically and radiographically in 300 individuals 20 to 40 years of age for signs of trauma from occlusion, pattern of occlusal contracts, and severity of periodontitis; only the mesiofacial aspect was examined for probing depth and clinical attachment levels. Teeth with contacts in CR, working, non-working or protrusive positions did not exhibit any greater severity of periodontitis than teeth without these contacts. Teeth with wear facets or thickened lamina dura had less attachment loss and more bone support than teeth without these findings. Only 14 teeth demonstrated signs of traumatic occlusion (bidigital mobility, functional mobility, widened PDL space). These teeth also had greater probing depths, loss of attachment, and less bone support and higher gingival and calculus indices. Contrary to Kepic and O'Leary's (1978) findings, Pihlstrom et al. found that teeth with uneven marginal ridges had more attachment loss. Unfortunately, Pihlstrom et al. did not examine second molar teeth, the site where Shefter and McFall reported the highest prevalence of non-working contacts.

In an 8-year longitudinal study of 82 patients and 1,974 teeth, Fleszar et al. (1980) examined the relationships between tooth mobility and periodontal therapy. All patients received initial preparation, occlusal adjustment, one of three modes of surgical treatment and 3-month supportive periodontal treatment. There was a mean difference of 1.57 mm in attachment gain between Types 0 and 3 mobility for teeth with 7 to 12 mm pockets, 2 years postoperatively. Pockets of clinically mobile teeth did not respond as well to treatment as firm teeth with comparable initial disease severity; however, mobile teeth were successfully treated and maintained.

ANIMAL STUDIES

Rat Model

Stahl et al. (1957) studied the effects of vertical occlusal trauma in normal and protein-deprived rats. Trauma was induced by placing amalgam to the level of the cusps in a channel carved in first and second maxillary molars. Animals with the occlusal irritant and normal diet for 6 weeks showed changes, particularly in furcation areas, consisting of disorganization of fiber bundles, edema, and degeneration of fibers. Protein-deprived animals had similar but more severe changes.

Itoiz et al. (1963) used 3 different methods to create occlusal trauma in rats: amalgam placed in a channel carved in the occlusal surface of molars, cementation of a pinhead in the molar, and cementation of a stainless steel arch wire between the 2 upper first molars. Traumatic changes were analyzed in the opposite molars, using histologic and histometric methods. Trauma from occlusion resulted in areas of necrosis in the periodontal ligament, increase in bone resorption, and areas of cementum resorption in the furcation areas.

Glickman et al. (1966) studied in rats the effect of alloxan diabetes on the tissue response to increased occlusal forces produced by overfilling a continuous trench on the occlusal surfaces of upper right first and second molars. They concluded that alloxan diabetes aggravated and prolonged the effects of trauma from occlusion by inhibiting the reparative phase.

Dotto et al. (1967) studied the vascular changes resulting from occlusal trauma in rats. They used quantitative and histometric methods and described an increased vascularization which reached statistically significant values after 21 days of trauma and which persisted for the duration of the experiment (4 months). Blood vessels that normally occupy a position closer to the bone showed a displacement toward the cemental surface.

Primate Model

Zander and Mühlemann (1956) used 9 monkeys and placed a hollow screw-type device that applied a horizontal force on teeth. Six of the animals were subjected also to various systemic stresses. No differences were found between systemically stressed and non-stressed animals. All animals subjected to trauma showed necrosis and hyalinization of the periodontal ligament, osteoclastic activity in pressure zones, and new bone formation in tension areas.

Glickman et al. (1961) studied the effect of splinting teeth with and without occlusal interferences on the supporting structures in 5 adult monkeys. Animals were sacrificed after 10 to 132 days; the remaining animal was a control. The findings indicated that furcations were the areas most susceptible to occlusal trauma, while only slight

changes occurred in interdental areas. When an excessive force was applied to 1 tooth in a splint, the periodontal tissues of all splinted teeth suffered comparable injury.

Glickman and Smulow (1962) created excessive occlusal forces upon the periodontal tissues of 6 adult monkeys by constructing gold crowns in abnormal occlusal relationships. The animals were sacrificed after 10 to 132 days. The authors reported that excessive occlusal forces alter the pathway of gingival inflammation into the underlying periodontal tissues and affect the pattern of bone destruction. Excessive occlusal pressure was more significant than tension in determining the pathway of gingival inflammation. Injury to the periodontium induced by artificial alterations in the occlusion is reversible. Periodontal injury induced by attrition tended to persist.

Glickman and Smulow (1968) also analyzed the effect of chronic trauma in monkeys by combining a high gold crown to cause hyperocclusion with an orthodontic appliance and a spring to bring the tooth back to its original position when the teeth were apart. The experiment lasted 6 months. The authors mention that chronic trauma from occlusions occurs in 3 stages: injury, repair, and adaptive alterations.

Comar et al. (1969) placed cast gold crowns with occlusal interferences and gross marginal overhangs in 4 Rhesus monkeys, sacrificed at 5, 14, 21, and 98 days. This study failed to show a change in the pathway of inflammation under the influence of trauma from occlusion.

Kenney (1971) placed gold inlays which were "high" in centric and protrusive in upper incisors of 4 Rhesus monkeys. The animals had moderate gingivitis and were scaled 2 weeks prior to crown cementation. Histologic evidence of tramatic occlusion or orthodontic movement was seen in all animals; the inlays did not produce any change in the intensity or distribution of the inflammatory cells.

Pihlstrom and Ramfjord (1972) compared the periodontal status of non-functional teeth to functional teeth clinically, radiographically, and histologically in Rhesus monkeys. Non-functional teeth exhibited more plaque and gingival inflammation, increased loss of bony support, a narrowing of the PDL (within 3 months), and increased deposition of cementum.

The Eastman Dental Center (Polson et al., 1976A, 1976B, 1979; Polson and Zander, 1983; Polson, 1986) studies utilized squirrel monkeys to examine the role of occlusion in periodontal disease. Marginal periodontitis was initiated using silk ligatures to enhance plaque retention. Primarily horizontal, non-excessive jiggling forces were applied by placing orthodontic ligatures in alternating interproximal sites on a daily basis. The following questions were addressed in these studies: Does occlusal trauma cause periodontal disease? Does occlusal trauma influence the progression of periodontal disease? Is bone loss reversible when trauma is removed in a normal periodontium (adaptive changes) versus an inflamed reduced periodontium? Is bone loss reversible when inflammation is removed and trauma remains in an inflamed reduced periodontium? Is bone loss reversible when both inflammation and trauma are removed? Does trauma affect intrabony pockets any differently than suprabony pockets?

Polson (1974) produced a single episode of trauma subjacent to an established periodontitis. There was no difference in loss of connective tissue attachment and loss of alveolar bone between experimental and control teeth. Meitner (1975) examined the effect of jiggling trauma on marginal periodontitis. There was no difference in three of four pairs of surfaces examined, indicating that it was unlikely jiggling trauma had accelerated the loss of connective tissue attachment. Polson et al. (1976A), in a similar study of the normal periodontium, reported no loss of connective tissue attachment. There was some loss in alveolar crest height and considerable reduction in volume (40%) of interproximal bone. Subsequently, Polson et al. (1976B) showed these adaptive changes to be largely reversible when jiggling forces were withdrawn and areas allowed to heal. When jiggling trauma was removed from teeth with an inflamed but reduced periodontium, there was no decrease in tooth hypermobility and no bone regeneration, suggesting that bone regeneration may be inhibited in the presence of inflammation.

Kantor et al. (1976) removed both the jiggling forces and inflammation. No alteration in connective tissue attachment levels occurred but new bone formation did occur without an increase in alveolar bone height. When marginal inflammation is resolved where tooth mobility is due only to marginal periodontitis (no superimposed trauma), tooth mobility is significantly reduced (Polson et al., 1979). In the latter study, no coronal gain of connective tissue attachment or crestal alveolar bone level occurred, although bone density increased and PDL widths decreased.

Polson and Zander (1983) investigated the effect of trauma on surgically-created intrabony defects versus similar non-traumatized defects. Although a greater loss of bone volume occurred in the traumatized sites, no differences were observed in loss of connective tissue attachment. These findings concur with the earlier findings of Polson et al.

Dog Model

Glickman and Weiss (1955) induced trauma from occlusion in 6 dogs by means of cast onlays cemented to anterior teeth. Animals were sacrificed after 3 to 110 days. In spite of forces of sufficient severity to produce notable changes in the periodontal ligament and extensive resorption in the alveolar bone, they produced no deepening of the gingival sulcus and no change in the position of the junctional epithelium on the root. This investigation clarified a point debated at the time that was based on two papers (Box, 1935; Stones, 1938), now only of historical interest.

Goldman (1956) placed high crowns in a dog for 5 days.

After sacrifice and perfusion with india ink, he observed that forces strong enough to obliterate blood supply in the periodontal ligament did not affect gingival blood supply.

Utilizing a beagle dog model, the Gothenburg group addressed many of the same questions as the Eastman Dental Center group. Lindhe and Svanberg (1974) performed experiments in 6 beagle dogs that were fed a soft diet which facilitated dental plaque formation. During a pre-experimental period of 7 weeks, periodontitis was induced by 1) surgically creating a bony pocket and 2) adapting a copper band to the exposed root surface. Two dogs were sacrificed at the end of this period, and tissues prepared for histological examination. In the remaining 4 dogs, trauma from occlusion was produced on the mandibular left fourth premolar by the installation of a cap splint and a bar device. The contralateral premolar served as control. At the start of, and at regular intervals during an experimental period of 180 days, tooth mobility, gingival inflammation, and plaque accumulation were assessed. After sacrifice, radiographs were taken and the tissues prepared for histology. Only the test teeth showed a gradually increasing horizontal mobility, but gingival inflammation and plaque index were similar on both sides. Radiographs revealed 1) horizontal bone loss in both test and control areas and 2) angular bone destruction only in the test areas. Histological sections showed that the degree of apical proliferation of the pocket epithelium was more pronounced in test than in control regions.

In a subsequent experiment, Svanberg and Lindhe (1974) created trauma from occlusion in beagle dogs with and without previously-created experimental periodontitis. The dogs were sacrificed after 7, 14, 30, and 180 days. The findings indicated that dogs with a healthy periodontium differed in their reaction to a jiggling type of occlusal trauma when compared with dogs with an established periodontitis. Whereas the periodontal ligament in the former group had become adapted to the altered occlusion, that of the latter showed increased vascular leakage, leukocyte migration, and osteoclastic activity.

In 1976, Lindhe and Ericsson reported on experiments performed in 5 dogs fed a soft diet which allowed dental plaque accumulation. Experimental periodontal breakdown was introduced on day 0. After 180 days, experimental periodontitis was introduced in the mandibular fourth premolars. On day 280, the pockets around the fourth premolars were surgically eradicated, a notch placed at the bottom of the pocket, and trauma from occlusion removed from 1 of the 2 mandibular fourth premolars. From day 280 to 370, the teeth of the animals were brushed twice daily. The animals were then sacrificed. Results indicated that jiggling-type occlusal trauma and tooth hypermobility do not adversely affect healing following periodontal surgery.

Ericsson et al. (1977) demonstrated that it is possible to shift a supragingival plaque subgingivally by orthodontic tipping or apical movement, resulting in intrabony pocket formation.

Ericsson and Lindhe (1982) studied the effect of a prolonged period of jiggling force application on the rate of progression of ligature-induced, plaque-associated marginal periodontitis in the beagle dog. This investigation demonstrated that jiggling forces enhance the rate of periodontal destruction induced by the ligature and plaque, and, therefore, act as a co-destructive factor.

Ericsson and Lindhe (1984) showed that the degree of periodontal breakdown, initiated and maintained by ligature placement and plaque accumulation, was similar around teeth with a wide periodontal ligament space and teeth with a normal width. In other words, progression of plaque-associated lesions appeared to be unrelated to the width of the periodontal ligament space and to the degree of horizontal tooth mobility.

Lindhe and Ericsson (1982) removed jiggling forces superimposed on an experimental periodontitis and observed a reduction in tooth mobility and PDL width but no change in the periodontal lesion; i.e., no improvement in connective tissue attachment level.

Significant differences in experimental design between the Eastman and Gothenburg groups include the animal model, means of inducing periodontitis and occlusal trauma, and degree and direction of occlusal force.

Conclusions From Human and Animal Studies

1. Trauma from occlusion does not initiate gingivitis.
2. Trauma from occlusion does not initiate connective tissue attachment loss.
3. Occlusion may play a secondary role in the progression of periodontal disease.
4. Inflammation should be removed initially and potential occlusal factors subsequently reevaluated.
5. Healing following surgical treatment of periodontal disease may be more advantageous in non-mobile than in mobile teeth.
6. Tooth mobility is not necessarily synonymous with trauma from occlusion.

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Section 7. Habits (Factitial/Smoking)

DEFINITIONS

Habit: An act that has become a repeated performance, almost automatic, such as bruxism or tongue thrusting.

Factitious: Pertaining to a state or situation produced by other than natural means; self-inflicted.

FLOSSING CLEFTS

Fourteen (14) flossing clefts were observed in 10 patients ranging in age from 22 to 42 years. Diagnostic suspicions were confirmed after observing patients' flossing techniques. Of the 14 clefts, 2 were classified as acute and 12 chronic. Clefts were consistently associated with effective plaque control and probing depths ranging from 1 to 3 mm. All "injury sites" were asymptomatic with the exception of the 2 ulcerated lesions. Histologically, the depressions were lined with stratified squamous epithelium exhibiting a thin layer of parakeratin and chronic inflammatory cells dispersed throughout the underlying connective tissue. The morphology of the flossing clefts was not found to constitute an impediment to plaque control (Hallmon et al., 1986).

FACTITIAL INJURIES

Forty-nine (49) cases of self-inflicted gingival injuries have been reported in the literature. These are usually seen in children younger than 12 and more frequently involve females. Most reported injuries resulted from "scratching" or "picking" the gingiva with a fingernail. Features common to self-inflicted injuries are: 1) failure to correspond

to any known disease; 2) bizarre configuration with sharp outlines; 3) lesions within reach of patient's hands; and 4) may occur singly, but often multiple injuries may be seen (Stewart and Kernohan, 1972). Motivations reported include work avoidance, attention gathering, emotional or psychotic disorders and narcotics acquisition. A case was reported in which a 25-year-old man presented with gingival recession and mobility of the mandibular anterior teeth. After oral hygiene (OH) instruction and debridement, the condition of the mandibular incisors improved while similar lesions became evident in the maxillary premolar regions. After several appointments which included biopsy and consultations, it was ascertained that the patient was vigorously brushing and flossing for three 30-minute sessions daily. Once proper oral hygiene was applied, the lesions resolved (Pattison, 1983).

SMOKING

Arno et al. (1958) examined 1,016 individuals for gingivitis as it related to various factors including tobacco consumption. They found a significant correlation between tobacco consumption and gingivitis when hygiene and age were kept constant.

Arno et al. (1959) analyzed the relationship betwen tobacco consumption and radiographic bone loss in a group of 728 men aged 21 to 45. They reported that alveolar bone loss increased with increasing tobacco consumption.

Summers and Oberman (1968) analyzed the presence and prevalence of periodontal disease in 408 subjects 20 years of age and older and its relation to 12 pertinent social and physiological variables, including smoking. They found that periodontal disease was more severe in smokers for all age groups. The authors speculate that smoking may affect periodontal disease directly as a source of gingival irritation, and/or indirectly by affecting the gingival tissue response through vascular alterations. They also noted that smokers had poorer oral hygiene than non-smokers.

Bergström and Eliasson (1987) examined 235 subjects 21 to 60 years of age, with above average oral hygiene status and dental care habits; 72 were smokers. Alveolar bone height was significantly reduced in smokers, even after correcting for age and oral hygiene. The authors concluded that smoking is a risk factor for periodontal disease.

Sheiham (1971) studied two random samples of industrial workers in England and Northern Ireland. Examination incorporated the oral hygiene index and Russell's periodontal index. In both populations, smokers had more debris, calculus, and periodontal disease than non-smokers. Those who smoked 1 to 10 cigarettes per day had cleaner mouths and less severe disease than those who smoked more. Comparable levels of periodontal disease were observed in smokers and non-smokers with similar oral hygiene.

Ismail et al. (1983) reviewed data from the National Health and Nutrition Examination Survey (1974) to investigate the association between periodontal health and reported use of different types of tobacco products. Approximately 3,000 individuals responded to a smoking questionnaire and received a dental examination. Smokers had higher periodontal (PI), debris, calculus, and oral hygiene index scores than non-smokers. After controlling for age, OH, and other factors, the smokers had significantly higher PI scores than the non-smokers. No significant differences were found between the duration, type of tobacco, or the number of cigarettes smoked and the PI.

Baab and Oberg (1987) studied 12 periodontally healthy habitual smokers (19 to 25 years) to determine gingival and skin blood flow, heart rate, and blood pressure during active smoking. Laser Doppler fiberoptic probes were used to determine blood flow. Intraoral laser probes were placed 1 mm into the sulcus of a single molar or canine. Gingival blood flow increased, skin flow decreased, and blood pressure and heart rate increased. The study failed to confirm the findings of Clarke et al. (1981) which demonstrated decreased gingival blood flow after interarterial nicotine/epinephrine administration. It should be noted that the laser Doppler readings are sensitive to movement and may have been affected by lip/tongue movements during smoking.

Bergström and Preber (1986) induced experimental gingivitis in 20 dental students, 10 of whom were smokers. Plaque rate formation was similar in both groups, but smokers displayed a less pronounced inflammatory response. Danielsen et al. (1990) reported the same results in a similar study. These findings may indicate that smokers have a reduced capacity to mount and maintain an effective defense against the plaque challenge.

Preber and Bergström (1986) analyzed the effect of smoking on non-surgical periodontal treatment. In both smokers and in non-smokers, treatment reduced probing depth; however, the reduction was consistently greater in non-smokers.

Miller (1987) analyzed the factors associated with unsatisfactory results in cases of root coverage. The author reported a 100% correlation between failure to obtain root coverage and heavy smoking (more than 10 cigarettes/day). Light or occasional smokers (5 cigarettes/day or less) responded as favorably as non-smokers. Heavy smokers who refrained from smoking during the first 2 weeks of healing had results comparable to non-smokers.

Preber and Bergström (1990) studied the influence of cigarette smoking on the outcome of surgical therapy (Widman flap) in 54 patients with moderate to advanced periodontitis, of whom 24 were smokers. The authors found that smoking impaired the results of surgical therapy including a statistically significant difference in probing depth reduction at the 12-month follow-up.

Raulin et al. (1988) studied the in vitro effects of different concentrations of nicotine on human fibroblasts. Fibroblast attachment to glass and healthy extracted human teeth was evaluated after exposure to nicotine in concentrations of 25, 50, 100, 200, and 400 ng/ml. The lowest

concentration of nicotine (25 ng/ml) disrupted the attachment process, producing a haphazard orientation of the fibroblasts and surface characteristics of poorly-attached fibroblasts. Fibroblasts changed from well-attached cells with smooth surfaces with few microvilli and thin cytoplasmic extensions to cells with rough surfaces containing many blebs, microvilli, and broad cytoplasmic extensions that did not appear well-attached. Plasma levels of nicotine in tobacco users varied from 22 to 73 ng/ml.

Kraal and Kenney (1979) compared the ability of polymorphonuclear leukocytes (PMNs) from smokers and non-smokers to respond to chemoattractants. Twenty (20) healthy male subjects (10 smokers and 10 non-smokers) with no periodontitis were selected. Blood and saliva samples were collected at baseline and again 1 to 10 days later. The second sampling took place after both groups smoked one cigarette. PMNs and sera were isolated from blood samples of each subject. PMNs from each subject were tested for chemotactic activity against autologous untreated serum, treated serum and saliva in Boyden chambers. No difference was demonstrated in the ability of PMNs from smokers and non-smokers to react to the chemo-attractants and no difference was found between the ability of chemotactic agents from smokers and non-smokers to attract PMNs.

Goultschin et al. (1990) analyzed periodontal needs and the smoking habits of 344 hospital personnel. They reported that smoking and the number of cigarettes smoked had a clearly deleterious effect on the periodontal status and that younger women were more susceptible to this effect.

Haber et al. (1993) analyzed the role of smoking as a risk for periodontitis in diabetic and non-diabetic patients. Among non-diabetics, the prevalence of periodontitis was markedly higher in current smokers as compared to never smokers. The effect of smoking among IDDM subjects was similar to that observed in the non-diabetic group.

Stoltenberg et al. (1993) studied a group of 615 adults and concluded: 1) after matching for age, sex, plaque, and calculus, the odds of having a mean posterior proximal probing depth equal to or greater than 3.5 mm were 5.3 times greater for smokers than for non-smokers; 2) the prevalence of *P. gingivalis*, *A. actinomycetemcomitans*, *P. intermedia*, *E. corrodens*, and *F. nucleatum* does not differ between smokers and non-smokers; and 3) *A. actinomycetemcomitans*, *P. intermedia*, *E. corrodens*, and smoking were each associated with increased mean posterior proximal probing depth. However, cigarette smoking was a stronger risk indicator for the presence of a mean probing depth equal to or greater than 3.5 mm than any of the 5 bacteria commonly associated with periodontal disease.

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Section 8. Systemic Factors

DIABETES MELLITUS

Gingivitis

Gusberti et al. (1983) studied 77 insulin-dependent diabetes mellitus (IDDM) children, aged 6 to 15, and measured blood glucose levels (via glycosylated hemoglobin and fasting blood sugar) and the incidence of gingivitis. Prior to puberty, poorly-controlled diabetic patients with increased blood glucose had a higher incidence and severity of gingivitis than controlled diabetics. During puberty, there was a general increase in gingivitis independent of the blood

glucose levels. This suggested that before puberty, altered glucose metabolism can enhance the severity of gingivitis.

Cianciola et al. (1982) studied the prevalence of periodontal disease in 263 IDDM patients who were compared to 108 age-matched controls. The population ranged in age from 4 to 33 with most of the patients aged 4 to 18. These authors found that there was a significant increase in gingivitis after age 11 in IDDM patients which was greater than the non-diabetic controls. They also noted that granulation tissue may exude from the gingival crevice in IDDM patients with severe periodontitis.

Ervasti et al. (1985) examined 50 IDDM adult patients who were matched by age, sex, and social class with a control group. They reported no significant difference between the diabetic group as a whole and the control group. However, when diabetic patients were grouped into well-controlled, moderately well-controlled, and poorly-controlled patients, the authors observed several trends. Well-controlled diabetics had significantly less gingival bleeding than the control population while poorly-controlled diabetics had significantly more gingival bleeding than well- or moderately-controlled diabetics or the control population. In general, the number of non-bleeding surfaces diminished as the control worsened, with control of diabetes one of the most prognostic independent variables. These studies indicate that the level of diabetic control is the important factor in the level of gingivitis, with well-controlled diabetics apparently responding in a manner similar to the normal population.

Periodontitis

Glavind et al. (1968) studied controlled diabetics, aged 20 to 40, and compared them to a normal population. The investigators found no difference in the populations up to age 30; however, patients older than 30 or patients who had been diagnosed with diabetes longer than 10 years had significantly more periodontal attachment loss. Patients with vascular changes in the retina also had more attachment loss.

Cohen et al. (1970) compared diabetic and non-diabetic patients over a 2-year period and consistently observed more gingival inflammation and attachment loss in the diabetic patients at each examination. Although both groups had soft deposits on the teeth, the amount present in the diabetic group was less.

Sznajder et al. (1978) examined 83 diabetics and 65 non-diabetics 9 to 50 years of age, and reported increased attachment loss in diabetics over 30 years old, with no differences in plaque and calculus between diabetics and non-diabetics.

Cianciola et al. (1982) demonstrated increased bone and attachment loss (periodontitis) in IDDM patients, compared to controls (siblings of the diabetics and non-related, non-diabetic patients), despite comparable plaque indices. In the IDDM patients, there was a sharp increase in periodontitis observed at age 13. From age 4 to 12, no periodontitis occurred in the IDDM patients. From age 13 to 18, 11.3 to 16% of the IDDM patients demonstrated periodontitis. This incidence rose to 39% for patients > 19. Overall, among subjects between 11 to 18 years old, periodontitis was found in 9.8% of the IDDM patients compared to 1.7% of the control patients. The authors found that the pattern of bone loss was initially similar to that seen in LJP and was related to the chronological age of the patient rather than the duration of the diabetes.

Tervonen and Knuutila (1986) reported no difference in the level of periodontitis when comparing well-controlled diabetics to non-diabetic controls. However, poorly-controlled diabetics demonstrated increased loss of attachment and alveolar bone.

Novaes et al. (1991) compared the periodontal status of 30 Brazilian IDDM patients ages 5 to 18 with non-diabetic controls. They concluded that: 1) a statistically higher accumulation of plaque occurs among the diabetic patients (1.23 versus 0.81), among female diabetics (1.34 versus 1.10), and among older patients (difference significant at the 5% level); 2) the gingival index was higher among diabetics than controls (0.52 versus 0.15), with no significant difference with respect to age and sex; 3) probing depth did not differ significantly between diabetics and controls in relation to increasing age, but in relation to sex, diabetic females showed deeper pockets in the palatal region; and 4) alveolar bone loss was significantly greater in diabetics than in non-diabetics in the upper and lower anterior region.

Emrich et al. (1991) studied the relationship between diabetes mellitus and oral health in 1,342 Pima Indians from the Gila River Indian Community in Arizona, which has the world's highest reported incidence and prevalence of NIDDM (Type 2) diabetes mellitus. The authors found that diabetes increases the risk of developing destructive periodontal disease about threefold. This increased risk cannot be explained by age, sex, hygiene, or other dental measures.

Seppälä et al. (1993) evaluated the progression of periodontal disease in subjects aged 35 to 55 years with long-standing, insulin-dependent diabetes mellitus. Regarding age, sex, type, and duration of diabetes, environment, and nutrition, the participants of this study constituted a homogenous group. They report that under similar plaque conditions, poorly-controlled diabetics have more gingivitis, more bleeding on probing, greater loss of attachment, and more bone loss than well-controlled subjects.

In contrast to the above studies, Barnett et al. (1984) examined forty-five 10- to-18-year-old diabetic patients and found no correlation between the degree of diabetic control or the duration of diabetes compared to either the gingival index or the periodontal index. While this study conflicted with previous studies, it should be pointed out that none of the patients in this study exhibited any loss of interproximal bone, thus making comparison with previous studies difficult. In addition, these subjects were a rather homogeneous

group from a private endocrinology practice and were probably very compliant.

Possible Etiologic Factors

Vascular changes. Degenerative vascular changes seen in other tissues are also seen in the gingiva; i.e., increased thickness of the basement membrane and vessel walls. It is postulated, though not proven, that these changes interfere with the delivery of nutrients to the tissues with the resulting decreased oxygen diffusion and decreased elimination of metabolic wastes contributing to an increase in the severity of periodontitis and a decrease in wound healing (Frantzis et al., 1971).

Collagen breakdown. Increased collagen breakdown (through the stimulation of collagenase activity) and altered collagen metabolism (decreased collagen synthesis; altered collagen maturation) are felt to be present in diabetic patients. These defects may be endogenous since diabetics have been found to produce an increase in gingival collagenase activity under germ-free conditions. The above defects may contribute to impaired wound healing and an increased severity of periodontitis in the diabetic patient (Golub et al., 1983; Ramamurthy and Golub, 1983). Golub et al. (1983) found that the administration of minocycline reduced collagenolytic activity 62% in a conventional rat population and by 70% in a germ-free diabetic rat population. In humans, minocycline caused significant reductions in the gingival index, gingival crevicular fluid, active and total collagenase activity, and Gram-negative organisms. It was felt that the minocycline reduced the breakdown of intact collagen and inhibited the production of collagen digestion fragments.

Altered oral microbial flora. Studies have shown that the microbial flora is different in the diabetic. In IDDM patients with periodontal disease, *Capnocytophaga* sp. is thought to be the predominant organism (Mashimo et al., 1983). This alteration in the microbial flora may lead to the increase in periodontal disease.

Altered defense mechanism. Polymorphonuclear leukocytes (PMNs) functions, such as chemotaxis and phagocytosis, have been shown to be decreased in diabetic patients with periodontal disease (Manouchehr-Pour et al., 1981; Manouchehr-Pour and Bissada, 1983; Leeper et al., 1985). These defects may, in fact, be genetic. Leeper et al. (1985) demonstrated that normal siblings of diabetic patients demonstrate decreased PMN chemotaxis. In addition, these authors noted that decreased PMN chemotaxis was more pronounced in poorly-controlled diabetics. This defect in the body's immune system may predispose the diabetic to periodontal disease.

Increased glucose has been found in the gingival crevicular fluid (GCF). This alters the environment and may allow the growth of different subgingival bacteria and/or alter PMN function (Kjellman et al., 1970).

Effects of Periodontitis on Diabetes

It is known that the presence of acute infection makes diabetic control more difficult. Similarly, it is postulated that the presence of periodontal disease may exacerbate the clinical symptoms of diabetes and make diabetic control more difficult.

Williams and Mahan (1960) reported a significant reduction in insulin requirements in 7 of 9 patients with diabetes and periodontal disease who underwent periodontal therapy. As such, diabetes may be adversely influenced by periodontal disease and conversely, periodontal disease may be more severe in the diabetic patient. This is important in that periodontal therapy may alter the patient's insulin requirement, thus requiring an adjustment in the insulin dosage. Therefore, it is important to inform the patient's physician prior to initiating periodontal therapy.

In contrast, Parrish (1985) found that treatment of periodontal disease did not alter the patient's insulin requirements. It is possible that during periodontal therapy, the poorly or minimally-compliant diabetic patients may take a greater interest in their overall health and become more compliant with their diabetic treatment.

LEUKEMIA

DEFINITION

Leukemias: Malignant neoplasms of the hematopoietic stem cells, characterized by diffuse displacement of the bone marrow by neoplastic cells. In most cases, the leukemic cells spill over into the blood, where they may be seen in large numbers. These cells may also infiltrate the liver, spleen, lymph nodes, and other tissues throughout the body (Robbins and Kumor, 1987).

Classifications

Leukemias are classified as acute or chronic and according to the cell type involved.

Acute Leukemias: Immature cells, with a rapidly fatal course.

Chronic Leukemias: Relatively well-differentiated leukocytes and prolonged course.

Lymphocytic and Myelocytic Leukemias: These refer to the cell types involved and can be acute or chronic.

Monocytic Leukemia: This is an extremely rare form of the disease.

There are 8 to 10 new cases of all leukemias per 100,000 population each year, divided as follows: acute mylogenous leukemia (AML), 46%; chronic lymphocytic leukemia (CLL), 29%; chronic myelocytic leukemia (CML), 14%; and acute lymphocytic leukemia (ALL), 11%. Leukemias represent 3% of all cancers in the United States.

Oral Manifestations: Oral manifestations are very rare in chronic leukemia, and the following descriptions refer almost exclusively to acute leukemia.

Barrett (1984) classified the gingival lesions in acute leukemia as follows:

1. Direct infiltration
2. Direct drug toxicity
   A. Erosion/ulceration
   B. Epithelial retention
   C. Connective tissue hyperplasia
3. Graft versus host disease
4. Secondary to marrow/lymphoid tissue depression
   A. Hemorrhage
   B. Neutropenic ulceration
   C. Infections
      a. Viral
      b. Fungal
      c. Bacterial

Leukemic Infiltration of the Periodontium: Dreizen et al. (1983) studied 1,076 leukemic patients and found that 66 (6.1%) had leukemic infiltrates in the skin and/or gingiva. In 33 of these 66 patients (50%), lesions were confined to the gingiva, 28 (42.4%) had only skin lesions, and 5 (7.6%) had both. Gingival infiltrates were found in 38 (3.6%) of the 1,049 dentulous patients and in none of the 27 edentulous patients. Patients with acute monocytic leukemia (AMoL) had the highest incidence of gingival infiltrate (66.7%), followed by those with acute myelomonocytic leukemia (AMML) (18.5%), and those with acute myelocytic leukemia (AML) (3.7%).

Microscopically, the gingiva exhibits a dense, diffuse infiltration of predominantly immature leukocytes in the attached and marginal gingiva. The periodontal ligament may also be infiltrated with mature and immature leukocytes (Carranza, 1990).

Carranza et al. (1965) and Brown et al. (1969) investigated the periodontal changes in AKR mice, which develop leukemia spontaneously. They reported the presence of infiltrate in marrow spaces and in the periodontal ligament, resulting in osteoporosis of the alveolar bone with destruction of the supporting bone, disappearance of the periodontal fibers, and tooth exfoliation.

Bleeding. Gingival bleeding is a common finding in leukemic patients. Bleeding occurs secondary to thrombocytopenia as a result of the replacement of the bone marrow by leukemic cells. Lynch and Ship (1967) reported oral bleeding aas a presenting sign in 17.7% of patients with acute leukemia and in 4.4% of patients with chronic leukemia.

Oral ulcerations and infections. Viral, fungal, and bacterial infections can occur in the oral mucosa owing to the lowered tissue resistance caused by the granulocytopenia that results from the leukemic replacement of bone marrow cells. These can include exacerbation of existing gingivitis or periodontitis as well as acute necrotizing ulcerative gingivitis.

Periodontal management of leukemic patients. Periodontal treatment in leukemic patients should be modified because of the enhanced susceptibility to infection, increased bleeding tendency, and effects of drugs that the patient may be receiving.

Consultation with the hematologist is needed in order to determine the treatment plan. Acute leukemia patients should receive only emergency treatment, while attempting to avoid tissue injury. Antibiotics; other microbials, such as chlorhexidine rinses; and antifungal agents should be used if needed. Patients with chronic leukemia and those in remission can receive scaling and root planing but periodontal surgery should be avoided. If treatment is absolutely necessary, bleeding time should be taken on the day of the intervention and the procedure postponed if results are low (Otomo-Corgel, 1990).

PREGNANCY/ORAL CONTRACEPTIVES

Management of the Pregnant Patient

While pregnancy is not a disease state, special considerations in the dental management of these patients are required. Physiologic changes include increases in heart rate, cardiac output, red cell mass, respiratory vital capacity, oxygen consumption and respiratory rate. Increased energy demands by the fetus and increased snacking may elevate the mother's insulin requirements, unmasking a prediabetic state. The safety of the developing baby is also of concern and treatment should be planned for times when the fetus is least affected. Because organogenesis occurs mainly in the first trimester, most developmental defects take place during this time. Most medications appear to cross the placental barrier and ingestion of materials (drugs) by the mother is the second most common cause of teratogenesis (Gier and Janes, 1983). CNS depression with narcotic use and spontaneous abortions following nitrous oxide administration have been reported. Non-steroidal anti-inflammatory drugs may interfere with closure of the ductus arteriosus if taken during the third trimester.

Additionally, tetracycline, vancomycin, and streptomycin should be avoided because of staining of teeth (fourth to ninth month), and ototoxic/nephrotoxic effects. Erythromycin, penicillin, and cephalosporins are considered safe, but consultation with the patient's obstetrician is recommended before prescribing any drug. As the fetus continues to grow, the mother's bladder and abdominal vessels are impinged upon and the diaphragm displaced upward causing decreased respiratory volume. While emergency treatment can be accomplished any time during the pregnancy, the second trimester is considered the best time to render treatment since organogenesis is complete and the mother is not as uncomfortable as during the first and third trimesters (Chiodo and Rosenstein, 1985). Radiographic exposure to the fetus is zero if proper technique and equipment is used (Alcox, 1978).

Effect of Pregnancy on the Periodontium

Estrogens, progestins, and gonadotropins interrelate to maintain the menstrual cycle. The main function of estro-

gens during the reproductive cycle is to faciliate cellular proliferation of the stromal cells, glands, and blood vessels of the endometrium (Zachariasen, 1989).

Progesterone has the opposite effect, increasing vascular permeability, PMNs in the gingival sulcus, and prostaglandin E-2 (Kalkwarf, 1978). The pattern of pregnancy gingivitis seems to follow the hormonal cycle. It initially increases with rising gonadotropin levels, is maintained from the fourth to eighth month (with rising estrogen and progesterone levels) and falls off in the last month with the abrupt decrease in hormone secretion (Löe and Silness, 1963). O'Neal (1979) compared gingival and plaque index scores to plasma levels of estradiol and progesterone for 26 subjects at weeks 14 and 30 of gestation. He reported that plaque scores decreased, gingivitis scores increased, and that other hormone levels rose. However, a direct association between the hormone levels and gingival changes could not be demonstrated.

Kornman and Loesche (1980) also studied the effect of pregnancy using 20 subjects and 11 controls. Monthly examinations were performed to assess the plaque index, gingival index, and bleeding score. Subgingival plaque samples were taken with a curet and sonicated prior to culturing. They found that during the second trimester there was an increase in gingivitis and gingival bleeding without an increase in plaque levels. The ratio of bacterial anaerobes to aerobes and the proportions of *B. melaninogenicus, P. intermedia* (2.2% to 10.1%), and *Porphyromonas gingivalis* (Pg) increased. Plaque uptake of steroids and *B. melaninogenicus* increased during the third trimester. The authors suggest that estradiol or progesterone can substitute for menadione (vitamin K) as an essential growth factor for *P. intermedia*, but not *P. gingivalis* or *B. coherences.*

In 1981, Jensen et al. studied the effect of hormone levels on the gingival status of a larger group of females. Participants included 54 pregnant, 23 non-pregnant on oral contraceptives, and 27 non-pregnant subjects. Results revealed that the pregnant group had a 2 to 3 times higher mean gingival crevicular fluid flow than the non-pregnant groups. No difference was observed between the two non-pregnant groups. The pregnant group also had higher GI scores than either non-pregnant group. The pregnant group had a 55 times greater recovery rate for *Bacteroides* species compared to the non-pregnant group. The non-pregnant group on oral contraceptives had a 16 times greater increase compared to the non-pregnant group.

Oral Contraceptive Therapy

Kalkwarf (1978) conducted a cross-sectional study of 168 females on various birth control pill (BCP) formulations. He observed that those taking oral contraceptives had significantly higher gingival inflammation levels and significantly less oral debris. Responses varied among different brands, with some producing more exaggerated effects. No correlation was noted between gingival inflammation, debris levels, and duration of time that the subject had been taking BCPs. He suggested that the periodontal effects might have been due to 1) alteration of the microvasculature; 2) gingival permeability; or 3) increasing synthesis of prostaglandins.

Some medications can interfere with the desired effect of BCPs and allow pregnancy. Rifampin induces hepatic enzymes responsible for the metabolism of steroid contraceptives and also causes an increase in plasma sex-hormone binding-globulin capacity, making less free steroid available. Ampicillin, other penicillins, and tetracycline interfere with BCPs via a different mechanism. Steroid contraceptives are conjugated in the liver and excreted back into the intestines in bile. Bacterial enzymes hydrolyze the conjugates and free the steroids allowing reabsorption. The newer lower level estrogen and progesterone pills rely on this reabsorption of the respective steroids from the intestinal tract to maintain adequate blood levels. The antibiotics listed above suppress the intestinal flora that produce the hydrolytic enzymes. This interferes with reabsorption resulting in lower inadequate blood levels of steroids. It is imperative that the patient be advised to use alternative means of birth control during periods of therapeutic or prophylactic exposure to the noted antibiotics (Barnett, 1985).

DIET AND NUTRITION

DEFINITION

Malnutrition: Any disorder of nutrition; it may be due to unbalanced or insufficient diet or to defective assimilation or utilization of foods (Dorland's, 1988).

The Recommended Dietary Allowance (RDA) is determined by the Food and Nutrition Board of the National Academy of Sciences (National Research Council) and is designed for the maintenance of good nutrition of practically all healthy people in the United States. The RDA exceeds the minimum daily requirement.

EFFECT OF NUTRITION ON THE PERIODONTIUM

Vogel et al. (1984) described 4 ways that the pathogenesis of periodontal disease could be influenced through nutrition:

Immune and inflammatory process. Subclinical vitamin C or iron deficiencies can cause defects in PMN function. Iron deficiencies can also cause macrophage dysfunction. Zinc regulates the inflammatory process by stabilizing membranes and decreasing lysosomal and histamine release.

Bone metabolism. The $Ca:PO_4$ ratio is 1:2.8 in a large segment of the population (ideal 1:1). The association between a decreased $Ca:PO_4$ ratio and increased alveolar bone loss in the presence of inflammation is contradictory.

Collagen metabolism. Vitamin C, iron, and zinc play a role in collagen metabolism. Deficiencies can result in decreased resistance of gingival tissue to plaque.

Epithelial barrier function. Subclinical deficiencies of

protein, zinc, folic acid, vitamin C, or iron may cause a reversible increase in permeability.

DePaola (1984) noted that end-organ deficiencies could impair the repair process. However, supplementation with vitamin C or folic acid did not prevent or arrest periodontal disease.

Fermentable carbohydrates do not appear to play a significant role in periodontal disease; however, they should be of concern to the periodontist, due to their role in root caries (Robinson, 1984).

Vogel and Wechsler (1979) compared 4-day nutrition surveys of 35 periodontitis patients and 1,222 general population subjects. They found that the means for both groups were above the recommended daily allowances (RDA). The calcium-phosphate ratio for the periodontal group was 0.62 (ideal = 1) and 13 of the 35 had deficient calcium intake. The daily dietary intake of periodontitis patients was not significantly different from the general population.

VITAMIN C

Cotran et al. (1989) indicated that most mammals and some amphibians and reptiles can synthesize ascorbic acid from glucose via glucuronic acid since they possess gluconolactone oxidase. Humans, as well as other primates, lack this oxidase and cannot synthesize ascorbic acid. Ascorbic acid is present in milk, some animal products (e.g., liver and fish), and is abundant in many fruits and vegetables.

A deficiency in vitamin C produces scurvy. With the abundance of ascorbic acid in so many foods, scurvy is not a world problem. However, it may be found in affluent populations as a conditioned deficiency, particularly among the elderly, those who live alone, alcoholics, and others who have erratic and irregular eating patterns. It may appear in infants maintained on formulas of processed milk without adequate supplementation.

Scurvy results in the following symptoms, which are more marked in children than in adults: purpura and ecchymosis of skin, most prominently along the back of lower legs, and in the gingival mucosa. Loose attachment of the periosteum and the hemorrhagic diathesis leads to extensive subperiosteal hematomas and bleeding into the joint space. Skeletal changes occur mainly in children and consist of a primary disturbance in the formation of the osteoid matrix (not mineralization, as in rickets).

Gingival swelling, hemorrhages, and secondary bacterial infection are commonly seen in advanced scurvy, but the deficiency only predisposes to the bacterial infection. Wound healing and localization of focal infections are both impaired in scurvy. Anemia is also a common finding.

Glickman (1948A) placed 16 guinea pigs on a vitamin C-free diet; 9 were used as controls. Animals were sacrificed after 35 days. Histological findings showed that gingival inflammation was not a prominent finding and was not increased in the controls or experimentals. Pockets, when present, were deeper in experimentals. Edema, hemorrhage, and collagen were seen in the periodontal ligaments of vitamin C-deficient animals.

In a subsequent paper, Glickman (1948B) induced gingival inflammation in vitamin C-deficient and control animals and reported an exaggerated periodontal destruction in the deficient animals, due to inability to form a peripheral limiting connective tissue barrier, reduction in inflammatory cells, diminished vascular response, and inhibition of fibroblast formation and differentiation to form osteoblasts.

Waerhaug (1958) placed 4 monkeys on a vitamin C-deficient diet for 42 to 257 days. Clinical signs of scurvy appeared after 90 days. Histologically, after 257 days, the monkeys had nearly complete destruction of the fibers of the periodontal ligament, particularly those inserted into the bone, but not as much as those inserted into cementum, increased osteoclastic resorption, and hemorrhages. Fibers located above the alveolar crest and below the epithelial attachment were the least affected. Tooth loss occurred only at late stages.

Woolfe et al. (1980) reviewed the relationship between ascorbic acid and periodontal disease. The following possible etiological relationships were noted:

1. The periodontium contains a significant amount of collagen, which is constantly being broken down and resynthesized. Insufficient levels of ascorbic acid influence collagen metabolism and the ability of the tissue to withstand insult and repair itself. However, no experimental evidence to support this concept has been reported.

2. Bone changes in ascorbic acid deficiency occur very late in the deficiency state. Furthermore, osteoporosis in the scorbutic monkey is not found in association with periodontal pockets.

3. Ascorbic acid deficiency increases the permability of the oral mucosa.

4. Ascorbic acid in vitro enhances PMN chemotaxis but does not influence its phagocytic activity. The importance of this is not clear.

5. Ascorbic acid is necessary to maintain the integrity of the intercellular cement substance of capillary walls.

6. Vitamin C deficiency may alter the ecologic equilibrium of plaque bacteria, although this has not been proven.

7. Human studies have not shown a correlation of vitamin C levels and disease incidence or severity.

A subsequent study by Woolfe et al. (1984) analyzed the effect of megadoses (1 gm) of ascorbic acid daily on gingival clinical parameters and the vitamin content of blood and gingival tissues. Ten non-deficient individuals, carefully matched according to age, periodontal status, and oral hygiene level, received either the vitamin or a placebo. After 1 week, all patients were scaled and root planed and given oral hygiene instructions. After 2, 6, and 7 weeks, blood samples and clinical parameters were obtained. A gingival biopsy was taken at week 6.

Correlations between the clinical parameters and ascor-

bic acid levels at the different time periods revealed no significant differences between the vitamin and placebo groups. This suggested that the use of megadoses of vitamin C in normal human subjects does not have a predictable or strong effect on the gingival response to periodontal therapy.

AGING FACTORS INFLUENCING THERAPY

The treatment decision relative to the patient's periodontal needs should not be based on age alone. The relative state of health is more important than the chronological age. Unless there is a contraindication, the health care provider is obligated to provide the elderly patient with the same state of the art treatment offered to younger patients. Only the patient has the right to make treatment decisions based on their longevity (Greenwell and Bissada, 1989).

EFFECT OF AGE ON THE PERIODONTIUM

Using 4 cadaver jaws of increasing age, Grant and Bernick (1972) studied the effect of age upon the periodontium. They found that cellularity decreased and collagen fiber coarseness increased. Tensile strength increased while thermal contraction, the ratio between ground substance and collagen, collagen turnover, and water content all decreased.

Van der Velden (1984) reviewed the literature and reported the following changes in the periodontium may accompany aging: There is a gradual breakdown of the periodontium with age which may relate to either age or the cumulative effect of longer exposure to periodontitis. The epithelium becomes thinner, less keratinized, and shows increased cell density. The connective tissue becomes denser, coarsely textured, and exhibits fewer cellular elements. The PDL shows less fiber and cellular content and becomes irregular. With age, there is an increase in the width of the cementum, with cementum formation being essentially cellular. The periodontal surface of the bone becomes more jagged, collagen fibers insert less regularly, there are more interstitial lamella and fewer cells in the osteogenic layer. The width of the PDL appears to decrease with age and unchanged function.

Van der Velden et al. (1985) investigated the rate of development of experimentally induced gingival inflammation in relation to the susceptibility to periodontal disease. By selection according to age, a younger (25 to 39 years) and an older (45 to 54 years) age group, with a comparable reduced but healthy periodontium was studied. This equal amount of periodontal breakdown may suggest that the younger age group represented individuals with a relatively higher degree of susceptibility to periodontal disease. At the start of the experiment, each patient was instructed to abstain from oral hygiene procedures in one quadrant of the mouth for a period of 18 days. Results showed that all subjects developed signs of gingival inflammation. Regarding the development of redness and swelling, no differences could be assessed between the two age groups. However, analysis of the bleeding scores revealed that bleeding on probing developed more rapidly in the younger age group. It was concluded that those patients who have suffered from a more rapid form of periodontal disease also develop inflammation (bleeding on probing) more rapidly.

TREATMENT RESPONSE

Lindhe et al. (1985) studied the effect of age on healing following periodontal surgery and found no significant difference between 3 age groups (< 40, 40 to 49, > 49) regarding dimensional alteration of the dentogingival tissues at buccal or interproximal sites. Similar changes in attachment levels, probing depths, and degree of gingivitis were observed for all age groups.

Robinson (1979) recommends more frequent recall appointments for elderly patients due to increased recession and greater amounts of exposed cementum. He suggests oral prophylaxis twice a month for the first 3 months followed by a 3-month recall program.

Picozzi and Neidle (1984) indicated that aging alters the patient's response to pharmacologic agents. Geriatric pharmacology is complicated by multiple disease states, multiple medications, non-compliance, and altered pharmacodynamics and pharmacokinetics. While absorption is not altered, distribution is affected by a decrease in total body water, increased fat:lean ratio and decline in plasma proteins. Metabolism may be altered by liver disease. Renal excretion might be impaired and kidney function begins to decline at about age 40.

DRUG-INDUCED GINGIVAL HYPERPLASIA

DEFINITION

Gingival Hyperplasia: An enlargement of the gingiva due to an increase in the number of cells.

Carranza (1990) classified gingival enlargements as inflammatory, non-inflammatory or fibrotic, combined, conditioned (hormonal, nutritional, blood diseases, idiopathic) neoplastic, and developmental. Drug-induced gingival enlargements are either non-inflammatory or combined. The three major drugs or classes of drugs implicated in this process are phenytoin, cyclosporin, and the calcium channel blocking agents such as nifedipine.

Phenytoin. Phenytoin was introduced in 1938 for the control of epileptic seizures. Kimball (1939) was among the first to report gingival overgrowth associated with phenytoin, reporting that 57% of patients taking the drug had gingival overgrowth. It has since been estimated that of the 2 million individuals taking phenytoin, approximately 40 to 50% will develop gingival overgrowth to some extent (Butler et al., 1987). Overgrowths appear to be more common in children and young

adults, with no predilection for gender or race. Rates of occurrence appear unaffected by the duration of treatment.

Angelopoulos (1975) reviewed the literature and described the clinical and histologic appearance of phenytoin-induced gingival overgrowth. Clinically, in the vast majority of cases the first sign is an enlargement of the interdental papillae. Less commonly, the marginal gingiva may begin increasing in size. Gradually, gingival changes become more prominent, and enlargement takes the form of coalescent lobulations representing the hyperplastic papillae and extending labially and, less often, lingually. Lobulations are usually separated by a small cleft and commonly exhibit partial coverage of the anatomical crown to varying degrees. Overgrowths are localized to the anterior regions in a majority of cases, and the degree of overgrowth is most marked in anterior areas. Vestibular gingiva is more commonly affected than lingual gingiva and it is generally agreed that there are no clinical signs of overgrowth in edentulous regions. In uncomplicated phenytoin-induced overgrowth, the tissue has a normal pink color and is hard, firm, resilient, and rubbery. It may also be stippled and have a granular or smooth appearance and may not bleed easily.

Secondary inflammation resulting from plaque retention and other local irritants may cause these areas to become dark red, edematous, spongy, and friable. Histologically, in the majority of cases there are chronic inflammatory cells, mainly lymphocytes and plasma cells. The overlying epithelium is characterized by thin, elongated rete ridges and acanthosis. Basic changes in the connective tissue are a proliferation of fibroblasts and increased formation of collagen fibers. The amount of ground substance has also been reported to increase, and is associated with fibroblastic activity.

Dahllof et al. (1984) studied the volume density of various connective tissue components in phenytoin-induced overgrowths and reported a significant increase in the non-collagenous matrix and a corresponding decrease in the collagenous matrix of overgrowth tissue as compared to control specimens. The density of cells in both groups was the same (the specimens examined did not contain a significant inflammatory infiltrate due to rigorous plaque control prior to biopsy). Because the non-collagenous matrix is composed of glycosaminoglycans (GAGs), the authors proposed that increased synthesis of GAGs which bind large amounts of water and thereby occupy large volumes in the tissue might explain observed increases in volume of the non-collagenous matrix compartment.

In summary, when compared to normal gingiva, phenytoin-induced gingival overgrowths demonstrated a relative decrease in epithelium, increases in connective tissue and inflammation, and no change in vascularity. This indicates the main changes involve the connective tissue and inflammatory components rather than epithelium; however, one must remember the histopathological findings in this condition are by no means specific or pathognomonic.

While the exact mechanism of this process remains unknown, various theories have been proposed. The risk factor most associated with gingival overgrowth is poor oral hygiene. Seymour et al. (1987) found significant correlation between plaque score and gingival overgrowth in epileptic patients on phenytoin therapy. Pihlstrom et al. (1980) confirmed that a preventive program of frequent prophylaxis and oral hygiene reinforcement was effective in minimizing gingival enlargements. Although they further concluded that plasma and salivary levels of phenytoin were not correlated with the minimal degree of overgrowth observed in their study, there are conflicting reports regarding the association of dose and serum levels of phenytoin and the severity of gingival overgrowth.

Others have proposed the existence of fibroblast subpopulations which preferentially proliferate in response to phenytoin ingestion. Hassell (1982) and Hassell et al. (1986) demonstrated that fibroblasts from overgrowth lesions exhibited enhanced protein synthesis and produced inactive collagenase, thereby creating a net connective tissue overgrowth in affected individuals. Sooriyamoorthy and Gower (1989) evaluated the effect of phenytoin on the metabolism of testosterone by human gingival fibroblasts and reported an increased number of receptors for 5-a-dihydrotestosterone on fibroblasts removed from hyperplastic tissue. Since phenytoin stimulates the conversion of testosterone to 5-a-dihydrotestosterone, it may provide a metabolic pathway to enhance gingival growth.

Mallek and Nakamoto (1981) reviewed the role of folic acid and its relation to phenytoin-induced overgrowth. Among the side effects of anticonvulsant drugs in general, and dilantin specifically, is a decreased serum level of folic acid. The authors suggest that because folic acid metabolites play a complex role in regulating the cell division of human skin fibroblasts, it is possible that a deficiency of folic acid could alter this regulation and thereby cause uncontrolled proliferation of fibroblasts and their products.

Backman et al. (1989) and Drew et al. (1987) reported beneficial effects following the administration of folic acid. Finally, the role of genetics in this condition has recently received considerable attention.

Dill et al. (1993) note that phenytoin increases macrophage production of platelet-derived growth factor (PDGF), an important cytokine in connective tissue growth and repair, and that excessive production of PDGF could lead to redundant growth.

Cyclosporin. Cyclosporin is a powerful immunosuppressant agent primarily used to prolong the survival of allogeneic transplants in humans. The proposed mechanism of action is specific and reversible inhibition of immunocompetent lymphocytes (particularly T-cells). The incidence of gingival overgrowth varies from study to study, with a range of between 25 to 81% (Seymour and Jacobs, 1992).

Clinically, cyclosporin overgrowth closely resembles that of phenytoin. Rateitschick-Pluss et al. (1983) histologically

examined cyclosporin-associated gingival enlargements, identifying primarily connective tissue covered by irregular, multilayered, parakeratinized epithelium of varying thickness. In some areas, epithelial ridges penetrated deep into the connective tissue, with the latter being highly vascularized and exhibiting irregularly arranged collagen fiber bundles. Focal accumulations of infiltrating inflammatory cells were also observed. While a degree of fibroplasia characterized by the presence of increased numbers of fibroblasts has been noted within the gingival connective tissue (Wysocki et al., 1983), other studies have failed to demonstrate an increase in the numerical density of fibroblasts (McGaw and Porter, 1988). Such contrasting findings may be due to differences in the evolutionary stage of the overgrowth with changes in fibroblast density occurring as the lesion progresses. Accordingly, cyclosporin-induced gingival enlargement may not be a true hyperplasia and hence the term gingival overgrowth or enlargement is more appropriate.

The ultrastructural features of cyclosporine A-induced gingival hyperplasia were studied by Mariani et al. (1993). The authors reported that, although many fibroplasts are present, there is a particular abundance of amorphous material compared to fibrous substance, as well as marked plasma cell infiltration. The ultrastructural features presented by these cells (marked development of rough endoplasmic reticulum, Golgi apparatus, and plasmatic granules) indicate a distinct synthetc immunoglobulin activity. The authors concluded that cyclosporine enlargement is a local manifestation of a general phenomenon.

Although the etiology of cyclosporin-induced gingival overgrowth is unknown, it has been hypothesized that the drug acts only as an important cofactor in the pathogenesis of gingival enlargement. There is little doubt the fibroblast plays an important role in the pathogenesis of this condition; however, individual patient sensitivity to the drug or its metabolites, plasma concentrations of the drug, dental plaque scores, and gingivitis have all been proposed as important contributing factors (Wysocki et al., 1983; Seymour et al., 1987).

Although Seymour and Smith (1991) reported that plaque control measures alone did not prevent gingival overgrowth in cyclosporin-treated adult renal transplant patients, Hancock and Swan (1992) provided clinical evidence in a case report that plaque control without drug withdrawal or surgical excision can be successful in significantly reducing established nifedipine-induced gingival overgrowth.

Renal transplant patients medicated with a combination of cyclosporin and nifedipine have a significantly higher gingival overgrowth score ($P = 0.046$) when compared with the group receiving cyclosporin alone (Thomason et al., 1993).

Nifedipine. Nifedipine is a calcium channel blocking agent used in the treatment of vasospastic angina, chronic stable angina, and ventricular arrhythmias. Its principal action is to inhibit the influx of extracellular calcium ions across cardiac and vascular smooth muscle cell membranes, without changing serum calcium concentration. This prevents the contractile processes of cardiac and vascular smooth muscle from occurring, resulting in a dilatation of the main coronary and systemic arteries. The incidence of gingival overgrowth in response to nifedipine, and the role of drug dosage and duration are presently speculative (Butler et al., 1987).

Clinically, nifedipine-induced gingival overgrowth closely resembles phenytoin enlargement. Histologically, Lucas et al. (1985) observed that tissues from nifedipine- and phenytoin-induced overgrowths were remarkably similar. Both exhibited increased extracellular ground substance as well as increased numbers of fibroblasts. In addition, fibroblasts with numerous, large cytoplasmic structures resembling secretory granules were the striking electron microscopic finding in specimens examined. Because the authors believed that these granules represented newly synthesized ground substance prior to extrusion from the fibroblast, they concluded that an increase in ground substance is the primary cause of overgrowth in these conditions.

Steele et al. (1994) evaluated 120 dentate patients taking calcium antagonists for more than 3 months and a control group. The authors reported that 38% of the patients taking nifedipine, 21% of the patients taking diltiazem, and 19% of the patients receiving verapamil had gingival enlargement, compared with only 4% among controls.

Romanos et al. (1993) demonstrated the localization of collagen types I, III, IV, V, VI, and VII, as well as the glycoprotein fibronectin in nifedipine-induced gingival enlargement. Following indirect immunofluorescence (incubation with antibodies against these extracellular components), the tissue sections showed a diffuse distribution, with anti-types I and III in the stroma and fluorescent staining of the basement membranes of the epithelium, blood vessels, and nerves with collagen type IV antibodies. The increased number of vessels were localized near the surface of the lesion. Collagen type V (filamentous) and collagen type VI, (microfibrillar) components were also localized in the tissue, demonstrating completely different patterns of distribution. Collagen type V appeared "crater-like" and type VI displayed a "honeycomb-shaped" structural model. The blood vessels were not stained but the adjacent areas demonstrated intense fluorescence with these antibodies. Collagen type VII showed a characteristic linear staining near the epithelial basement membrance. In contrast to these, fibronectin localized with a varied intensity in the different areas of the tissue and presented a "cloud-like" structure. This study suggests differences between the matrix components in nifedipine-induced hyperplasia and confirms the heterogeneity of the matrix in health and in gingival alterations.

Morisaki et al. (1993) studied the relationship between gingival inflammation and nifedipine-induced gingival en-

largement in rats. They noted marked gingival overgrowth in the molar regions, regardless of gingival infection although the latter increased the degree of enlargement.

Treatment of Drug-Induced Gingival Hyperplasia

The best treatment of drug-induced gingival enlargement is discontinuing use of the associated drug. The enlargement will slowly become smaller and disappear in a matter of weeks to months. However, this is not practical with most patients because of the drug's important role in medical treatment. Therefore, prevention of secondary inflammation and surgical treatment of the enlargement become the only realistic choices (Carranza, 1990).

Treatment of drug-induced gingival overgrowth is based upon the severity of overgrowth and the ultimate goals of therapy. Both non-surgical and surgical approaches to treatment have been used successfully. Non-surgical therapy consisting of thorough scaling and root planing plus improvement in oral hygiene is the primary method of treating the inflammatory component of gingival overgrowth. It is of little benefit for reducing the fibrous component. Adjunctive therapy such as the daily use of chlorhexidine gluconate mouthrinses may also be considered. Although dramatic results can be obtained using non-surgical treatment alone, some lesions will not respond adequately and require surgical intervention. Surgical approaches to gingival overgrowth are gingivectomy and the flap technique. Gingivectomy is simple and facilitates maintenance care, but it creates an open wound and potential for post-operative complications (Carranza, 1990).

The flap technique thins gingival tissues internally and repositions them apically without significantly removing or altering the external surface of the gingiva (Carranza, 1990). This technique facilitates wound closure and maintenance care, and reduces potential for post-operative complications. It is, however, more technically demanding when compared to the gingivectomy technique (Carranza, 1990). Thus far, no definitive statement can be made regarding the long-term success of surgical therapy (Rateitschak-Pluss et al., 1983).

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