Informational Paper

Modulation of the Host Response in Periodontal Therapy*

This paper was prepared by the Research, Science, and Therapy Committee of the American Academy of Periodontology to provide the dental profession an overview of current and potential methods to modulate the host response in the treatment of periodontal diseases. Specifically, it discusses components of periodontal disease pathogenesis (i.e., immune and inflammatory responses, excessive production of matrix metalloproteinases and arachidonic acid metabolites, and regulation of bone metabolism) and their modulation. *J Periodontol 2002;73:460-470.*

Plaque biofilm and associated host responses are involved in the pathogenesis of periodontitis. Current data suggest that a small group of predominately Gram-negative, anaerobic or microaerophilic bacteria within the biofilm are often associated with disease initiation and progression.[1] Organisms strongly implicated as etiologic agents include *Porphyromonas gingivalis, Actinobacillus actinomycetemcomitans,* and *Bacteroides forsythus.*[2] The microbial challenge consisting of antigens, lipopolysaccharide (LPS), and other virulence factors stimulates host responses which result in disease limited to the gingiva (i.e., gingivitis) or initiation of periodontitis.[3] Protective aspects of the host response include recruitment of neutrophils, production of protective antibodies, and possibly the release of anti-inflammatory cytokines including transforming growth factor-β (TGF-β), interleukin-4 (IL-4), IL-10, and IL-12.[4] Perpetuation of the host response due to a persistent bacterial challenge disrupts homeostatic mechanisms and results in release of mediators including proinflammatory cytokines (e.g., IL-1, IL-6, tumor necrosis factor-α [TNF-α]), proteases (e.g., matrix metalloproteinases), and prostanoids (e.g., prostaglandin E_2 [PGE_2]) which can promote extracellular matrix destruction in the gingiva and stimulate bone resorption.[4]

The determination that periodontal tissue destruction is primarily due to the host response has created areas of research directed at altering an individual's reaction to the bacterial challenge. Various host modulatory therapies (HMT) have been developed or proposed to block pathways responsible for periodontal tissue breakdown. Specific aspects of disease pathogenesis which have been investigated for modulation include regulation of immune and inflammatory responses, excessive production of matrix metalloproteinases and arachidonic acid metabolites, and regulation of bone metabolism. Currently, one systemically administered agent that modifies the host response is commercially available (i.e., sub-antimicrobial dose doxycycline†) for the adjunctive treatment of chronic periodontitis. This treatment and other therapeutic methods under investigation will be discussed.

REGULATION OF IMMUNE AND INFLAMMATORY RESPONSES

Microbial plaque is recognized as the primary etiologic agent for periodontal disease initiation and progression.[5] Thus, generation of protective antibodies via immunization has been investigated as a method to prevent periodontitis.[6] Antigens used for active immunization have included bacterial whole cells,[7-10] outer components (e.g., *P. gingivalis* fimbriae[11]), and synthetic peptides.[12] The immunization of non-human primates in ligature-induced periodontitis models with *P. gingivalis*[10] or a *P. gingivalis* virulence factor called cysteine protease,[13] has demonstrated partial reductions in alveolar bone loss. However, development of a periodontitis vaccine has been hindered by the multifactorial etiology of periodontal diseases and microbial complexity of biofilms. Successful vaccine development may depend on identification of microbial species essential for disease pathogenesis (e.g., *P. gingivalis, B. forsythus*)[14] and/or shared antigenic determinants (epitopes) among pathogenic species.[15]

Initial host responses to bacterial infections include activation and recruitment of neutrophils and macrophages. These cells subsequently release mediators including reactive oxygen species, which are antagonistic to plaque biofilms, but which in excess may

* This paper was developed under the direction of the Research, Science, and Therapy Committee and approved by the American Academy of Periodontology in January 2002.

† Marketed under the trademark Periostat by CollaGenex Pharmaceuticals, Inc., Newton, PA.

initiate inflammation.[16] For example, nitric oxide (NO) is a free radical involved in host defense that can be toxic when present at high levels and it has been implicated in a variety of inflammatory conditions.[16-21] In this regard, a study utilizing a ligature induced periodontitis rat model demonstrated that administration of an NO inhibitor (mercaptoethylguanidine) resulted in decreased bone loss.[22] Further preclinical studies are warranted to evaluate the effect of this agent on periodontal disease progression. Other host inflammatory mediators being investigated for modulation include nuclear factor kappa B and endothelial cell adhesion molecules.[23-27] However, the role of these inflammatory mediators in periodontitis needs to be elucidated.

Constituents of the biofilm also stimulate host cells to produce proinflammatory cytokines including IL-1β and TNF-α, which can induce connective tissue and alveolar bone destruction.[28] These cytokines are present in diseased periodontal tissues and gingival crevicular fluid (GCF).[29] The catabolic activities of these cytokines are controlled by endogenous inhibitors that include IL-1 and TNF receptor antagonists. When administered for therapeutic purposes, these antagonists can reduce inflammation.[30-33] The use of cytokine receptor antagonists to inhibit periodontal disease progression has been investigated in a ligature induced periodontitis non-human primate model.[34,35] It was demonstrated that IL-1/TNF blockers partially inhibited disease progression.[35] However, the use of cytokine antagonists to treat human periodontal disease needs to be evaluated.

Cytokines implicated in suppression of the destructive inflammatory response include IL-4, IL-10, IL-11, and TGF-β. Both IL-4 and IL-10 can target macrophages and inhibit the release of IL-1, TNF, reactive oxygen intermediates, and NO.[36-38] IL-4 also induces programmed cell death (apoptosis), which reduces the number of infiltrating inflammatory macrophages.[39,40] It can also upregulate the production of IL-1 receptor antagonists.[37] The evidence that IL-4 is deficient in diseased periodontal tissues,[41] and the finding that exogenous IL-4 administration in experimental arthritis reduces inflammation,[42] suggest that use of this cytokine may provide a therapeutic benefit in the treatment of periodontal diseases. Recently, recombinant human IL-11, which inhibits production of TNF-α, IL-1, and NO,[43,44] was also shown to reduce disease progression in a ligature-induced periodontitis canine model.[45] Another cytokine, granulocyte colony stimulating factor (GCSF), which enhances neutrophil production, was used to treat cyclic neutropenia and improved periodontal disease status over a 15-year period.[46] However, unresolved issues regarding cytokine modulation therapy include identifying the ideal method to maintain or inhibit cytokines long term, and understanding the systemic implications associated with altering cytokine levels on tissue homeostasis.[28] Therefore, additional animal and human studies are needed to determine the safety and efficacy of anti-inflammatory cytokines in the treatment of periodontitis.

PRODUCTION OF MATRIX METALLOPROTEINASES

The matrix metalloproteinases (MMPs) are a family of zinc- and calcium-dependent endopeptidases secreted or released by a variety of infiltrating cells (i.e., neutrophils and macrophages) and resident cells (i.e., fibroblast, epithelial, osteoblast, and osteoclast) found in the periodontium.[47] MMPs function at a neutral pH to degrade constituents of the extracellular matrix (e.g., collagen, gelatin, laminin, fibronectin, and proteoglycan).[48] A number of physiologic events (i.e., embryonic development and tissue remodeling[49]) and pathologic conditions (i.e., periodontitis,[48] arthritis,[50] and cancer[51]) are characterized by MMP activity.

One hypothesis regarding periodontal disease pathogenesis is that host cells stimulated directly or indirectly by components of the plaque biofilm secrete MMPs which are associated with altered connective tissue remodeling and alveolar bone resorption.[52] Although several periodontal pathogens (e.g., *P. gingivalis* and *A. actinomycetemcomitans*) produce MMPs, including collagenase, these proteinases are not considered to be the major destructive enzymes associated with disease progression.[53] In addition, recognition that endogenous MMPs are primarily responsible for tissue destruction and not bacterial proteinases adds further rationale for the investigation of host modulatory approaches in periodontal therapy.

Host cells responsible for the excessive MMPs in periodontitis have not been definitively demonstrated. Several studies implicated polymorphonuclear leukocyte-type collagenase (MMP-8) and gelatinase (MMP-9) as the source of excess active enzymes present.[52,54-57] In addition, MMP-13 (collagenase-3) is believed to be a mediator of bone resorption and cartilage destruction and has been identified in GCF from chronic periodontitis patients.[57] It has also been demonstrated that MMP-8 may originate from cell

types other than neutrophils including fibroblasts and mesenchymal cells.[4,58] Additional studies are required to verify the origin of MMPs and their roles in disease pathogenesis.

Recognition that the level of activated MMPs and their endogenous inhibitors is related to various pathological conditions including periodontal disease has resulted in treatment strategies that increase endogenous inhibitors or include the administration of exogenous (synthetic) inhibitors. Endogenous or natural inhibitors of MMP activity include tissue inhibitors of MMP (TIMP) and α_2-macroglobulin. While TIMP levels increase during pathologic conditions, this increase may not compensate for elevated concentrations of active MMPs.[59] Furthermore, cell culture studies have demonstrated that recombinant TIMP can reduce stimulated bone resorption.[60] Therefore, administration of recombinant TIMP might be an effective treatment modality and should be evaluated.[60]

Several synthetic MMP inhibitors are being studied in clinical trials.[61,62] The synthetic MMP inhibitors most extensively investigated are the family of tetracycline antibiotics which can inhibit host-derived MMPs by mechanisms independent of their antimicrobial properties.[63] In vivo animal and human studies have demonstrated that tetracyclines inhibit MMP levels in gingival tissue and GCF with concomitant improvements in periodontal status.[52,57,63-66] Tetracyclines appear to inhibit MMP activity and extracellular matrix destruction by multiple non-antimicrobial mechanisms (e.g., chelation, inhibition of activation of pro-MMP molecules).[67]

The development of HMT utilizing tetracyclines has primarily involved the use of a reduced dose of doxycycline (20 mg bid). This dose has been reported not to exhibit antimicrobial effects, but can effectively lower MMP levels.[57] This reduced dose has been referred to as subantimicrobial dose doxycycline (SDD).[68] Studies evaluating the safety and efficacy of SDD for the United States Food and Drug Administration (FDA) include several multicenter, placebo-controlled, double-blind, randomized clinical trials in patients diagnosed with chronic periodontitis.[68,69]

Three 12-month studies (total n = 437) evaluated the safety and efficacy of SDD when used in conjunction with supragingival scaling and a dental prophylaxis (SSDP).[68] Administration of SDD as an adjunct to SSDP provided statistically significant improvements in both probing depth reduction and clinical attachment gain (Table 1). These studies demonstrated no increased incidence of side effects associated with SDD administration.[68]

Table 1.

Effect of SDD*† Plus SSDP‡ on Clinical Parameters[68]

Clinical Parameters	Initial Probing Depth	
	4-6 mm	≥7 mm
Clinical Attachment Gain (mm)		
SDD plus SSDP	0.67	1.27
Placebo plus SSDP	0.44	0.95
Difference	0.23	0.32
Probing Depth Reduction (mm)		
SDD plus SSDP	0.71	1.39
Placebo plus SSDP	0.46	0.96
Difference	0.25	0.43

* SDD = subantimicrobial dose doxycycline.
† Doses included: 10 mg qd (n = 80); 20 mg qd (n = 119); 20 mg bid (n = 119).
‡ SSDP = supragingival scaling and dental prophylaxis.

The phase III trial (total n = 190) evaluated the safety and efficacy of SDD used in combination with scaling and root planing (SRP) over a 9-month period among patients with chronic periodontitis. The study design incorporated subgingival SRP at the baseline visit that was not repeated at follow-up time points (i.e., 3, 6, and 9 months).[69] The gain in clinical attachment level (CAL) and probing depth (PD) reductions within the 2 treatment groups (SRP + placebo vs. SRP + SDD) are presented in Table 2. The data indicate that there was a statistically significant improvement when SDD was utilized as an adjunctive treatment at sites with initially moderate (4 to 6 mm) and severe (≥7 mm) probing depths (Table 2). In severe sites (≥7 mm PD), the additional improvements beyond SRP provided by SDD in PD reduction and CAL gains were 0.48 mm (P <0.01) and 0.38 mm (P <0.05), respectively. These improvements were maintained for a 3-month period after cessation of therapy.[70] It should be noted that patients treated in both cohorts (i.e., SRP + placebo or SRP + SDD) exhibited PD reductions and gains in CAL of a similar magnitude at sites that had initial probing depths of 4 to 6 mm and at those sites greater than 7 mm. This is an unusual finding since following scaling and root planing the gain in clinical attachment is usually less than probing depth reduction. Mechanisms that may account for this difference include coronal migration of the gingival margin and attachment apparatus or measurement error.

In the phase III clinical trial, it also was reported

Table 2.

Effect of SDD*† Plus SRP‡ on Clinical Parameters[69]

Clinical Parameters	Initial Probing Depth		
	0-3 mm	4-6 mm	≥7 mm
Clinical Attachment Gain (mm)			
SDD plus SRP	0.25	1.03	1.55
Placebo plus SRP	0.20	0.86	1.17
Difference	0.05	0.17	0.38
Probing Depth Reduction (mm)			
SDD plus SRP	0.16	0.95	1.68
Placebo plus SRP	0.05	0.69	1.20
Difference	0.11	0.26	0.48

* SDD = subantimicrobial dose doxycycline.
† Dose included: 20 mg bid.
‡ SRP = scaling and root planing.

that patients administered adjunctive SDD demonstrated fewer sites with disease progression (clinical attachment loss of ≥2 mm) than individuals treated with scaling and root planing alone (0.3% versus 3.6% of the treated sites, respectively) at sites with severe periodontitis (PD ≥7 mm).[69] These data also indicate that a single administration of SRP alone effectively inhibited disease progression in most sites (96.4%) during the 9-month study. Therefore, suppression of the biofilm by mechanical instrumentation remains the primary objective of treatment.

With regard to the issue that low dose antibiotics could result in microbial resistance, several in vivo human studies have indicated that long-term (i.e., 9 to 18 months) administration of SDD does not result in emergence of resistant organisms or alteration of the subgingival microflora.[71,72] Whether continuous administration or multiple applications to the same individual over longer time intervals result in microbial resistance or the emergence of resistant strains has not been determined.

The adjunctive use of SDD might prove beneficial in patients with increased susceptibility to disease progression. In this respect, a recent study compared the efficacy of scaling for 30 minutes with and without adjunctive SDD among patients who consistently exhibited elevated GCF collagenase levels prior to treatment.[73] It was determined that patients who received periodically administered SDD (12 weeks on, 12 weeks off, 12 weeks on) demonstrated less clinical attachment loss than individuals who received scaling alone during a 36-week period (0.15 mm versus 0.8 mm).[73] However, it should be noted that patients did not receive root planing in this study or quarterly periodontal maintenance. In addition, prospective clinical trials are needed to validate that measurement of GCF collagenase can determine disease susceptibility.

Overall, the studies indicate that SDD therapy provides a defined, but limited improvement in periodontal status when used in conjunction with scaling and root planing (Table 2). However, the phase III trial included SRP only at the baseline visit. Therefore, it is unclear what benefits would be achieved when SDD is combined with quarterly maintenance visits.[74] Furthermore, it has been questioned whether the magnitude of the clinical benefits derived from adjunctive SDD substantiates its routine use in the treatment of chronic periodontitis.[75] Therefore, dental practitioners must determine those patients who would significantly benefit from SDD administration.

In addition to use of SDD in host modulatory therapy, 10 different chemically modified tetracyclines (CMTs) have been developed, 9 of which inhibit MMPs and do not possess antimicrobial properties.[47] CMTs have been reported to reduce the progression of experimentally induced periodontitis in animal models.[76,77] However, inhibition of human periodontitis with CMTs has not been reported at this time. The development of recombinant TIMP and synthetic MMP inhibitors offers promising therapeutic approaches for the treatment of conditions characterized by excessive MMP activity.

PRODUCTION OF ARACHIDONIC ACID METABOLITES

Another pathway involved in periodontal disease pathogenesis involves the synthesis and release of prostaglandins and other arachidonic acid metabolites within periodontal tissues.[78] Both bacterial and host factors initiate tissue damage. This damage allows phospholipids in plasma membranes of cells to become available for action by phospholipase A_2 and thereby results in production of free arachidonic acid (AA). AA can be metabolized via the cyclooxygenase (CO) or lipoxygenase (LO) pathways. Two isoforms of cyclooxygenase are now recognized.[79] Cyclooxygenase 1 (COX-1) is constitutively (i.e., continuously) expressed and is important for physiologic functions including gastric cytoprotection. Cyclooxygenase 2 (COX-2) is inducible, upregulated by proinflammatory cytokines, and thought to be involved in

inflammation.[79] The final products of the CO pathway include prostaglandins, prostacyclin, and thromboxane, whereas the end results of the LO pathway include leukotrienes and other hydroxyeicosatetraenoic acids. Elevated levels of PGE_2 and other AA metabolites have been reported in GCF and periodontal tissues in patients exhibiting gingivitis, periodontitis, and peri-implantitis.[80,81] Mean crevicular PGE_2 concentrations are also significantly elevated in patients who exhibit disease progression compared to periodontally stable individuals.[82] One proposed approach to modulate the host response is inhibition of enzymes responsible for the release of these destructive products.

The discovery that non-steroidal anti-inflammatory drugs (NSAIDs) block the enzyme CO and reduce prostaglandin synthesis led to in vitro studies evaluating NSAIDs as inhibitors of bone resorption.[83,84] Inhibition of periodontal disease progression utilizing a NSAID was first demonstrated with indomethacin in a ligature-induced canine periodontitis model.[85] Multiple NSAIDs including indomethacin,[86] flurbiprofen,[87] ibuprofen,[88] naproxen,[89] meclofenamic acid,[90] and piroxicam[91] have demonstrated the ability to inhibit gingivitis[91] and progression of periodontitis in both ligature-induced[85,86] and naturally occurring periodontal disease animal models.[87-89]

Ketoprofen, an NSAID which can block both the CO and LO pathways, has recently received attention.[92] Its administration as a racemic cream (1%), (S)-enantiomer dentifrice (0.3%, 3.0%) or (S)-enantiomer capsule (10.0 mg) was noted to prevent the progression of alveolar bone loss in ligature-induced periodontitis models.[93,94] Ketoprofen appears to be enantioselective with pharmacological benefits restricted to the (S)-enantiomer.[95] The use of enantioselective NSAIDs (e.g., S-ketoprofen) may provide greater efficacy at lower doses and with fewer side effects than other NSAIDs.[94]

In humans, clinical trials have assessed the efficacy of topically and systemically administered NSAIDs in the treatment of experimental gingivitis[96] and chronic[97] and aggressive periodontitis.[98,99] The most extensive clinical trial that investigated a systemically administered NSAID (flurbiprofen) demonstrated significantly lower bone loss rates over an 18-month period.[96] However, disease progression returned upon withdrawal of the agent. Therefore, it appears that the drug did not provide any residual effect and would require prolonged administration to maintain periodontal status.

The topical administration of NSAIDs is an alternative method to deliver these agents. In general, topical application of NSAIDs is possible because these drugs are lipophilic and are absorbed into gingival tissues.[100] NSAIDs that have been evaluated for topical administration include ketorolac tromethamine rinse[101,102] and S-ketoprofen dentifirice.[94,103] In multi-center placebo controlled trials both of these drugs were associated with reductions in the rate of alveolar bone loss when used in conjunction with mechanical instrumentation.[102,103] However, further studies are required to determine whether these NSAIDs provide clinically significant improvements when utilized as adjuncts to scaling and root planing.

Extensive data acquired in animal and human clinical trials have demonstrated the potential clinical utility of NSAIDs in the management of periodontitis. However, adverse effects associated with prolonged systemic administration of non-selective NSAIDs that possess both COX-1 and COX-2 inhibitory activity include gastrointestinal upset and hemorrhage,[104] renal,[105] and hepatic impairment.[106] These adverse events associated with systemic use of NSAIDs have precluded their incorporation into treatment regimens. Recently, selective NSAIDs called coxibs (COX-2 inhibitors) have been developed that selectively block the isoenzyme associated with inflammation (COX-2).[107] Clinical trials have demonstrated that use of these agents cause significantly fewer serious gastrointestinal adverse events than does treatment with non-selective NSAIDs.[108] Safety and efficacy evaluations continue for these drugs.[109] However, at this time no NSAID formulation is FDA approved for the management of periodontal diseases.

Lipoxins are a series of oxygenated arachidonic acid derivatives formed by interactions between individual LO and appear to function as endogenous anti-inflammatory mediators.[110] Recently, it was demonstrated that lipoxins are produced by peripheral blood neutrophils from patients diagnosed with aggressive periodontitis.[111] In addition, lipoxins have also been found in the GCF of these individuals.[111] In a mouse model, it was shown that administration of metabolically stable analogues of lipoxins blocked *P. gingivalis* elicited neutrophil infiltration and also reduced PGE_2 levels.[111] These results support the concept that lipoxins may be involved in the regulation of local acute inflammatory responses in periodontal disease. However, additional studies are needed to elucidate the role of lipoxins in the pathogenesis of periodontitis.

A compound which has received interest as both an antibacterial and anti-inflammatory agent is triclosan. Triclosan (2, 4, 4[1]–trichloro-2-hydroxydiphenyl ether) is a non-ionic antimicrobial agent. Triclosan also inhibits CO and LO and thus may interfere with the production of AA metabolites.[112] Use of a dentifrice‡ containing sodium fluoride (0.243%) and triclosan (0.3%) with 2.0% PVM/MA copolymer (the non-proprietary designation for a polyvinylmethyl ether maleic acid copolymer) reduced the frequency of deep periodontal pockets and the number of sites exhibiting attachment and bone loss in patients deemed highly susceptible to periodontitis.[113] Additional studies are warranted to examine the effect of this combination of drugs on periodontitis. At this time, the triclosan/copolymer dentifrice is indicated for the reduction of plaque, calculus, gingivitis, and caries.

REGULATION OF BONE METABOLISM

Several studies have demonstrated a relationship between tooth loss and osteoporosis.[114-116] Preliminary evidence also suggests that osteoporosis and osteopenia may be risk indicators for periodontal diseases.[117-119] Both diseases begin to manifest their effects predominately after the age of 35 and have common risk factors that may interfere with healing (e.g., smoking, influence of disease, or medications).[120] Thus, therapeutic strategies used to prevent and manage osteoporosis and osteopenia may also inhibit periodontal bone loss. In this regard, large epidemiological studies have been performed to determine whether hormone replacement therapy (HRT) can reduce the number of teeth lost in postmenopausal women.[121,122] These studies have reported conflicting results regarding the use of HRT and tooth retention.[121,122] A potential source of bias in these studies is the possibility that patients who seek care to prevent osteoporosis may also pursue preventive dental care. At present, limited evidence exists to support the concept that calcium supplementation[116,123] or HRT[124,125] can reduce tooth loss or progression of periodontitis. Longitudinal studies are in progress that address these issues. A new class of drugs used to manage osteoporosis which may have beneficial effects on the periodontium are the bisphosphonates. Bisphosphonates are non-biodegradable analogs of pyrophosphate that have a high affinity for calcium phosphate crystals and that inhibit osteoclast activity.[126] These compounds also appear to inhibit MMP activity through a mechanism that involves chelation of cations.[127] One of these drugs, alendronate, has been evaluated in ligature-induced periodontitis models and assessed for changes in bone density. Alendronate inhibited the loss of bone density in these models.[128,129] However, minimal effects were demonstrated on clinical parameters. A pilot human clinical study was performed to assess the efficacy of alendronate in slowing alveolar bone loss associated with periodontits.[130] The relative risk of progressive bone loss assessed by digital subtraction radiography was less (0.45) for alendronate-treated patients compared with placebo-treated patients.[130] Additional studies using topically administered bisphosphonates have reported reductions in root resorption associated with orthodontic tooth movement and alveolar bone resorption following periodontal surgery.[131,132] Future randomized, controlled, longitudinal studies that evaluate therapies for the treatment of osteoporosis should also examine the effectiveness of the treatment on periodontal disease parameters.

SUMMARY

The current paradigm for the etiology and pathogenesis of periodontal diseases includes the initiation of disease by specific bacteria within a biofilm. These bacteria stimulate immune responses that can result in tissue destruction. To prevent disease initiation and progression, mechanical and antimicrobial pharmaceutical agents are used to reduce the plaque biofilm. In this respect, considerable evidence exists that these methods are effective in managing the majority of patients with periodontitis.[133] Currently, due to an improved understanding of the pathogenesis of periodontal diseases, an additional approach to therapy with respect to modulation of the host response has received attention. In this regard, a triclosan dentifrice with antimicrobial properties approved to treat gingivitis has also demonstrated anti-inflammatory properties related to its host modulatory effects. In addition, the FDA has recently approved subantimicrobial dose doxycycline for systemic administration as an adjunct to scaling and root planing for the treatment of chronic periodontitis.

There are situations in which conventional therapy does not always achieve the desired clinical outcome. For example, certain patients possess non-microbial risk factors which are difficult to reduce or eliminate (e.g., smoking, diabetes) or are beyond the clinician's ability to control (e.g., genetic predisposition[134]). In

‡ This dentifrice is marketed under the trademark Total by Colgate-Palmolive Co., New York, NY.

these instances and for specific groups of periodontal disease susceptible individuals, the use of HMT in conjunction with antibiofilm treatments may prove to be advantageous. However, this concept needs to be validated in controlled clinical trials. As methods that modulate the host response become available, they may be useful as adjunctive therapies for a variety of clinical situations. Ultimately, practitioners will need to determine the utility of HMT therapies as they emerge based on the specific needs of each individual patient.

REFERENCES

1. Page RC, Kornman KS. The pathogenesis of human periodontitis: An introduction. *Periodontol 2000* 1997; 14:9-11.
2. Consensus report on periodontal diseases: Pathogenesis and microbial factors. *Ann Periodontol* 1996;1: 926-932.
3. Offenbacher S. Periodontal diseases: Pathogenesis. *Ann Periodontol* 1996;1:879-925.
4. Page RC. The pathobiology of periodontal diseases may affect systemic diseases: Inversion of a paradigm. *Ann Periodontol* 1998;3:108-120.
5. Haffajee AD, Socransky SS. Microbial etiologic agents of destructive periodontal diseases. *Periodontol 2000* 1994;5:78-111.
6. Ishikawa I, Nakashima K, Koseki T, et al. Induction of the immune response to periodontopathic bacteria and its role in the pathogenesis of periodontitis. *Periodontol 2000* 1997;14:79-111.
7. Klausen B, Evans RT, Ramamurthy NS, et al. Periodontal bone level and gingival proteinase activity in gnotobiotic rats immunized with *Bacteroides gingivalis*. *Oral Microbiol Immunol* 1991;6:193-201.
8. Genco CA, Kapczynski DR, Cutler CW, Arko RJ, Arnold RR. Influence of immunization on *Porphyromonas gingivalis* colonization and invasion in the mouse chamber model. *Infect Immun* 1992;60:1447-1454.
9. Persson GR, Engel LD, Whitney CW, et al. Immunization against *Porphyromonas gingivalis* inhibits progression of experimental periodontitis in nonhuman primates. *Infect Immun* 1994;62:1026-1031.
10. Ebersole JL, Brunsvold M, Steffensen B, Wood R, Holt SC. Effects of immunization with *Porphyromonas gingivalis* and *Prevotella intermedia* on progression of ligature-induced periodontitis in the nonhuman primate *Macaca fascicularis*. *Infect Immun* 1991;59: 3351-3359.
11. Evans RT, Klausen B, Sojar HT, et al. Immunization with *Porphyromonas (Bacteroides) gingivalis* fimbriae protects against periodontal destruction. *Infect Immun* 1992;60:2926-2935.
12. Evans RT, Klausen B, Genco RJ. Immunization with fimbrial protein and peptide protects against *Porphyromonas gingivalis*-induced periodontal tissue destruction. *Adv Exp Med Biol* 1992;327:255-262.
13. Moritz AJ, Cappelli D, Lantz MS, Holt SC, Ebersole JL. Immunization with *Porphyromonas gingivalis* cysteine protease: Effects on experimental gingivitis and ligature-induced periodontitis in *Macaca fascicularis*. *J Periodontol* 1998;69:686-697.
14. Grossi SG, Genco RJ, Machtei EE, et al. Assessment of risk for periodontal disease. II. Risk indicators for alveolar bone loss. *J Periodontol* 1995;66:23-29.
15. Vasel D, Sim T, Bainbridge B, Houston L, Darveau R, Page RC. Shared antigens of *Porphyromonas gingivalis* and *Bacteroides forsythus*. *Oral Microbiol Immunol* 1996;11:226-235.
16. Wahl SM, Hines KL, Imamichi T, Tian H, Shepheard S, McCartney-Francis NL. Regulation of chronic inflammation. In: Genco R, Hamada S, Lehner T, McGhee J, Mergenhagen S, eds. *Molecular Pathogenesis of Periodontal Disease*. Washington DC: American Society for Microbiology Press; 1994:183-190.
17. Nathan C. Nitric oxide as a secretory product of mammalian cells. *FASEB J* 1992;6:3051.
18. Borghton-Smith NK, Evans SM, Hawkey CJ, et al. Nitric oxide synthase activity in ulcerative colitis and Crohn's disease. *Lancet* 1993;342:338-340.
19. Brahn E, Banquerigo ML, Firestein GS, Boyle DL, Salzman AL, Szabo C. Collagen induced arthritis: Reversal by mercaptoethylguanidine, a novel anti-inflammatory agent with a combined mechanism of action. *J Rheumatol* 1998;25:1785-1793.
20. Miller MJ, Thompson JH, Zhang XJ, et al. Role of inducible nitric oxide synthase expression and peroxynitrite formation in guinea pig iletis. *Gastroenter* 1995;109:1475-1483.
21. Szabo C. Alterations in nitric oxide production in various forms of circulatory shock. *New Horizons* 1995;3: 2-32.
22. Lohinai Z, Benedek P, Feher E, et al. Protective effects of mercaptoethylguanidine, a selective inhibitor of inducible nitric oxide synthase, in ligature-induced periodontitis in the rat. *Br J Pharmacol* 1998;123:353-360.
23. Christman JW, Lancaster LH, Blackwell TS. Nuclear factor kappa B: A pivotal role in the systemic inflammatory response syndrome and new target for therapy. *Intens Care Med* 1998;24:1131-1138.
24. Lum RT, Kerwar SS, Meyer SM, et al. A new structural class of proteasome inhibitors that prevent NF-kappa B activation. *Biochem Pharmacol* 1998;55: 1391-1397.
25. Hayflick JS, Kilgannon P, Gallatin WM. The intercellular adhesion molecule (ICAM) family of proteins. New members and novel functions. *Immunol Res* 1998;17:313-327.
26. Wilson JL, Walker JS, Antoon JS, Perry MA. Intercellular adhesion molecule-1 expression in adjuvant arthritis in rats: Inhibition by kappa-opoid agonist but not by NSAID. *J Rheumatol* 1998;25:499-505.
27. Zhou L, Pope BL, Chourmouzis E, Fung-Leung WP, Lau CY. Tepoxalin blocks neutrophil migration into cutaneous inflammatory sites by inhibiting Mac-1 and E-selectin expression. *Eur J Immunol* 1996;26:120-129.
28. Gemmell E, Marshall R, Seymour GJ. Cytokines and prostaglandins in immune homeostasis and tissue destruction in periodontal disease. *Periodontol 2000* 1997;14:112-143.

29. Stashenko P, Jandinski JJ, Fujiyoshi P, Rynar J, Socransky SS. Tissue levels of bone resorptive cytokines in periodontal disease. *J Periodontol* 1991; 62:504-509.
30. Mullarkey MF, Leiferman KM, Peters MS, et al. Human cutaneous allergic late-phase response is inhibited by soluble IL-1 receptor. *J Immunol* 1994;152:2033-2041.
31. Rosenbaum JT, Boney RS. Use of a soluble interleukin-1 receptor to inhibit ocular inflammation. *Curr Eye Res* 1991;10:1137-1139.
32. Russel DA, Tucker KK, Chinookoswong N, Thompson RC, Kohno T. Combined inhibition of interleukin-1 and tumor necrosis factor in rodent endotoxemia: Improved survival and organ function. *J Infect Dis* 1995;171:1528-1538.
33. Windsor AC, Walsh CJ, Mullen PG, et al. Tumor necrosis factor-alpha blockade prevents neutrophil CD18 receptor upregulation and attenuates acute lung injury in porcine sepsis without inhibition of neutrophil oxygen radical generation. *J Clin Invest* 1993;91:1459-1468.
34. Assuma R, Oates T, Cochran D, Amar S, Graves DT. IL-1 and TNF antagonists inhibit the inflammatory response and bone loss in experimental periodontitis. *J Immunol* 1998;160:403-409.
35. Delima AJ, Oates T, Assuma R, et al. Soluble antagonists to interleukin-1 (IL-1) and tumor necrosis factor (TNF) inhibits loss of tissue attachment in experimental periodontitis. *J Clin Periodontol* 2001;28: 233-240.
36. Howard M, O'Garra A, Ishida H, DeWaal Malefyt R, De Vries J. Biological properties of interleukin 10. *J Clin Immunol* 1992;12:239-247.
37. Wong HL, Costa GL, Lotze MT, Wahl SM. Interleukin-4 differentially regulates monocyte IL-1 family gene expression and synthesis in vitro and in vivo. *J Exp Med* 1993;177:775-781.
38. Wong HL, Lotze MT, Wahl LM, Wahl SM. Administration of recombinant IL-4 to humans regulates gene expression, phenotype and function in circulating monocytes. *J Immunol* 1992;148:2118-2125.
39. Mangan DF, Mergenhagen SE, Wahl SM. Apoptosis in human monocytes: Possible role in chronic inflammatory diseases. *J Periodontol* 1993;64:461-466.
40. Mangan DF, Robertson B, Wahl SM. IL-4 enhances programmed cell death (apoptosis) in stimulated human monocytes. *J Immunol* 1992;148:1812-1816.
41. Fujihasi K, Yoshiharu J, Beagley KW, et al. Cytokines and periodontal disease: Immunopathological role of interleukins in chronic inflamed gingival tissues. *J Periodontol* 1993;64:400-406.
42. Allen JB, Wong HL, Costa GL, Bienkowski M, Wahl SM. Suppression of monocyte function and differential regulation of IL-1 and IL-1ra by IL-4 contribute to resolution of experimental arthritis. *J Immunol* 1993; 151:4344-4351.
43. Trepicchio WL, Bozza M, Pednault G, et al. Recombinant human interleukin-11 attenuates the inflammatory response through downregulation of proinflammatory cytokine release and nitric oxide production. *J Immunol* 1996;157:3627-3634.
44. Leng SX, Elias JA. Molecules in focus: Interleukin-11. *Int J Biochem Cell Biol* 1997;29:1059-1062.
45. Martuscelli G, Fiorellini JP, Crohin CC, Howell TH. The effect of interleukin-11 on the progression of ligature-induced periodontal disease in the beagle dog. *J Periodontol* 2000;71:573-578.
46. Baer PN, Iacono VJ. Cyclic neutropenia: Report of a case with a 15-year follow-up. *Periodont Clin Invest* 1994;16:14-19.
47. Ryan ME, Golub LM. Modulation of matrix metalloproteinase activities in periodontitis as a treatment strategy. *Periodontol 2000* 2000;24:226-238.
48. Birkedal-Hansen H. Role of matrix metalloproteinases in human periodontal disease. *J Periodontol* 1993;64: 474-484.
49. Gross J, Lapiere C. Collagenolytic activity in amphibian tissues: A tissue culture assay. *Proc Natl Acad Sci USA* 1962;48:1014-1020.
50. Martel-Pelletier J, Pelletier JP. Wanted-the collagenase responsible for the destruction of the collagen network in human cartilage! *Br J Rheum* 1996;35: 818-820.
51. Azzam H, Arand G, Lippman M, Thompson E. Association of MMP-2 activation potential with metastatic progression in human breast cancer cell lines independent of MMP-2 production. *J Natl Cancer Inst* 1993;85:1758-1764.
52. Golub L, Sorsa T, Lee HM, Ciancio S, Sorbi D, Ramamurthy N. Doxycycline inhibits neutrophil (PMN)-type matrix metalloproteinases in human adult periodontitis gingiva. *J Clin Periodontol* 1995;21:1-9.
53. Sodek J, Overall C. Matrix metalloproteinases in periodontal tissue remodeling. *Matrix* 1992;(suppl.):352-362.
54. Sorsa T, Uitto VJ, Suomolainen M, Vauhkonen M, Lindy S. Comparison of interestial collagenases form human gingiva, sulcular fluid and polymorphonuclear leukocytes. *J Periodont Res* 1988;23:386-393.
55. Overall C. Sodek J, McCulloch A, Birek P. Evidence for polymorphonuclear leukocyte collagenase and 92-kilodalton gelatinase in gingival crevicular fluid. *Infect Immun* 1991;59:4687-4692.
56. McCulloch C. Collagenolytic enzymes in gingival crevicular fluid as diagnostic indicators of periodontitis. *Ann NY Acad Sci* 1994;732:152-164.
57. Golub L, Lee H, Greenwald R, et al. A matrix metalloproteinase inhibitor reduces bone-type collagen degradation fragments and bone-type collagenase in gingival crevicular fluid during adult periodontitis. *Inflamm Res* 1997;4:310-319.
58. Sorsa T, Mantyla P, Ronka H, et al. Scientific basis of a matrix metalloproteinase-8 specific chair-side test for monitoring periodontal and peri-implant health and disease. *Ann NY Acad Sci* 1999;878:130-140.
59. Alpagot T, Bell C, Lundergan W, Chambers DW, Rudin R. Longitudinal evaluation of GCF MMP-3 and TIMP-1 levels as prognostic factors for progression of periodontitis. *J Clin Periodontol* 2001;28:353-359.
60. Hill P, Reynolds J, Meikle M. Inhibition of stimulated bone resorption in vitro by TIMP-1 and TIMP-2. *Biochem Biophys Acta* 1993;1177:71-74.
61. Galardy R, Cassabonne M, Giese C, et al. Low mo-

lecular weight inhibitors of corneal ulceration. *Ann NY Acad Sci* 1994;732:315-323.
62. Brown P. Clinical trials of a low molecular weight matrix metalloproteinase inhibitor in cancer. *Ann NY Acad Sci* 1994;732:217-221.
63. Golub LM, Lee HM, Lehrer G, et al. Minocycline reduces gingival collagenolytic activity during diabetes: Preliminary observations and a proposed new mechanism of action. *J Periodont Res* 1983;18:516-526.
64. Golub LM, Ramamurthy NS, McNamara T, et al. Tetracyclines inhibit tissue collagenase activity. *J Periodont Res* 1984;19:651-655.
65. Golub L, Wolff M, Lee H, et al. Further evidence that tetracyclines inhibit collagenase activity in human crevicular fluid and from other mammalian sources. *J Periodont Res* 1985;20:12-23.
66. Golub L, Wolff M, Roberts S, Lee HM, Leung M, Payonk G. Treating periodontal diseases by blocking tissue-destructive enzymes. *J Am Dent Assoc* 1994;125:163-169.
67. Golub L, Lee H, Ryan M, Giannobile W, Payne J, Sorsa T. Tetracyclines inhibit connective tissue breakdown by multiple non-antimicrobial mechanisms. *Adv Dent Res* 1998;12:12-26.
68. Ciancio S, Ashley R. Safety and efficacy of sub-antimicrobial-dose doxycycline therapy in patients with adult periodontitis. *Adv Dent Res* 1998;12:27-31.
69. Caton J, Ciancio SG, Bleiden TM, et al. Treatment with subantimicrobial dose doxycycline improves the efficacy of scaling and root planing in patients with adult periodontitis. *J Periodontol* 2000;71:521-532.
70. Caton JG, Ciancio SG, Blieden TM, et al. Subantimicrobial dose doxycycline as an adjunct to scaling and root planing: post-treatment effects. *J Clin Periodontol* 2001;28:782-789.
71. Thomas J, Walker C, Bradshaw M. Long-term use of subantimicrobial dose doxycycline does not lead to changes in antimicrobial susceptibility. *J Periodontol* 2000;71:1472-1483.
72. Walker C, Thomas J, Nangò S, Lennon J, Wetzel J, Powala C. Long-term treatment with subantimicrobial dose doxycycline exerts no antibacterial effect on the subgingival microflora associated with adult periodontitis. *J Periodontol* 2000;71:1465-1471.
73. Golub LM, McNamara TF, Ryan ME, et al. Adjunctive treatment with subantimicrobial doses of doxycycline: Effects on gingival fluid collagenase activity and attachment loss in adult periodontitis. *J Clin Periodontol* 2001;28:146-156.
74. The American Academy of Periodontology. Parameter on periodontal maintenance. *J Periodontol* 2000;71: 849-850.
75. Greenstein G, Lamster I. Efficacy of subantimicrobial dosing with doxycycline: Point/counterpoint. *J Am Dent Assoc* 2001;132:457-466.
76. Golub LM, Evans RT, McNamara TF, Lee HM, Ramamurthy NS. A non-antimicrobial tetracycline inhibits gingival matrix metalloproteinases and bone loss in *Porphyromonas gingivalis*-induced periodontitis in rats. *Ann NY Acad Sci* 1994;733:96-111.
77. Llavaneras A, Ramamurthy NS, Heikkilä P, et al. A combination of a chemically modified doxycycline and a bisphosphonate synergistically inhibits endotoxin-induced periodontal breakdown in rats. *J Periodontol* 2001;72:1069-1077.
78. Howell TH, Williams RC. Nonsteroidal antiinflammatory drugs as inhibitors of periodontal disease progression. *Crit Rev Oral Biol Med* 1993;4:177-196.
79. DeWitt DL, Meade EA, Smith WL. PGH synthase isoenzyme selectivity: The potential safer anti-inflammatory drugs. *Am J Med* 1993;95:40S-44S.
80. Paquette DW, Williams RC. Modulation of host inflammatory mediators as a treatment strategy for periodontal diseases. *Periodontol 2000* 2000;24:239-252.
81. Salvi GE, Williams RC, Offenbacher S. Nonsteroidal anti-inflammatory drugs as adjuncts in the management of periodontal diseases and peri-implantitis. *Curr Opin Periodontol* 1997;4:51-58.
82. Offenbacher S, Odle BM, Van Dyke TE. The use of crevicular fluid prostaglandin E_2 levels as a predictor of periodontal attachment loss. *J Periodont Res* 1986;21:101-112.
83. Goldhaber P, Rabadjija L, Beyer WR, Kornhauser A. Bone resorption in tissue culture and its relevance to periodontal disease. *J Am Dent Assoc* 1973;87:1027-1033.
84. Gomes BC, Hausmann CE, Weinfeld N, DeLuca C. Prostaglandins: Bone resorption stimulating factors released from monkey gingiva. *Calcif Tissue Res* 1976;19:285-293.
85. Nyman S, Schroeder HE, Lindhe J. Suppression of inflammation and bone resorption by indomethacin during experimental periodontitis in dogs. *J Periodontol* 1979;50:450-461.
86. Williams RC, Jeffcoat MK, Howell TH, et al. Indomethacin or flurbiprofen treatment of periodontitis in beagles: Comparison of effect of bone loss. *J Periodont Res* 1987;22:403-407.
87. Williams RC, Jeffcoat MK, Kaplan ML, Goldhaber P, Johnson HG, Wechter WJ. Flurbiprofen: A potent inhibitor of alveolar bone resorption in beagles. *Science* 1985;227:640-642.
88. Williams RC, Jeffcoat MK, Howell TH, et al. Ibuprofen: An inhibitor of alveolar bone resorption in beagles. *J Periodont Res* 1988;23:225-229.
89. Howell TH, Jeffcoat MK, Goldhaber P, et al. Inhibition of alveolar bone loss in beagles with the NSAID naproxen. *J Periodont Res* 1991;26:498-501.
90. Kornman KS, Blodgett RF, Brunsvold M, Holt SC. Effects of topical applications of meclofenamic acid and ibuprofen on bone loss, subgingival microbiota and gingival PMN response in the primate *Macaca fascicularis*. *J Periodont Res* 1990;25:300-307.
91. Howell TH, Fiorellini JP, Weber HP, Williams RC. Effect of the NSAID piroxicam, topically administered, on the development of gingivitis in beagle dogs. *J Periodont Res* 1991;26:180-183.
92. Harris RH, Vavra I. Ketoprofen. In: Rainsford KD, ed. *Anti-Inflammatory and Anti-Rheumatic Drugs,* vol 2. Boca Raton, FL: CRC Press; 1985:151-169.
93. Li KL, Vogel R, Jeffcoat MK, et al. The effects of ketoprofen creams on periodontal disease in rhesus monkeys. *J Periodont Res* 1996;31:525-532.

94. Paquette DW, Fiorellini JP, Martuscelli G, et al. Enantiospecific inhibition of ligature-induced periodontitis in beagles with topical (S)-ketoprofen. *J Clin Periodontol* 1997;24:521-528.
95. Jamali F, Mehvar R, Pasutto FM. Enantioselective aspects of drug action and disposition: Therapeutic pitfalls. *J Pharm Sci* 1989;78:695-715.
96. Heasman PA, Offebacher S, Collins JG, Edwards G, Seymour RA. Flurbiprofen in the prevention and treatment of experimental gingivitis. *J Clin Periodontol* 1993;20:732-738.
97. Williams RC, Jeffcoat MK, Howell TH, et al. Altering the progression of human alveolar bone loss with the non-steroidal anti-inflammatory drug flurbiprofen. *J Periodontol* 1989;60:485-490.
98. Jeffcoat MK, Page RC, Reddy MS, et al. Use of digital radiography to demonstrate the potential of naproxen as an adjunct in the treatment of rapidly progressive periodontitis. *J Periodont Res* 1991;26:305-311.
99. Reddy MS, Palcanis KG, Barnett ML, Haigh S, Charles CH, Jeffcoat MK. Efficacy of meclofenamate sodium (Meclomen) in the treatment of rapidly progressive periodontitis. *J Clin Periodontol* 1993;20:635-640.
100. Gevi M, Merlo M. Ketoprofen lysine by topical route in sports traumatology. *Curr Therapeutic Res* 1983;34:844-850.
101. Jeffcoat MK, Reddy MS, Haigh S, et al. A comparison of topical ketorolac, systemic flurbiprofen, and placebo for the inhibition of bone loss in adult periodontitis. *J Periodontol* 1995;66:329-338.
102. Jeffcoat MK, Page RC, Reddy M, et al. Prevention of alveolar bone loss in periodontitis with ketorolac oral rinse: A dose response study. *J Dent Res* 1998;77 (Spec. Issue)2951(abstr):1000.
103. Paquette DW, Williams R, Fiorellini J, et al. Topical (S)-ketoprofen and the treatment of adult periodontitis. *J Dent Res* 1998;77(Spec. Issue)2953(abstr):1001.
104. Hawkey CJ. Gastroduodenal problems associated with non-steroidal anti-inflammatory drugs (NSAIDs). *Scand J Gastroenterol* 1993;200(Suppl.):94-95.
105. Lindsley C, Warady B. Non-steroidal anti-inflammatory drugs. Renal toxicity. Review of pediatric issues. *Clin Pediatr* 1990;29:10-13.
106. Velo G, Milianino R. Nongastrointestinal adverse reactions to NSAIDs. *J Rheumatol* 1990;20(Suppl.):42-45.
107. Fitzgerald GA, Patrono C. The coxibs, selective inhibitors of cyclooxygenase-2. *N Engl J Med* 2001;345:433-442.
108. Simon LS, Lanza FL, Lipsky PE, et al. Preliminary study of the safety and efficacy of SC-58635, a novel cyclooxygenase 2 inhibitor: Efficacy and safety in two placebo-controlled trials in osteoarthritis and rheumatoid arthritis, and studies of gastrointestinal and platelet effects. *Arthritis Rheum* 1998;41:1591-1602.
109. Bezerra MM, de Lima V, Alencar VBM, et al. Selective cyclooxygenase-2 inhibition prevents alveolar bone loss in experimental periodontitis in rats. *J Periodontol* 2000;71:1009-1014.
110. Serhan CN. Lipoxins and novel aspirin-triggered 15-epilipoxins (ATL): A jungle of cell-cell interactions or a therapeutic opportunity? *Prostaglandins* 1997;53:107-137.
111. Pouliot M, Clish CB, Petasis NA, VanDyke TE, Serhan CN. Lipoxin A4 analogues inhibit leukocyte recruitment to *Porphyromonas gingivalis:* A role for cyclooxygenase-2 and lipoxins in periodontal disease. *Biochemistry* 2000;39:4761-4768.
112. Gaffar A, Scherl D, Affitto J, Coleman EJ. The effect of triclosan on mediators of gingival inflammation. *J Clin Periodontol* 1995;22:480-484.
113. Rosling B, Wannfors B, Volpe AR, et al: The use of a triclosan/copolymer dentifrice may retard the progression of periodontitis. *J Clin Periodontol* 1997;24:873-880.
114. Daniel HW. Postmenopausal tooth loss. Contributions to edentulism by osteoporosis and cigarette smoking. *Arch Intern Med* 1983;143:1678-1682.
115. Taguchi A, Tanimoto K, Suei Y, et al. Tooth loss and mandibular osteopenia. *Oral Surg Oral Med Oral Pathol Oral Radio Endod* 1995;79:127-132.
116. Krall EA, Garcia RI, Dawson-Hughes B. Increased risk of tooth loss is related to bone loss at the whole body, hip, and spine. *Calcif Tissue Int* 1996;59:433-437.
117. von Wowern N, Klausen B, Kollerup G. Osteoporosis: A risk factor in periodontal disease. *J Periodontol* 1994;65:1134-1138.
118. Wactawski-Wende J, Grossi SG, Trevisan M, et al. The role of osteopenia in periodontal disease. *J Periodontol* 1996;67:1076-1084.
119. Tezal M, Wactawski-Wende J, Grossi SG, Ho AW, Dunford R, Genco RJ. The relationship between bone mineral density and periodontitis in postmenopausal women. *J Periodontol* 2000;71:1492-1498.
120. Jeffcoat MK, Chestnut C. Systemic osteoporosis and oral bone loss. *J Am Dent Assoc* 1993;124:49-56.
121. Grodstein F, Colditz G, Stampfer G. Postmenopausal hormone use and tooth loss: A prospective study. *J Am Den Assoc* 1996;127:370-377.
122. Paganini-Hill A. Benefits of estrogen replacement therapy on oral health: The leisure world cohort. *Arch Intern Med* 1995;155:2325-2329.
123. Nishida M, Grossi SG, Dunford RG, Ho AW, Tresvisan M, Genco RJ. Calcium and the risk for periodontal disease. *J Periodontol* 2000;71:1057-1066.
124. Jacobs R, Ghyselen J, Koninchx P, van Steenberghe D. Long term bone mass evaluation of mandible and lumbar spine in a group of women receiving hormone replacement therapy. *Eur J Oral Sci* 1996;104:10-16.
125. Norderyd OM, Grossi SG, Machtei EE, et al. Periodontal status of women taking postmenopausal estrogen supplementation. *J Periodontol* 1993;64:957-962.
126. Fleisch H. Bisphosphonates: Pharmacology and use in the treatment of tumor-induced hypercalcaemic and metastatic bone disease. *Drugs* 1991;42:919-944.
127. Nakaya H, Osawa G, Iwasaki N, Cochran DL, Kamoi K, Oates TW. Effects of bisphosphonate on matrix metalloproteinase enzymes in human periodontal ligament cells. *J Periodontol* 2000;71:1158-1166.
128. Brunsvold MA, Chaves ES, Kornman KS, Aufdemorte TB, Wood R. Effects of bisphosphonate on experi-

mental periodontitis in monkeys. *J Periodontol* 1992; 63:825-830.
129. Reddy MS, Weatherford TW III, Smith CA, West BD, Jeffcoat MK, Jack TM. Alendronate treatment of naturally occurring periodontitis in beagle dogs. *J Periodontol* 1995;66:211-217.
130. Jeffcoat MK, Reddy MS. Alveolar bone loss and osteoporosis: Evidence for a common mode of therapy using the bisphosphonate alendronate. In: Davidovitch Z, Norton L, eds. *The Biologic Mechanism of Tooth Resorption and Replacement by Implants*. Boston: Harvard Society for the Advancement of Orthodontics; 1996:365-373.
131. Igarashi K, Adachi H, Mitani H, Shinoda H. Inhibitory effect of the topical administration of a bisphosphonate (risedronate) on root resorption incident to orthodontic tooth movement in rats. *J Dent Res* 1996;75: 1644-1649.
132. Yaffe A, Golomb G, Breuer E, Binderman I. The effect of topical delivery of novel bisacylphosphonates in reducing alveolar bone loss in the rat model. *J Periodontol* 2000;71:1607-1612.
133. Cobb CM. Non-surgical pocket therapy: Mechanical. *Ann Periodontol* 1996;1:443-490.
134. Kornman KS, Crane A, Wang H-Y, et al. The interleukin-1 genotype as a severity factor in adult periodontal disease. *J Clin Periodontol* 1997;24:72-77.

ACKNOWLEDGMENTS

This paper was written by Dr. Richard J. Oringer. Members of the 2001-2002 Research, Science and Therapy Committee include Drs. Terry D. Rees, Chair; Timothy Blieden; Petros Damoulis; Joseph Fiorellini; William Giannobile; Gary Greenstein; Henry Greenwell; Vincent Iacono; Richard Nagy; Angelo Mariotti; Robert J. Genco, Consultant; Barry Wagenberg, Board Liaison.