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Future Treatment and Diagnostic Strategies for Periodontal Diseases

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Treatment of periodontal diseases has undergone a series of changes—perhaps not quite a revolution—over the past 20 years [1–6]. The goal of treatment has always been to regenerate lost periodontal tissues, but clinicians have had to "settle" for treatments that lead to disease cessation and healing if not outright regeneration. That said, there are newer treatment strategies that may become available over time that will allow clinicians to achieve limited or more robust regeneration of the periodontium. Because of the absence of reliable methods for regeneration, new approaches to disease control are also being pursued that will benefit those suffering chronic periodontal diseases [7,8]. In addition to novel therapeutics, there has been increasing focus on the development of more sensitive and specific diagnostic tests for periodontal diseases [9–11]. It is hoped that such tests will allow the clinician to determine whether a patient has active disease and what sort of attachment loss might be expected if the patient were not treated. In addition, by developing newer diagnostic tests, it will also be possible to focus therapy more on the disease process. Using collagenase levels as an example, if a diagnostic test shows this to be elevated [9], in addition to treating the microbial trigger, one might also attempt to regulate (reduce) collagenase levels or activity to prevent further tissue degradation.

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Periodontal disease diagnosis

Periodontal diseases are probably one of the most common bacterial infections in humans. It has become evident that only a few of the several hundred species of microorganisms within the gingival crevice and the periodontal pocket play a significant role in initiation and progression of the disease [10,12]. Thus, such pathogens at low levels should be considered as part of the normal oral flora. The notion of a "critical mass" of these periodontal pathogens has recently been introduced because of their presence in healthy gingival sites, albeit in low numbers [13]. The inflammatory and degradative processes associated with chronic periodontitis are likely induced by a critical mass of different pathogens, thereby leading to tissue destruction, possibly by way of three different pathways:

1. Pathogens may directly release proteolytic enzymes that degrade periodontal structures without the intervention of host cells.
2. Pathogens may elaborate products such as toxins, enzymes, and lipopolysaccharide that may trigger host cell populations to express degradative enzymes.
3. Pathogens may stimulate an immune response resulting in release of proinflammatory cytokines such as interleukin (IL)-1, IL-6, and tumor necrosis factor α [14].

The components of the periodontal tissue extracellular matrix, especially collagens, appear to be the main target of degradation in periodontal diseases. Among host proteases degrading the extracellular matrix, matrix metalloproteinases (MMPs) seem to be highly associated with tissue destruction and remodeling events in periodontal diseases.

Regarding the balance between pathogens and host responses, reliable diagnostic tests should focus on three main objectives:

1. Determine the presence and the proportions of pathogens in diseased sites or in susceptible patients.
2. Identify factors that indicate the first steps of disease activity in apparently healthy sites that may appear clinically normal.
3. Detect patients in whom the host response is unable to balance pathogen aggressiveness or diagnose the degree of genetic predisposition at an early age when periodontal destruction has not yet developed.

To achieve these goals, microbiologic testing, analysis of disease activity, and genetic analyses have been proposed to identify patients at increased risk for periodontal disease [15].

Microbiologic testing

Periodontal diseases are considered a mixed infection. It has never been possible to prove that specific bacteria directly cause periodontal disease

according to Koch's postulates. In consequence, the ideal that a single causative agent of the disease would be identified and a rapid chairside test would be used to assess the bacterial risk has never been reached.

To be considered true periodontal pathogens, bacteria should fulfill the following criteria [16]:

- They must occur at higher numbers in disease-active lesions compared with healthy or disease-inactive sites.
- Their elimination should lead to arrest of disease progression.
- They should express virulence factors relevant to the disease process.
- They should evoke a specific immune host response.
- They should be able to induce similar periodontal destruction in relevant animal models.

Several types of microbiologic tests have been developed and are available on the market.

First, it must be noted that the information generated by microbiologic analysis of a sample collected from a periodontal pocket is highly dependent on sampling technique. Two methods can be used to collect subgingival plaque samples: curettes and paper points. Both methods require careful removal of supragingival plaque to avoid contamination.

It has been shown that it is possible to remove 60% to 90% of the bacteria populating a diseased pocket with the use of a curette, whereas only about 6% to 41% of bacteria are sampled with the use of a paper point [17,18]. Moreover, with the latter method, it has been suggested that most of the sampled bacterial mass is from the outer layers of the subgingival biofilm; however, the inner layers may contain the more-pathogenic species [19].

The following microbiologic tests have been proposed:

Microscopic identification

This method is limited to the determination of the relative proportion of coccal and the more-pathogenic, filamentous-shaped bacteria [20]. This technique cannot be used to help in selection of an antimicrobial therapeutic agent if desired or to predict recurrence of the disease. In fact, bacteria thought to be periodontal pathogens cannot be identified or distinguished by microscopic assessment alone. The monitoring of plaque maturation does not give value over conventional clinical evaluation for the assessment of therapeutic efficacy; hence, as a chairside diagnostic system, the cost-to-benefit ratio is essentially negative.

Cultures

Bacterial culture is still considered the "gold standard" against which other microbiologic identification methods must be compared. It is a quantitative method and most cultivable microorganisms can be identified.

Nevertheless, the technique has limitations such as (1) the inability to detect noncultivable organisms such as spirochetes; (2) high cost; (3) the short time required for transportation to the culture laboratory before cells die and cannot be cultured (24–48 hours); and (4) a prolonged period before results are obtained.

Enzymatic assays

Although enzymatic assays permit detection of bacteria that possess trypsinlike enzymes, other pathogenic bacteria that do not produce such enzymes are not detected. Two tests have been developed: the BANA test (PerioScan; Oral B, Redwood, California) [21] and the PerioCheck test (Sunstar, Osaka, Japan) [22].

Both of these tests can be done at chairside and are interpreted or rated by the use of color intensity scores. For the BANA test, trypsinlike enzymes from *Tannerella forsythensis*, *Treponema denticola*, and *Porphyromonas gingivalis* hydrolyze the substrate *N*-benzoyl-DL-arginine-2-naphthylamide, thereby producing a blue-black color, the intensity of which is proportional to the total amount of the three bacteria [23,24].

The PerioCheck test differs from the BANA test in that a different substrate is used. Neither test can be used to distinguish between the relative proportions of the three bacteria and, of course, cannot identify the presence of other potential pathogens that do not produce trypsinlike enzymes.

Given these issues, their utility in diagnosis is limited due to a low reliability to predict clinical disease progression [22].

Immunoassays

Detection of immunoglobulin against bacterial antigens present in serum by the use of immunoassays (ELISA, agglutination assays, immunofluorescence) requires the development of polyclonal or monoclonal antibodies that recognize specific lymphocyte epitopes [25–28].

The advantages of immunoassays are (1) the detection of specific virulence factors of given bacteria; (2) the investigation of the specific role of protein (eg, cytolethal distending toxin CdT from *Actinobacillus actinomycetemcomitans*); and (3) their low cost for large-scale studies.

It is unfortunate that there are also the following disadvantages: (1) local sampling cannot be done, so site-specific disease parameters cannot be assessed; and (2) immunoassays cannot be used to determine bacterial virulence.

Nucleic acid probes

DNA extracts from samples of pocket-derived bacteria can be hybridized with so-called ‘‘anti-sense DNA probes’’ [29]. When these probes are also labeled with an enzyme such as alkaline phosphatase, they can be detected

using enzyme-staining assays, thus indicating the presence of DNA from specific bacteria. The probe sequences may be derived from (1) whole genomic DNA; (2) randomly cloned sequences of nucleic acids from target bacteria (greater risk of false-positive reactions than whole genomic probes); and (3) synthetic oligonucleotides that hybridize to 16S ribosomal RNA-DNA sequences that contain highly conserved and extreme heterogeneous sequences that make them ideal for distinction of species [30].

Nucleic acid probes have other interesting advantages including easy sampling and transport (viability of bacteria is not a requirement), rapid analysis, high sensitivity and specificity, and the ability to detect a wide spectrum of bacterial species including the detection of noncultivable organisms. Despite these strengths, currently available molecular techniques cannot be used to assess antibiotic sensitivity or bacterial virulence. To address this problem, however, a variation of standard molecular identification was suggested in 1994 by Socransky et al [31] who described "Checkerboard" DNA-DNA hybridization analysis that may permit some inferences as to pathogenicity.

Polymerase chain reaction

Polymerase chain reaction is a molecular biologic method that allows for high-yield replication of DNA. Therefore, it allows for the synthesis of a vast number of copies of even the smallest samples of bacterial DNA [32]. A modification of the original polymerase chain reaction method, real-time polymerase chain reaction, permits not only detection of specific bacteria but also quantification. Polymerase chain reaction is generally considered reliable when used in combination with synthetic 16S ribosomal RNA probes, which are highly specific to given species.

Biosensors

Metabolites (eg, volatile sulfur compounds) from pathogenic bacteria can be detected by various physical methods [33,34]. Various pathogenic bacteria (*Treponema denticola, Porphyromonas gingivalis*, *Prevotella intermedia*, and *Tannerella forsythis*) can reduce sulphates, thereby producing significant levels S, HS, H_2S, and CH_3SH by degradation of serum proteins, cysteine, and methionine. A sulfide sensor, Perio 2000 (Diamond General Corp., Ann Arbor, Michigan) can measure levels of these compounds and report them as scores ranging from 0 to 5 in increments of 0.5. A score of 0 represents undetectable S ($<10^{-7}$ M sulfide), whereas a score of 5 represents a concentration of 10^{-2} M sulfide. This chairside technique can be used repeatedly on the same sites and produces results rapidly. This test, however, is nonspecific and only semiquantitative, and its usefulness is limited by the fact that not all pathogenic bacteria produce sulfides. Because the detectable species are highly pathogenic, however, the detection of high sulfide levels could indicate that this site is at higher risk of disease activity

and attendant attachment loss [34]. This indication could lead to earlier treatment and prevention of tissue loss. Furthermore, although it is conceivable that sulfide levels could be used to assess efficacy of treatment, this methodology still needs to be validated by clinical trials.

Currently, no single diagnostic approach can be used to provide enough information for the clinician to make a diagnosis that would necessarily be different from one derived from clinical assessment. Similarly, treatment decisions, apart from the need for adjunctive antibacterial therapy or perhaps MMP regulation (see later discussion), are not necessarily influenced by currently available testing methods. In this regard, the following questions remain unanswered:

1. Was a specific bacterial species present when the disease was initiated (is there a causal relationship)?
2. Were the bacteria present at the site after the disease occurred (is there an opportunistic relationship)?

Perhaps in the future, more attention should be paid to identification of common virulence factors (especially pathogen-associated molecular patterns) and how these virulence factors regulate the responses of different host cells like keratinocytes, Langerhans cells, dendritic cells, and macrophages [16].

Analysis of disease activity

Salivary and gingival crevicular fluid enzymes and other proteins have the potential to be useful markers of disease progression. Presently, more than 65 gingival crevicular fluid components have been examined and identified as potential markers of disease progression. These components fall into three general categories:

1. Host-derived enzymes such as MMPs and their inhibitors
2. Inflammatory mediators and host response modifiers such as cytokines
3. Tissue breakdown products such as glycosaminoglycans, osteonectin, osteopontin, and laminin

A major problem with measurement of enzymes is that it is often difficult to distinguish those associated with gingivitis and periodontitis sites from active and inactive disease sites. Enzymes like the collagenases (MMP-1, MMP-3, MMP-8, and MMP-13), elastase, and gelatinases (MMP-2 and MMP-9) may be significantly elevated in the presence of existing disease, but measurement of their levels to predict future destruction remains unclear (such as the test for aspartate aminotransferase [AST]) [35,36]. Hence, virtually all enzyme tests evaluated to date have demonstrated fairly high rates of false-positive findings (ie, although a test is ''positive,'' there may still not be any disease activity and therefore no disease progression). The same can be said about assays for inflammatory mediators.

The most promising gingival crevicular fluid markers of disease progression are probably host breakdown products (as opposed to the enzymes that breakdown host tissues). Among these products, chondroitin-4-sulfate (a cartilage- and bone-specific glycosaminoglycan) [37,38], pyridinoline cross-links of the carboxyterminal telopeptide of type I collagen, and RankL (receptor activator for NF-xB ligand) are potential markers of bone and connective tissue destruction [39,40].

Genetic analyses

The etiology of periodontal disease is multifactorial and thus influenced by genetics (ie, the host) and the environment [41]. With regard to genetics, studies have revealed that most forms of periodontal disease are likely associated with multiple modifying genes (the disease is said to be polygenic). For example, in Papillon-Lefèvre syndrome and in generalized forms of prepubertal periodontitis, Hart et al [42] identified and localized a modified gene on chromosome 11 that caused a decrease in cathepsin C activity. The same decrease in cathepsin C activity has been demonstrated in severe chronic periodontitis [43]. Other studies have focused on IL-1 gene polymorphism leading to the development of the periodontitis susceptibility trait test [44]. The periodontitis susceptibility trait test is the only genetic susceptibility test for severe periodontitis that is commercially available. The periodontitis susceptibility trait test evaluates the simultaneous occurrence of allele 2 at the IL-1A +4845 and IL-1B +3954 loci. A patient with allele 2 at both these loci is considered genotype positive and therefore more susceptible to develop severe periodontitis.

Although genetic tests might be used to identify a predisposition to disease (even before disease development) [45], treatment approaches and outcomes will still be influenced by environmental and behavioral factors whether or not the individual is genetically susceptible to periodontal disease. Moreover, genetic testing gives no information on disease activity or susceptibility.

Although great strides are being made with respect to the development of diagnostic tests, there remains a great need for well-designed long-term longitudinal investigations and controlled clinical treatment studies.

Periodontal diseases—novel therapeutics

Regenerative treatment

From a historical perspective, regeneration of periodontal tissues lost as a result of periodontitis has been an elusive goal despite the development of widely available regenerative surgical techniques. Such approaches have involved the use of bone grafts to replace lost bone; however, bone is but

one component of the connective tissues composing the periodontium. Inasmuch as bone loss has been considered one of the major sequelae of periodontitis and is the most striking radiographic feature of periodontally diseased tissues, the use of bone grafting treatments has been popular. Critical analyses of clinical, histologic, and radiographic data, however, suggest that although correction of bone defects can be demonstrated [46,47], the regeneration of a new attachment apparatus following bone grafting including new bone, cementum, and a functionally oriented periodontal ligament does not generally occur except at the very base of the periodontal defect. Because bone grafting has been shown to have limited effectiveness with respect to regeneration of lost periodontium, other approaches have been developed that ostensibly would exploit the biologic principles that describe cellular domains [48]. If specific cell types occupy specific domains to the exclusion of other cell types, then the creation of an environment that would preferentially select for cells that might regenerate the periodontal ligament would provide for reliable regenerative treatment outcomes. To accomplish this, investigators have developed an array of membrane technologies. These treatments require the insertion of a membrane over a periodontal defect to, in effect, "exclude" epithelial cells from the previously diseased root surface, thereby permitting upward migration of periodontal ligament cells or their precursors. A variety of membrane materials has been developed, including some that had to be removed from the surgically treated site weeks or months later and some that were resorbable and could be left in place. Initial reports regarding the use of these membranes (a technique called guided tissue regeneration) were positive, but over the longer-term, it became apparent that apart from the use of guided tissue regeneration to regenerate bone (called guided bone regeneration) about implants or in other osseous sites requiring augmentation, periodontal regeneration could still not be expected to occur reliably [47] (Zohar and Tenenbaum, submitted for publication, 2005).

Enamel matrix derivatives

Taking advantage of developmental biologic studies of the periodontal attachment apparatus, it was noted that before development of cementum and new periodontal ligament, enamel matrix proteins are deposited directly onto dentine surfaces [49,50]. This observation led investigators to hypothesize that enamel matrix proteins might play an important role in the signaling for and recruitment of cells required for production of a normal tooth attachment apparatus. This observation further led to the notion that if such proteins could be purified or otherwise harvested, then they might prove useful in regenerative therapy. In this regard, it was thought that by adding such proteins to a previously diseased or exposed tooth root surface, they might signal a recapitulation of the embryologic developmental sequence, leading to the creation of a new gomphosis. As

a result, there is now a growing body of evidence based on randomized controlled trials [4,51] that enamel matrix proteins can be used for limited regeneration of the periodontium. In addition, further studies have demonstrated that these proteins may prove useful in periodontal plastics and root coverage procedures, thereby reducing or eliminating the need for the harvesting of connective tissue [51,52]. As the mechanisms underlying enamel matrix derivative effects are understood more precisely, it is likely that other related extracts or even purified proteins will become a part of the routine armamentarium of periodontists in the future when regenerative therapy is required.

Bisphosphonates to inhibit bone loss

The bisphosphonates are a class of drugs related to pyrophosphate [53]. Unlike pyrophosphate, which can be degraded by alkaline phosphatase [54] and pyrophosphatase, the bisphosphonates are resistant to degradation and have a high affinity for mineralized tissue [55]. One of the most important uses of bisphosphonates relates to their ability to inhibit bone resorption, presumably by direct or indirect inhibition of osteoclast cell activity [53]. This property could prove useful in the development of future therapeutic approaches to the prevention of periodontal bone loss [53,56] and possibly bone-supported implants [57,58]. In addition, it has been shown that local application of bisphosphonates reduces the bone loss that occurs following periodontal flap surgery [59]. In addition, given their affinity for mineralized tissues such as bone, the bisphosphonates, when tagged with a radionuclide such as technetium 99m, can also be used for diagnostic purposes. In this regard, the bisphosphonates would "home" to areas of bone that are undergoing active remodeling. Hence, the bisphosphonates would target or be concentrated in areas in which periodontal bone loss is about to occur or in other areas with increased remodeling in which bone loss may occur. Radioactively tagged bisphosphonates can be detected using various radiologic imaging methods and can be localized to sites where bone loss may occur. In fact, in using these methods, it is possible to identify sites within the periodontium in which bone loss will occur even before radiographic changes have occurred. Thus, although not discussed in detail previously, it is possible that these drugs could prove useful in the future not only for prevention of bone loss but also (from a diagnostic perspective) to identify areas where bone loss may occur much earlier than might be possible radiographically [60].

Bisphosphonates may stimulate bone formation

In addition to their ability to inhibit bone formation, it is also known that at certain concentrations, bisphosphonates inhibit mineralization [61]. This particular effect was thought to be essentially deleterious, and in fact,

second- and third-generation bisphosphonates were developed to increase their ability to inhibit bone resorption so that they could be used in lower doses and not interfere with mineralization [62]. This approach has proved to be effective, particularly for management of osteoporosis [62]; however, recent studies have suggested that inhibition of mineralization might be useful so long as it is a transitory phenomenon. In relation to this, it has been demonstrated that bone matrix (osteoid) formation is inversely proportional to mineralization [63]. When mineralization is inhibited using the first-generation bisphosphonate etidronate (HEBP), osteoid formation has been shown to double in vivo and in vitro [56,61,64]. When the HEBP is continually present, more osteoid forms but is poorly mineralized. Alternatively, when HEBP treatment (in culture or in vivo) is stopped, the newly formed "excess" osteoid mineralizes and, as demonstrated in cell culture, the mineral is even more dense than control. This property of HEBP could be exploited to stimulate new bone formation in the periodontium and elsewhere. It could prove useful for acceleration of osseointegration about implants; however, the dosage regime in this model has not been clearly worked out. HEBP treatment has also been shown to induce the periodontal ligament to produce high levels of the bone protein bone sialoprotein and to induce the ligament to produce bone tissue. Thus, it is possible that judicious local application or systemic administration of HEBP or similar agents could prove useful for regeneration of lost bone in implant or other sites and for the acceleration of endosseous implant integration in the future.

Antimicrobial therapy

Local delivery systems

It has been well established that most forms of periodontitis are related to chronic infection with periodontal pathogens [15] (usually gram-negative anaerobic species [34]). As a result, there has been an extensive amount of investigation related to the development of effective antimicrobial regimes for treatment of chronic, refractory, or other forms or periodontitis. Indeed, double-blind placebo-controlled randomized trials have demonstrated that antimicrobial treatment is an extremely useful adjunct for treatment of periodontitis [10,65]. Before the advent of antimicrobial therapy, so-called "refractory periodontitis" (eg, periodontitis demonstrating a downhill or extreme downhill course [65a]) might constitute about 20% of all cases. This figure, however, is now in the 5% range because it has been shown that the previously difficult-to-treat cases, or cases that do not respond well to conventional periodontal treatments, can be managed or improved with the use of antimicrobials [57,66]. That said, the use of systemic antimicrobial medications to treat a local infection has drawbacks including, for example, gastrointestinal side effects such as pseudomembranous colitis, allergic reaction [67], superinfection with commensal organisms, or development of

resistant organisms. Therefore, there have been a number of attempts to develop locally delivered antimicrobials to infected periodontal pockets [57]. The antimicrobials have included metronidazole in an ointment form (Elyzol), chlorohexidine (Periochip), and doxycycline in a fiber form (Actisite) or in a polymeric delivery system (Atridox) [66]. These locally delivered antimicrobials, and in particular Atridox, have been demonstrated to be efficacious in the treatment of localized periodontal pockets. On average, Atridox, for example, seems to be equally as effective as scaling and root planing but is more difficult to administer for generalized disease than for treatment of localized defects. This type of drug delivery system should definitely be considered for treatment of refractory periodontal pockets, infected implant sites, and possibly even in surgical sites. This approach may be particularly useful in the future for treatment of recall patients who present with localized sites showing recurrent disease.

Photodynamic therapy

Although local delivery of an agent such as doxycycline can be useful, the use of self-polymerizing gels can be difficult when considering treatment of generalized periodontitis. Moreover, it has been demonstrated that full-mouth "decontamination" may lead to better short-term and possibly longer-term outcomes when managing periodontal diseases compared with staged decontamination approaches [68]. Agents delivered in gel or fiber form, however, cannot readily be delivered to periodontal pockets within the whole mouth and certainly cannot be used in the eradication of periodontal pathogens from nondental oral surfaces (eg, cheeks, tongue, and tonsil bed in addition to periodontal pockets). In addition, although the antimicrobials mentioned previously are delivered in high concentrations to minimize bacterial resistance, this does not preclude the possibility that resistant bacteria will be selected following treatment.

To address these problems, other approaches for antimicrobial therapy for periodontitis have been investigated, including an approach known as photodynamic therapy. Photodynamic therapy essentially involves the use of light-activated drugs to kill periodontal pathogens. This therapeutic tool was initially investigated for treatment of malignancy because chemotherapeutic drugs could be given to patients systemically in an essentially inert form and then activated by administering light (usually laser) at the site of a tumor, thereby killing tumor cells without making a patient ill from chemotherapy [69]. Photodynamic therapy has also been used successfully for the management of macular degeneration [70]. Recently, it has been demonstrated that toluidine blue, when activated by laser light, can be used to kill periodontal pathogens [71]. Hence, it was postulated that toluidine blue or other photoactivated drugs could be used to treat periodontitis, presumably by laser activating such chemicals after they have been instilled within periodontal pockets. The problem with this approach, however, is that it would be necessary to irradiate every single pocket following lavage

with the photoreactive agent, and full-mouth decontamination would be equally as difficult as suggested earlier for locally delivered antimicrobials [72].

Clinical trials focusing on the use of laser-activated drugs are underway for treatment of periodontitis. Future trials will likely take advantage of broad-spectrum light, thereby permitting more effective elimination of periodontal pathogenic bacteria that are resident in the oral cavity as a whole. This approach could lead to more robust treatment responses and would serve as a useful adjunct for management of periodontal infection in conjunction with conventional therapy. This treatment would also prove useful for periodontal maintenance, during periodontal surgery, and in periodontal management of infected endosseous implant surfaces.

Inhibition of matrix degradation

As discussed previously with respect to diagnostic tests, matrix degradation is a major hallmark and even a predictor of bone and periodontal attachment loss. Hence, there have been major efforts devoted to the development of treatment approaches that interfere with or completely block matrix degradation. The bisphosphonates, previously addressed in relation to their ability to inhibit bone resorption, do not inhibit destruction of connective tissue matrices, although the authors' laboratory has some evidence suggesting that HEBP might interfere with MMP activity [72a]. Most investigation in this area has focused on the use of tetracycline and its derivatives for prevention of connective tissue (even hard connective tissue) destruction mediated by MMPs. To this end, it has been suggested that given that MMPs are elevated in the presence of periodontitis, particularly in persons with diabetes mellitus, a major goal of therapy would be to reduce MMP activity. In addition to tetracycline's antimicrobial actions, it has the ability to inhibit MMP activity [57,73,74]. This nonantimicrobial action of MMP inhibition has also been demonstrated with the tetracycline derivative doxycycline [66]. When administered in doses that are nonantibacterial, doxycycline has been shown to prevent periodontal breakdown due to its ability to inhibit MMP enzyme activity [57]. Tetracycline's anti-colagenolytic activity has given rise to the development and use of Periostat (CollaGenex Pharmaceuticals, Inc., Newtown, Pennsylvania), a form of low-dose doxycycline for management of periodontitis. Low-dose doxycycline may prove useful in the management of refractory periodontal diseases or other forms of chronic periodontitis that for various reasons cannot be managed with conventional therapy. For instance, patients who are medically compromised and who cannot tolerate conventional in-office treatment could benefit from low-dose doxycycline. In the authors' experience, low-dose doxycycline has proved to be very helpful in management of periodontitis in a large hospital-based population of young and old patients. Despite its effectiveness, it does not appear that low-dose doxycycline would be a first-line choice of conventional periodontal

therapy, but it definitely shows promise in management of difficult-to-treat patients or difficult-to-manage forms of periodontitis. Furthermore, it is probable that drugs designed to inhibit MMP or other proteinase activity will be developed further to be more specific in targeting proteinases of interest (eg, MMP-8 in the case of periodontitis). It is possible that certain proteins or peptides related to decorin [75] will become therapeutic adjuncts. Decorin binds to collagen and may prevent its degradation, which could be an interesting approach to management of periodontal breakdown because in this case, MMP activity would not be inhibited, but the drug's effects would be through alteration of the substrates.

Management of periodontal diseases in smokers

It clearly has been demonstrated that individuals who smoke cigarettes are at greater risk for the development of periodontitis, have more severe periodontitis, and do not respond to treatment of periodontitis as well as those who do not smoke [8,10,76]. This finding was thought to be a lifestyle issue (eg, poor oral hygiene), but a number of studies have shown that compared with nonsmokers, smokers do not necessarily have more bacterial plaque and their plaque is not populated by more periodontal pathogens. Therefore, there must be constituents of cigarette smoke that trigger or act as cofactors to initiation and progression of periodontitis. For obvious reasons, nicotine has received much attention in the literature and, indeed, it has the ability to cause a number of changes in the immune system and in the vasculature that could lead to exacerbation of periodontal disease risk and severity [77–79]. In addition, there are hundreds of other potentially toxic compounds in cigarette smoke that likely damage periodontal tissues. The authors' research group has focused on a particular class of agents found in high levels in cigarette smoke and in the environment: aryl hydrocarbons [80]. The most prevalent aryl hydrocarbons in cigarette smoke are benzo-α-pyrene and dimethyl benzanthracene [81]. Benzo-α-pyrene in particular has been shown to directly inhibit osteoblast differentiation [80]. To carry out further studies, the authors used a prototypical aryl hydrocarbon (dioxin) to study the effects of these agents on bone tissues and bone cells. These studies confirmed that aryl hydrocarbons inhibit osteoblast differentiation and bone production. Moreover, they interfere with osteoclast cell formation (Tenenbaum et al, unpublished data), an action that leads to overall reductions in bone remodeling, which could exacerbate periodontal diseases. Moreover, the authors' laboratory demonstrated that the aryl hydrocarbon benzo-α-pyrene acts in a synergistic manner with lipopolysaccharide from one of the periodontal pathogens described earlier (*Porphyromonas gingivalis*) in blocking bone cell differentiation and function [80]. These deleterious effects were shown to be mediated through the aryl hydrocarbon receptor (a cytosolic receptor). Of importance, the authors identified an agent commonly found in red wine,

resveratrol, which is an aryl hydrocarbon receptor antagonist that inhibits the effects of aryl hydrocarbons. Hence, it may be possible in the future to use agents such as resveratrol or synthetic and more powerful analogs to ameliorate some of the effects of smoking on the periodontium and other tissues. Certainly, smoking cessation is the ultimate goal, but this has not proved to be as effective as its proponents would like. Thus, other approaches such as the inhibition of aryl hydrocarbon effects should be considered, especially because these agents are found in high levels within the environment, not only in cigarette smoke. It is with this in mind that a clinical trial focusing on the use of resveratrol to manage periodontitis in smokers is now underway.

Summary

It can be inferred from the foregoing that new technologies have been developed or are in development that could be used to enhance the ability to predict, diagnose, and treat periodontitis. Not all of these technologies will bear fruit; however, those that do will provide clinicians of the twenty-first century with more effective means of detection, prevention, and treatment of periodontitis than are currently available. Hence, periodontists and dentists will take on the role of physicians dedicated to the prevention and treatment of oral diseases and rely less on mechanical or nonbiologically based treatment modalities.

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