Position Paper

Periodontal Regeneration*

Untreated periodontal disease leads to tooth loss through destruction of the attachment apparatus and tooth-supporting structures. The goals of periodontal therapy include not only the arrest of periodontal disease progression, but also the regeneration of structures lost to disease where appropriate. Conventional surgical approaches (e.g., flap debridement) continue to offer time-tested and reliable methods to access root surfaces, reduce periodontal pockets, and attain improved periodontal form/architecture. However, these techniques offer only limited potential towards recovering tissues destroyed during earlier disease phases. Recently, surgical procedures aimed at greater and more predictable regeneration of periodontal tissues and functional attachment close to their original level have been developed, analyzed, and employed in clinical practice. This paper provides a review of the current understanding of the mechanisms, cells, and factors required for regeneration of the periodontium and of procedures used to restore periodontal tissues around natural teeth. Targeted audiences for this paper are periodontists and/or researchers with an interest in improving the predictability of regenerative procedures. This paper replaces the version published in 1993. *J Periodontol 2005;76:1601-1622.*

The regeneration of the tooth supporting structures which have been lost as a consequence of periodontal disease progression has been a somewhat elusive goal in periodontics. Although periodontal regeneration, i.e., the formation of new bone and new cementum with supportive periodontal ligament, is a possible objective of several periodontal therapeutic modalities, outcomes of such modalities are not always predictable. Despite conclusive evidence that some regeneration may occur following regenerative procedures,[1-3] complete regeneration may be an unrealistic goal for many situations due in part to the complexity of the biological events, factors, and cells underlying successful periodontal regeneration.

Currently, osseous grafting and guided tissue regeneration (GTR) are the two techniques with the most histologic documentation of periodontal regeneration.[4-6] Other regenerative therapies have also provided a promising potential for significantly improving clinical parameters and demonstrating substantial "fill" of treated defects. However, only limited histologic evidence of true regeneration has been demonstrated with the majority of these therapies. Therefore, future studies in these areas are certainly encouraged.

This informational paper describes the biological basis and clinical applicability of GTR in periodontics. Reviewed in this paper are: 1) cells and factors considered important for promoting periodontal regeneration; 2) results following the use of autogenous and allogenic bone grafts, guided tissue regeneration procedures, alloplastic (synthetic bone substitute) grafts, xenografts, and newly introduced materials; and 3) effects of root surface conditioning, e.g., demineralization, and flap management techniques on the results of regenerative therapies. Recommendations for future research directions aiming to improve the predictability and expand the arena of guided tissue regeneration procedures in periodontics will be suggested.

DEFINITIONS

Regeneration refers to the reproduction or reconstitution of a lost or injured part, in contrast to repair, which describes healing of a wound by tissue that does not fully restore the architecture or the function of the part.[7] Periodontal regeneration is defined histologically as regeneration of the tooth's supporting tissues, including alveolar bone, periodontal ligament, and cementum over a previously diseased root surface. New attachment is defined as the union of connective tissue or epithelium with a root surface that has been deprived of its original attachment apparatus. This new attachment may be epithelial adhesion and/or connective tissue adaptation or attachment and may include new cementum. It is to be distinguished from reattachment, which describes the reunion of epithelial and connective tissue with a root surface.[7]

Bone fill is defined as the clinical restoration of bone tissue in a treated periodontal defect. Bone fill does not address the presence or absence of histologic evidence of new connective tissue attachment or the formation of new periodontal ligament.[7] The term open probing clinical attachment has, therefore, been used to describe the tissue seen at reentry surgery after regeneration procedures.[8] However, this term has not been commonly

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used since the clinical attachment cannot be probed in the open environment. Guided tissue regeneration (GTR) describes procedures attempting to regenerate lost periodontal structures through differential tissue responses. It typically refers to regeneration of periodontal attachment.[7] Barrier techniques, using materials such as expanded polytetrafluoroethylene (ePTFE), polyglactin, polylactic acid, calcium sulfate, and collagen, are employed in the hope of excluding epithelium and the gingival corium from the root in the belief that they interfere with regeneration.[7]

BIOLOGIC FOUNDATION

Conventional periodontal surgical treatment modalities (surgical debridement and resective procedures) have been established as effective means of treating periodontal disease and arresting its progression.[9-14] Isolated reports of some regeneration of bone and the tooth supporting structures after conventional therapeutic modalities have been described.[15-19] These methods typically heal by repair, with a combination of connective tissue adhesion/attachment or formation of a long junctional epithelium.[20-22]

Regenerative periodontal therapy attempts to restore lost periodontal structures and functional attachment through the regeneration of cementum, periodontal ligament, and alveolar bone. In 1976, Melcher presented the concept of "compartmentalization," in which the connective tissues of the periodontium were divided into four compartments: the lamina propria of the gingiva (gingival corium), the periodontal ligament (PDL), the cementum, and the alveolar bone.[23] The principle of GTR was based on the exclusion of gingival connective tissue cells from the wound and prevention of epithelial downgrowth. These procedures allow cells with regenerative potential (periodontal ligament [PDL], bone cells, and possibly cementoblasts) entry into the wound site first.

Early attempts to achieve regeneration included the interdental denudation/infrabony technique,[17] the use of free gingival grafts to cover the surgical site,[24] and coronally advanced flap.[25-27] GTR procedures were then developed in which barrier membranes were used to accomplish the objectives of epithelial exclusion via controlled cell/tissue repopulation of the periodontal wound, space maintenance, and clot stabilization.[6,28,29] This section will discuss the wound healing principles and the available data regarding the origin of cells involved in periodontal regeneration.

Wound Healing Principles

Although many of the cellular and molecular events in the healing of periodontal wounds are similar to those seen elsewhere in the body, differences complicating the periodontal healing process do exist.[30] Animal research has confirmed that periodontal surgical wounds go through the same sequence of healing events as all incisional wounds, with the formation of a fibrin clot between the flap margin and the root surface, followed by replacement of this fibrin clot by a connective tissue matrix attached to the root surface.[31,32] Data also suggest that when this "fibrin linkage" is maintained, a new connective tissue attachment to the root surface develops. If the fibrin linkage is disrupted, a long junctional epithelium type attachment results.[33]

It has been suggested that these regenerative failures may result when the tensile strength of the fibrin clot is exceeded, resulting in a tear.[33] Mobility of the flap (wound margin) positioned directly adjacent to the potential regenerative site may be a potential cause of this tear.[34] On the other hand, healing of periodontal surgical wounds has been suggested to differ from other wounds due to several unique features.[35] Factors such as the presence of multiple, specialized cell types and attachment complexes, stromal-cellular interactions, diverse microbial flora, and avascular tooth surfaces complicate the process of periodontal regeneration.[35,36] Better understanding of these special factors involved in the periodontal wound healing process should allow for more predictable treatment outcomes following GTR procedures.

Origin of Regenerative Cells

In an effort to determine the origin of regenerative cells involved in GTR procedures, early studies transplanted disease-affected roots into the bone[37] or bone and gingival connective tissue.[38] These studies examined the response of these tissues to regenerative attempts. Neither bone nor gingival connective tissue induced the formation of new connective tissue attachment on the transplanted roots. Instead, root resorption and ankylosis were observed. The researchers, therefore, suggested that bone and connective tissue cells lacked the potential for regeneration.[37,38] However, later studies have reported that bone and gingival connective tissue cells may also contribute to the regenerative process.[39-44]

Although significant progress has been made toward understanding the factors and cells involved in the regeneration of the periodontium, the function and the relative contribution of periodontal ligament cells, osteoblasts, root surface cells, and paravascular cells in the regenerative environment is still not entirely understood. Some studies suggest that PDL cells have

the capacity to function as osteoblasts or cementoblasts under regenerative conditions.[45-50] Other data provide evidence that PDL cells may function as regulators/inhibitors of mineral formation and thus prevent ankylosis under regenerative conditions.[48,51-55] Some reports suggest that the PDL contains distinct subpopulations of cells that may either inhibit or promote formation of mineralized tissues.[48,55-58]

In fact, some in vivo and in vitro studies support a role for osteoblasts and not PDL cells in induction of cementum-like material.[23,45,46,59] Others report that PDL cells in vivo and in vitro exhibit limited osteoblastic properties.[36,51,56] In contrast to these studies, other researchers[46,60] identified a PDL cell population expressing classical osteoblast features. Current explanations for such differences include the heterogeneous nature of PDL cells, variations in design of in vitro studies, and loss of specific PDL cell characteristics in vitro. Current understanding seems to suggest that the origin of regenerative cells may be attributed to both bone and PDL cells, with the majority of evidence favoring PDL cells as the major source.[61]

BONE REPLACEMENT GRAFTS

Bone replacement grafts, such as autografts, allografts, xenografts, and alloplasts, remain among the most widely used therapeutic strategies for the correction of periodontal osseous defects.[62] The results from this systematic review[62] indicate that bone replacement grafts provide demonstrable clinical improvements in periodontal osseous defects compared to surgical debridement alone. With respect to the treatment of intrabony defects, the results of meta-analysis support the following conclusion: bone grafts increase bone level, reduce crestal bone loss, increase clinical attachment level, and reduce probing pocket depths when compared to open flap debridement procedures.[62] However, the value of bone grafts on the correction of furcation defects remains to be determined. Nonetheless, outcome from 15 controlled human clinical studies showed positive clinical benefits when grafts were used in the treatment of Class II furcation defects.[62]

Autogenous Bone Grafts, Extra- and Intraoral Donor Sites

Autogenous bone grafts of both extra- and intraoral sources have been used in periodontal therapy due to their osteogenic potential. Autogenous iliac cancellous bone with marrow has been shown in several case reports to demonstrate successful bone fill after being used in furcations, dehiscences, and intraosseous defects of various morphologies.[63-66] One extensive series of case reports showed a mean bone fill of 3.3 to 3.6 mm in intraosseous defects and a 2.5 mm increase in crestal bone height.[66] Histologic evaluation of treated sites, where a reference notch was placed at the alveolar crest, demonstrated some supracrestal bone apposition and was strongly suggestive of limited periodontal regeneration.[63]

Iliac grafts have been used either fresh or frozen. Root resorption may be a complication following use of fresh grafts.[63,67,68] Case reports indicate bone fill and some regeneration may occur following use of grafts of iliac autogenous cancellous bone with marrow.[63-66] However, the difficulties in obtaining the graft material and the possibility of root resorption with fresh grafts have limited their use in clinical practice.

Intraoral cancellous bone with marrow grafts is usually obtained from the maxillary tuberosity or a healing extraction site. Case reports from clinical treatments, including a large number of intraosseous defects grafted with intraoral bone, have demonstrated bone fill equal to that obtained with iliac grafts.[69-74] A mean bone fill of 3.4 mm, which predictably filled greater than 50% of the initial defect, was reported.[71,74] Data from a controlled study indicated a more modest bone fill of 1.2 mm in defects treated with autogenous intraoral grafts.[73] Other case reports have shown bone fill following use of cortical bone chips[72] and osseous coagulum or bone blend type grafts.[69,70]

Histologic evaluations of autogenous intraoral grafts come from case reports.[69-72,75-79] Authors have presented histologic evidence of regeneration and new connective tissue attachment following these procedures.[72,76-78] Others have reported the presence of a long junctional epithelium between the regenerated alveolar bone and the root surface in histologic studies of healing following grafting procedures.[80,81] The evidence suggests that clinically present bone fill is not necessarily a reliable prediction of histologic regeneration of a periodontal attachment apparatus following regenerative procedures.

Allogenic Bone Grafts

There are several types of bone allografts available from commercial tissue banks. These include iliac cancellous bone and marrow, freeze-dried bone allografts, and decalcified freeze-dried bone allografts. The role of allogenic bone grafts in periodontal regeneration has been recently reviewed in another Academy position paper[82] and a systematic review by Reynolds et al.[62] Hence, only a limited discussion of these materials will be included in this section.

Controlled clinical trials indicate bone fill ranging from 1.3 to 2.6 mm when freeze-dried bone allografts (FDBA) were used to treat periodontal defects.[83-85] Combining freeze-dried bone allografts with tetracycline has also shown promise in treating intraosseous defects resulting from juvenile periodontitis.[86,87] Human trials using cortical demineralized freeze-dried bone allografts (DFDBA) have demonstrated bone fill similar to that achieved with FDBA, ranging from 1.7 to 2.9 mm.[85,88-90] A recently published systematic review indicated that significant, consistently superior gains in bone fill with DFDBA compared to open flap debridement procedures.[62]

Controlled human histologic studies with this material, using root notches into existing calculus as the histologic reference point, have demonstrated periodontal regeneration. Regeneration achieved with the grafts was significantly more than that in non-grafted controls.[2,5] Grafts using decalcified freeze-dried cancellous bone[91] have shown less bone fill (mean 1.4 mm). This variation may reflect differences in the amount of bone-inductive proteins in the two tissues,[92-94] or it may reflect differences in study protocols. Although studies have demonstrated that different preparation of allograft material, both from one distributor and between distributors may have different biological activity,[95-100] DFDBA remains a viable treatment modality for attempts to regenerate the periodontal attachment apparatus.[82] Stricter standards from bone banks in evaluating the potency of their preparations, including the possibility of using bones from individuals under a specific age and/or free of bone diseases[101] and/or using fresh bone and developing assays that can test the inductive capacity of the material prior to sales,[98] may lead to more consistent and reliable clinical results.[82] Specific molecules with osteogenic activity have been identified. Increased research has been done on delivery systems for these molecules and on the potential for viral transmission. Research has also been done on variability in biological activity associated with human bone. These developments have resulted in an increased focus on developing regenerative therapies using recombinant osteogenic factors in appropriate delivery systems.

Alloplasts

An alloplast is a synthetic graft or inert foreign body implanted into tissue.[7] Presently, six basic types of alloplastic materials are commercially available: nonporous hydroxyapatite (HA), hydroxyapatite cement, porous hydroxyapatite (replamineform), beta tricalcium phosphate, PMMA and HEMA polymer (a calcium layered polymer of polymethylmethacrylate and hydroxyethylmethacrylate), and bioactive glass. It has been reported that porous and non-porous HA materials and PMMA and HEMA polymer are nonresorbable while tricalcium phosphate and bioactive glass are bioabsorbable.

In controlled clinical trials using both non-porous and porous materials as grafts, the grafted sites have shown significant clinical improvement compared to non-grafted controls.[102-04] The magnitude of defect closure ranged from 1.6 to 3.5 mm for grafted sites and 0.5 to 0.7 mm for non-grafted sites. A 5-year follow-up of non-porous hydroxyapatite-implanted intraosseous sites indicated continued clinical stability.[105] Case reports also indicate that defect closure is possible following grafts of tricalcium phosphate.[106,107] Defects grafted with PMMA and HEMA polymer have also shown significant clinical improvements when compared to non-grafted controls.[108,109] This group of bone grafts appears to yield a significant treatment effect; however, this effect was inconsistent across studies.[62]

While clinical results of using alloplast grafts to treat periodontal disease appear promising, histologically the grafts tend to be encapsulated by connective tissue with minimal or no bone formation.[106,110,111] Some histologic studies have demonstrated limited new bone in close approximation to the implant material[110,112] or alongside or within porous graft particles.[113] A single histologic case report suggested that some regeneration may be possible with porous HA grafts.[114] There is also some histologic evidence that a very limited amount of regeneration may be possible following PMMA and HEMA polymer grafts.[115] However, at present, it appears that alloplastic materials function as a non-irritating filler. Comparisons between bone allografts and alloplasts suggest that they produce similar clinical results.[116,117] In a recent systematic review paper, it was concluded that particulate bone allograft and bovine HA produced similar clinical outcomes.[62]

Also included as a bone substitute is the so-called bioactive glass.[118,119] This material is made from calcium salts, phosphate, sodium salts, and silicon. The addition of silicon allows for the formation of a silica gel layer over the bioactive glass particles. This layer promotes formation of a hydroxycarbonate-apatite layer onto which osteoblasts are said to proliferate and form bone.[120]

Clinical studies evaluating bioactive glass particles have reported mixed results.[118,119,121-124] While significantly greater improvements in clinical parameters compared to open flap debridement alone were reported

in some studies,[118,125] no additional benefit from the use of this material was found in another study.[119] Similar clinical results have also been reported after the use of bioactive glass when compared to DFDBA[121] and ePTFE membranes.[124] However, histologic evaluation of treated teeth indicated limited regenerative potential for these materials, with minimal bone regeneration and no signs of new cementum or periodontal ligament.[126] Future studies in this area are certainly needed to better understand how these materials work histologically.

Xenografts

Other types of bone substitutes used for grafting around periodontal defects include xenogenic materials. A xenograft (heterograft) is a graft taken from a donor of another species.[7] These grafting materials are also referred to as anorganic bone, since proprietary processes are suggested to remove all cells and proteinaceous material, leaving behind an inert absorbable bone scaffolding upon which revascularization, osteoblast migration, and woven bone formation supposedly occur.[127] There is very little human clinical data supporting the use of these materials for managing periodontal defects.[128-131]

Similar improvements in clinical parameters in intrabony defects to those treated with DFDBA were reported in one study.[131] Recent studies that used the combination of bovine HA and collagen membrane for the treatment of intrabony defects have demonstrated positive clinical outcomes (e.g., reduction in probing depth and gain in clinical attachment level).[132-134] Human histologic studies have also reported signs of periodontal regeneration in teeth treated with a bovine-derived xenograft.[128,134] For these materials, however, there is more evidence supporting bone fill or repair of bone for guided bone regeneration around implants, sinus lift procedures, and ridge augmentation.[135-141] In addition, resorption of these materials has been reported to occur very slowly, thereby possibly leading to protracted sequestration of the graft particles.[127]

Concerns over the risk of transmission of prion-mediated diseases from bovine-derived products have arisen.[142] Prions are pathogenic agents with novel modes of replication and transmission involved in bovine spongioform encephalopathy (BSE) and its related form transmitted to humans, Creutzfeldt-Jakob disease.[143] However, prions have not been reported to be found in bone, and the World Health Organization has labeled bone as Type IV (no transmission) for prion diseases.[144,145] In addition, risk analysis estimates of the possibility of transmission of BSE from bovine-derived bone graft substitutes have reported such risks to be negligible to nonexistent.[142,146] It must be recognized, though, that prions have long incubation periods ranging from 5 years in BSE in cows to more than 10 years in Creutzfeldt-Jakob disease in humans.[147]

GUIDED CELL REPOPULATION/GUIDED TISSUE REGENERATION

Guided tissue regeneration is consistently more effective than open flap debridement in the gain of clinical attachment and probing depth reduction in the treatment of intrabony and furcation defects.[148] No substantial differences were detected among barrier types, but barrier types could explain some inconsistent results.[148]

Research Support

It was suggested that cells that repopulate the root surface after periodontal surgery will determine the type of attachment that forms on the root surface during healing.[23] From this hypothesis came the development of procedures using barrier membranes to allow selective cellular repopulation of the root surface during periodontal regenerative attempts. In theory, these barriers retard apical migration of epithelium and exclude gingival connective tissue from the healing wound. In this manner, they favor healing influenced primarily from cells within the PDL space, including the cementum, perivascular environment, and adjacent alveolar bone. An early animal study[149] reported that it was possible to achieve, by mechanical means, new connective tissue attachment with newly formed cementum on roots deprived of cementum. This study suggested that cells originating from the PDL had the potential to form new cementum with investing principal fibers.[149]

Several barrier materials have been used in GTR studies, including both non-resorbable and bioabsorbable membranes. Early studies used a millipore filter[6] and an ePTFE membrane.[8,150,151] Rubber dam material has also shown effectiveness in limited case reports.[152,153] The fact that non-resorbable membranes require a second surgical procedure for removal led to studies using biodegradable membranes[84,154] and autogenous connective tissue grafts as membranes.[155]

Evidence continues to grow that there are a number of different materials that can effectively function as barrier membranes. Absorbable collagen barriers have proven to achieve better probing depth reduction, clinical attachment level (CAL) gain, and defect fill than open flap debridement and were equally successful

in comparative studies with non-resorbable membranes.[156-161] Polylactic acid membranes have shown success in case reports and clinical trials both in intraosseous and Class II furcation defects.[162-170] Continued research should result in a number of materials that can be effectively used in GTR procedures.

Non-Resorbable Membranes

Results using ePTFE to treat intraosseous defects show substantial bone fill averaging approximately 3.0 to 5.0 mm either with or without augmentation with graft materials.[150,151,171] However, results have been reported to vary depending on the type of defect treated, with 3-wall defects responding best.[151,172,173] Interestingly, a study comparing sites treated with an ePTFE membrane plus DFDBA versus allograft alone showed no significant differences between groups.[174] Additionally, a literature review of clinical studies evaluating the use of DFDBA in combination with barrier membranes has questioned the value of adding bone graft materials for this type of defect.[175]

When ePTFE membranes were used in controlled clinical trials treating mandibular Class II furcation defects, significant clinical improvement has been noted. However, only one study reported complete clinical closures.[176] Results using the ePTFE membrane augmented with decalcified FDBA[177] or composite grafts of autogenous intraoral grafts and tricalcium phosphate and/or DFDBA[178] have generally showed more bone fill on reentry. However, a later study showed no differences between grafted versus non-grafted sites.[179] Again, the majority of the defects were still considered "open" on reentry.[176-178] Unlike intrabony defects, treatment of furcation defects with a combination of GTR barriers and bone replacement grafts appears to produce greater clinical improvements than GTR alone.[180] Treatment of maxillary Class II furcation defects and mandibular Class III defects with similar membranes demonstrated clinical improvements as well, but of a more modest and unpredictable degree.[8,181-184]

Bioabsorbable Membranes

Non-resorbable membranes require a second surgical procedure with possible patient discomfort and membrane exposure, leading to bacterial colonization.[185-187] These factors have led to the development and utilization of various absorbable membranes for GTR procedures. Evaluations of both polylactic acid[166,167,188,189] and collagen membranes[156,157,161] have reported clinical improvements similar to those achieved with non-resorbable membranes.

Collagen membranes have been shown in animal studies and human clinical trials to be as effective as other GTR membranes in inhibiting epithelial migration and in promoting new connective tissue attachment.[158,160,190] Collagen is the predominant protein in alveolar bone and periodontal connective tissues. Some of the positive properties of collagen when used for GTR procedures include its hemostatic function through its ability to aggregate platelets. This feature may facilitate early clot formation and wound stabilization, both of which are considered essential for successful regeneration.[191] In addition, collagen possesses a chemotactic function for fibroblasts, which may aid in cell migration to promote primary wound closure, an essential component for successful GTR outcomes.[192] Several collagen-based barrier materials have recently been used for GTR procedures with promising clinical results.[158,160,190,193] As is the case with non-resorbable membranes, the addition of bone replacement grafts when utilizing bioabsorbable collagen membranes appears to improve the clinical results in furcation, but not intrabony, defects.[158,193]

In most studies, degradable polymers of polyglactic acid (PLA), polyglycolic acid (PGA), or mixtures of both PLA and PGA have also shown comparable clinical results to other materials, including ePTFE.[162,194-200] Some histologic studies of these barriers have also demonstrated evidence of regeneration of periodontal tissues.[164,170,201,202] Recently reported uses have also included the treatment of recession defects with favorable clinical results.[203-206] Despite differences in the mechanisms of membrane degradation, a study comparing a PLA/PGA copolymer to a type I collagen membrane in the treatment of intrabony defects has reported similar clinical improvements with the use of both membranes.[207]

Other Materials

A wide varities of other bioabsorbable materials have been used in GTR therapy. These include, but are not limited to, freeze-dried dura mater allografts, oxidized cellulose, alkali cellulose, and calcium sulfate. Mixed results have been reported when these materials were used in attempts to repair/regenerate periodontal defects.[26,208-212] However, it is very difficult to critically evaluate these materials as relatively little controlled research has been conducted and most of the supporting literature is in the form of case reports.

Nonetheless, a recent clinical study[212] compared the clinical efficacy of a combination of calcium sulfate dihydrate, as a binder and barrier, and DFDBA to ePTFE and DFDBA for the treatment of intrabony

defects. Results from this study indicate that calcium sulfate, when used as a binder and barrier in combination with DFDBA in intrabony defects, led to significant clinical improvement, as evidenced by reduction in probing depth, gains in clinical attachment level, and defect fill and resolution.[212] Future controlled clinical studies are needed to determine the true effects of these materials with greater certainty.

Clinical Applications

Barrier membranes have been utilized for the treatment of furcations, intrabony defects, and, more recently, for the correction of marginal tissue recession defects and for guided bone regeneration procedures.

A recent meta-analysis systematic review[148] suggested the following conclusions: 1) in the treatment of intrabony defects, GTR procedures, as compared with open flap debridement controls, resulted in significantly more favorable gains in CAL and PD reduction; 2) in the treatment of furction defects, GTR procedures, as compared with open flap debridement controls, resulted in significantly more favorable gains in vertical probing attachment level, reductions in vertical probing depth, and improvement in horizontal open probing attachment measurements; 3) in the treatment of intrabony defects, meta-analysis did not show any statistically significant superior results among barrier types evaluated; 4) in the treatment of furcation defects, type of barrier employed did affect the surrogate variable of vertical probing attachment level, since vertical probing attachment level was enhanced only with the use of ePTFE and polymeric barriers; 5) the use of augmentation materials in addition to a physical barrier enhances the regeneration outcome in the treatment of furcation defects treated with GTR; and 6) there is no advantage to the use of augmentation materials in addition to physical barrier in the treatment of intrabony defects. For GTR-based root coverage, a report showed 76.4% (±11.3%) root coverage with 100% root coverage at 33.1% (±20.4%) of the study sites.[213] Although both approaches (conventional and GTR-based root coverage) proved to be beneficial in achieving root coverage, connective tissue grafting techniques appear to have an advantage over GTR-based root coverage approaches, especially in areas with thin gingiva or minimal zone of keratinized gingiva.[213]

Furcation defects. Several studies have evaluated the use of GTR techniques in the treatment of furcation defects. Most studies reported favorable results in Class II mandibular furcations.[148,160,176,214-216] Less favorable results were found in mandibular and maxillary Class III defects[8,217,218] and maxillary Class II defects.[183,219] An early study[216] showed complete defect closure in 67% of Class II defects and 25% of Class III defects in the group receiving ePTFE membrane treatment. The results, however, have not been reproduced in other studies. Indeed, in a later publication, the same group[217] reported that none of the studied maxillary Class III defects achieved complete closure.

To determine the closure frequency of Class II furcation defects, a review of 50 papers was performed (1,016 furcation defects treated by various regenerative techniques: bone replacement grafts, coronally positioned flaps, guided tissue regeneration barriers, and open flap debridement).[180] General improvement in clinical furcation status was reported only about 50% of the time, with complete furcation closure in only 20% of furcation defects and partial defect fill (a change from Class II to Class I) in an additional 33% of cases. The most favorable results were reported using a combination of GTR and bone replacement grafts (91% overall improvement), while the least favorable results were found with open flap debridement (15% overall improvement). The authors concluded that if furcation closure is the primary goal of therapy, regenerative techniques do not appear to commonly meet that goal.

This conclusion is further supported by a recent meta-analysis systematic review paper.[148] Briefly, vertical probing attachment level was significantly enhanced by the addition of a particulate bone graft. As a subgroup, ePTFE plus bone graft resulted in a significantly greater gain in vertical probing attachment level compared to ePTFE alone. However, polymeric or cellulose barrier treatment were not enhanced by the use of a graft.[148] The results of these and other studies[8,148,160,176,216-219] have mainly limited the clinical applicability of GTR procedures for furcation defects to mandibular and some maxillary buccal Class II furcation defects.

Intrabony defects. Most studies have shown significantly greater probing depth reduction, CAL gain, and bone fill in membrane (either bioabsorbable or nonresorbable) treated groups than open debridement controls.[148,158,159,171,172,220-224] In reviewing studies presented during the last 20 years on the surgical treatment of intrabony defects,[175] the authors analyzed treatment results of open flap debridement, bone replacement grafts (BRG), and GTR and found CAL gain (1.5, 2.1, and 4.2 mm) and bone fill (1.1, 2.2, and 3.2 mm) for each treatment group, respectively. No difference was found between bioabsorbable and

non-resorbable barriers. However, it is important to mention that all treatments seem to leave a residual intrabony defect. Nonetheless, the shallowest remaining defects, around 1.5 mm, were found following GTR. These findings seem to suggest that GTR is an effective treatment modality for the management of intrabony defects. Seven studies examined the effect of the addition of an augmentation material under the physical barrier.[158,174,225-229] Five of these used DFDBA as their graft material. Meta-analysis of these results did not reveal any difference in clinical attachment gain when comparing GTR versus GTR plus bone graft.[148] This analysis suggests that additional usage of bone graft in a well-contained infrabony defect during GTR treatment may be unnecessary. Nonetheless, both procedures (GTR or GTR plus bone grafts) are proven effective in treating periodontal infrabony defects.

Gingival recession defects. GTR techniques have more recently been attempted for the treatment of marginal tissue recession defects with promising clinical and histological results. These include significant improvements in probing depths and clinical attachment levels and evidence of regeneration of a new periodontal attachment apparatus (bone, cementum, and periodontal ligament).[230-233] Clinical trials comparing GTR-based procedures with free gingival grafts and subepithelial connective tissue grafts have reported similar clinical results.[206,234,235] Nonetheless, GTR-based procedures often resulted in less root coverage as well as less predictability.

In summary, data from available resources indicate that GTR-based procedures are clinically effective in promoting root coverage.[213,236] In addition, using a barrier may also enhance more clinical attachment gain.[233,237] A recent case report and clinical study also indicated that DFDBA added as a space maintainer together with collagen membrane resulted in better root coverage.[238,239] It should also be noted that with the GTR-based procedure, adequate flap thickness (≥0.8 mm in the defect area) seems to have a great influence in improving the percent root coverage (26.7% versus 95.9% root coverage in thin and thick tissue, respectively).[203-206,240] Hence, careful case selection is crucial for the success of this procedure.

Factors Influencing Results/Limitations

Several studies have demonstrated the importance of patient selection, plaque control, and anti-infective therapy in achieving consistently positive results with GTR procedures. Favorable clinical results have been most often observed in healthy, non-smoking patients demonstrating good plaque control and compliance with recommended oral hygiene measures.[61] The effects of bacterial contamination have been noted in a study reporting an inverse relationship between observed plaque contamination of retrieved membranes and clinical attachment gain.[241] Colonization of membranes with black pigmented species[242] and the presence of bacteria in samples treated with regenerative procedures correlates with a diminished healing response.[243,244] However, a recent report indicates that membrane exposure had only a minimal effect on GTR results around natural teeth.[245] Other factors reported to influence the healing response include the patient's oral hygiene level[243] and smoking status.[246,247]

Defect-specific factors include the number of bony walls and the depth of the intrabony component, with 3-wall defects[151,172,173] and those ≥4 mm[175] achieving the best results. Gingival tissue thickness has also been linked to reduced clinical outcomes in GTR, including GTR-based root coverage procedures, with thin tissues achieving significantly less clinical improvements and percentages of root coverage.[206,248] Identification of these and other influencing factors should lead to more predictable treatment outcomes following GTR procedures through better patient and defect selection.

Overall, factors that may limit regenerative healing after GTR surgery can be categorized into barrier-independent (e.g., poor plaque control, smoking, occlusal trauma, suboptimal tissue health, mechanical habits that interfere with healing, inadequate overlying keratinized tissue and tissue thickness, improper surgical technique, premature plaque colonization and early mechanical insult, and loss of wound stability) and barrier-dependent (e.g., inadequate root-barrier seal, non-sterile technique, instability of the membrane, and premature membrane exposure/loss).[61] Most important among these are presence of a smoking habit, poor plaque control, and premature exposure of the barrier.

Coronally Positioned (Advanced) Flaps

Human clinical trials using flap management techniques designed to enhance clot protection and wound stability have been reported.[249] As a structure rich in osteoprogenitor cells, the periosteum has long been viewed as having regenerative potential.[26,250,251] This phenomenon is thought to result from a combination of the cellular activity of the periosteum and a barrier-type effect by the repositioned periosteum. Coronally positioned flaps have been used to treat mandibular Class II furcation defects. This procedure positions the flap margin away from the critical healing area (the furcation site) and secures it in that position during early healing time points.[252]

Reentry results from three studies[25-27] indicated an approximate mean 50% to 65%, by volume, bone fill in Class II mandibular furcation defects. Twenty-two of 46 furcation defects assessed for bone closure after reentries were judged closed. Thus, the horizontal portion of the furcation defect was closed via bone fill. While this approach shows promise, it appears necessary to test a larger number of patients with a longer follow-up period to fully evaluate the efficacy of this technique.

It is interesting to note that, before reentry, the large majority of these "closed" defects demonstrated residual furcation involvement clinically. A study comparing results following treatment of Class II furcation defects with coronally positioned flaps versus PTFE membranes showed no significant differences in clinical results.[249] Histologic results following treatment of supracrestal periodontal defects with this procedure have demonstrated new formation of connective tissue attachment with some periodontal regeneration.[253] When coronally positioned flaps were used to treat mandibular Class III furcations, improvements in probing depths and probing attachment levels were reported. However, at the conclusion of these studies, treated furcations were still routinely classified as Class III defects.[181,254]

Root Surface Conditioning

Root surface demineralization, usually with citric acid,[255,256] has been used as a part of regenerative procedures. This technique was originally suggested because of the ability of citric acid to modify the root surface by "detoxifying" the surface[257] and exposing collagen fibrils within the cementum or dentin matrix.[258] Some animal studies demonstrated substantial new connective tissue attachment following citric acid demineralization.[31,259,260] However, a favorable response was not universal.[261] Histologic evaluation in some human clinical trials demonstrated new connective tissue attachment and some regeneration following citric acid demineralization.[262,263]

Results from clinical trials indicate no additional improvement in clinical conditions when citric acid treatment is used in conjunction with surgical procedures, either without[25,263,264] or in combination with osseous grafts[73] or GTR techniques.[151,263] Attempts to combine root surface demineralization and fibronectin to induce a more significant regenerative response have shown promise during in vitro experimentation.[265] More recent studies[266,267] indicate that the use of materials with a less acidic pH, e.g., EDTA, may also expose collagen fibers, thus promoting cell attachment, without having a damaging effect on the surrounding tissues. However, when used in humans, this technique did not provide significant clinical improvements.[268] This conclusion is further confirmed by a recent meta-analysis systematic review which stated the use of citric acid, tetracycline, or EDTA to modify the root surface provides no benefit of clinical significance to regeneration in patients with chronic periodontitis.[269]

In summary, human trials with root surface demineralization have yet to show significant clinical improvement when compared to non-demineralized controls. Histologic evidence seems to suggest that new connective tissue attachment and limited regeneration may result from root surface demineralization. However, this histologic healing pattern does not result in significant improvement in clinical conditions beyond non-demineralized control sites. Conditioning of root surfaces appropriately is likely to be important for enhancing predictability of regenerative therapies. Research focused on identifying factors that can detoxify roots and also influence appropriate cell attachment is needed to identify appropriate root conditioning therapies.

MATRIX PROTEINS/GROWTH FACTORS

Periodontal research using growth factors and bone morphogenetic proteins (BMPs) to expand the amount of predictable regeneration is in the early stages of development. BMPs have been shown to possess unique properties for inducing ectopic bone formation[93] and new cementum formation.[270] While there is a large body of published clinical and histologic data for animal trials, the same is lacking for human trials.

The first human trials of the use of osteogenin combined with DFDBA were reported in 1991.[271] Results of the study indicated that osteogenin combined with DFDBA significantly enhanced regeneration of a new attachment apparatus in a submerged environment. These results were in agreement with several animal research studies reporting improved regenerative results when these molecules (e.g., BMP-2, BMP-7) are employed in treating periodontal defects.[270,272-276] A concern for a higher incidence of ankylosis has been noted in animal studies. One study indicated that 15 of 17 dogs had ankylosis following BMP-2 treatment.[270] However, this phenomenon has not been observed in sites treated with BMP-7.[276] Additional human clinical and histologic reports are needed to more fully elucidate the potential value and applicability of these agents in periodontal regeneration.

Other growth factors, mainly acting as a mitogen or differential factor on regenerating periodontal tissues,

include: transforming growth factor-β (TGF-β), platelet-derived growth factor (PDGF), insulin-like growth factor (IGF), and fibroblast growth factor (FGF). Human clinical data regarding the use of recombinant PDGF and IGF have been published.[277] When these molecules were added to periodontal intraosseous defects or furcations, mixed results were seen. In this study, the materials appear to work best in furcations, with bone fill of about 42% nine months after surgery.[277]

The delivery system for growth factors may play a role in regenerative response. Of particular interest are surface area, surface properties for cell-surface interactions, inflammatory and immune reactions, and degradation kinetics. Reported delivery systems are collagen as a sponge, membrane, or gel and gelatin with varying degrees of cross-linking.[272,278,279] Bone and cementum formation occur in different time spans in animal models. This factor has to be considered during the drug delivery. The degradation kinetics of bioabsorbable carriers seem to influence the type of new tissue formation. A fast degradation and fast release of BMP-2 induced bone formation to a greater extent, whereas cementum formation was significantly greater with the slow degrading and slow releasing BMP gelatin carrier.[272,279] Whether these findings apply to humans in an inflamed environment is unknown.

Since limited human clinical data are available, more studies will be needed to fully evaluate the potential of growth factors for enhancing periodontal regeneration. This interesting and promising area of research is detailed in another Academy position paper, The Potential Role of Growth and Differentiation Factors in Periodontal Regeneration.[280]

Other Materials

Enamel matrix derivative (EMD) has been approved by the U.S. Food and Drug Administration for use in achieving periodontal regeneration in angular bony defects.[281-285] EMD is a group of enamel matrix proteins isolated from developing porcine teeth.[286-295] Crude enamel matrix is removed from the developing teeth and the proteins are extracted and purified yielding a material which, when analyzed, yields three major groups of enamel matrix proteins at 20, 13, and 5kD molecular weight.[296-304] The freeze-dried protein extract is solubilized in a propylene glycol alginate carrier solution and applied to debrided, root-conditioned periodontal intrabony defects.[305-315]

Histologic evidence of periodontal regeneration has been shown in a human dehiscence model after application of enamel matrix derivative.[285] However, human case reports have reported inconsistent histologic evidence of regeneration.[316-318] An examination of two specimens followed up to 12 months failed to show evidence of new attachment formation.[316] However, others have reported that periodontal regeneration was possible after the use of EMD, but on an inconsistent basis.[319-323] In a 10-patient case series, evidence of regeneration was seen in three specimens, while new attachment (connective tissue attachment/adhesion only) was seen in three specimens, and the remaining four specimens exhibited healing with a long junctional epithelium.[317] These results may be supported by the findings of a recent in vivo study that reported that EMD was not an osteoinductive material, but rather an osteoconductive one.[324]

Most human clinical trials and case series of EMD have demonstrated significant improvements in probing measurements and radiographic evidence of bone fill.[325-327] A recent systematic review has concluded that there is evidence supporting the use of EMD for periodontal osseous defects to improve CAL and reduce PD, although long-term benefits have not been established.[328] In a randomized, placebo-controlled, split-mouth trial design, 1- and 2-walled defects treated with enamel matrix derivative were compared to defects treated with a vehicle placebo over 3 years.[282] At the end of the trial, statistically significant ($P<0.01$) reductions in probing depth (3.1 mm for test versus 2.3 mm for control) and attachment gain (2.2 mm for test versus 1.7 mm for control) were seen.

In regard to radiographic evidence of bone gain at 3 years post-treatment, the mean gain for enamel matrix derivative-treated sites was 2.7 mm, or 36% of the initial bone loss, compared to unchanged bone levels on the control sites.[282] The value of radiographic evidence of bone gain at 36 months in the test sites was equal to a mean 66% radiographic bone fill of the original defects treated.[282] On the other hand, a recent case series reported that the positive clinical results obtained from the use of EMD in intrabony defects in 21 patients were not confirmed by the radiographic results obtained from standardized, computerized radiographs after 12 months of healing and did not reveal significant improvements.[316] Similar results were also found at 36 months.[322] In vitro studies have shown the positive effect of EMD on proliferation of periodontal ligament cells, gingival fibroblasts, and cementoblasts.[329-332] Consequently, EMD was applied to promote wound healing in a placebo-controlled, randomized study.[333] EMD or a vehicle control were applied topically after root and soft tissue instrumentation. EMD-treated sites had less inflammation, less bleeding on probing, and less post-treatment discomfort. It appears that EMD

offers some potential for regenerative therapy around natural teeth and represents a novel method for enhancing regeneration outcomes. However, additional studies are needed to more thoroughly evaluate the mechanism of action and regenerative potential and to determine the long-term benefit of these agents when used for periodontal regenerative therapy.

Another material recently introduced as a possible biologic modulator for enhancing wound healing and periodontal regeneration is a putative collagen-binding peptide utilizing a combination of an anorganic bovine-derived hydroxyapatite matrix (ABM) and a synthetic clone of the 15 amino acid sequence of type I collagen (P-15).[334] P-15 is a collagen-derived cell-binding peptide that is reported to attract and bind fibroblasts and osteoblasts and promote PDL fibroblast attachment to the ABM carrier.[335-337] Limited human clinical trials have reported significantly greater hard tissue response (percent defect fill) for intrabony defects with the use of ABM/P-15 compared to open flap debridement or DFDBA[334] or ABM alone.[338-340] One human histologic evaluation showed evidence of regeneration (new cementum, bone, and periodontal ligament), although graft particles were still present at 6 months.[340] However, additional clinical and histologic data are needed to more clearly establish the potential value of this material in periodontal regenerative procedures.

CONCLUSION

The goals of periodontal therapy include the reduction or elimination of tissue inflammation induced by bacterial plaque and its by-products, correction of defects or anatomical problems caused by the disease process, and regeneration of lost periodontal tissues as a consequence of disease destruction. While continuing efforts seek to further our understanding of periodontal regeneration biology, we can also expect developments in biologic and materials sciences, providing new guided tissue regenerative materials and delivery systems. Most importantly, establishing a scientifically sound, evidence-based rationale is critical to the ultimate success of regenerative therapies.

Bone replacement grafts (e.g., autografts and allografts) have resulted in substantial bone fill as evidenced by many case studies and reports.[62-66,68] Controlled clinical trials,[83-85] however, have demonstrated more modest success. There is adequate clinical and histologic evidence of bone fill and periodontal regeneration to recommend the use of bone replacement grafts in clinical practice. Hence, these grafts are recommended for the treatment of infrabony as well as furcation defects.

Guided tissue regeneration employs barriers, nonresorbable or bioabsorbable, to control the cell and tissue repopulation of the periodontal wound. It has value as a regenerative procedure, particularly in 3-wall intrabony and gingival recession defects. This procedure has shown favorable, although less predictable, results in treating Class II furcation defects, particularly those involving mandibular teeth.[148,156-161,190,214-216] The clinical and histologic evidence of bone fill, tissue coverage and limited periodontal regeneration using GTR is convincing.[148] This procedure can thus be recommended for use in clinical practice (e.g., for the treatment of infrabony, furcation, and recession defects).

Flap management techniques (e.g., coronally advanced flap) to enhance wound stability during early healing have demonstrated substantial bone fill in mandibular Class II furcations and limited clinical improvement in mandibular Class III furcations.[25-27,81,252,254] Clinical studies using these techniques to treat other types of periodontal defects have not been reported.

Alloplasts (synthetic bone substitutes) and xenografts (animal-derived bone substitutes) function primarily as biocompatible space fillers. Use of these materials produces clinical results similar to other bone replacement grafts or guided tissue regeneration procedures,[102-109] although little if any periodontal regeneration can be expected with their use.[106,110,111]

Root surface modification using demineralization to promote new attachment has shown variably favorable results that are not reliably reproducible in humans.[261,263,268] Hence, the value of this approach in clinical practice remains limited.

Growth factors and proteins have shown promising results in pre-clinical trials,[90,270] although limited human clinical data[280,328] and long-term follow-up[280,316] are available. Additional studies are needed to establish clinical efficacy and long-term stability before this treatment is recommended as a routine clinical procedure.

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REFERENCES

1. Consensus report. Periodontal regeneration around natural teeth. *Ann Periodontol* 1996;1:667-670.

2. Bowers GM, Chadroff B, Carnevale R, et al. Histologic evaluation of new attachment apparatus formation in humans. Part I. *J Periodontol* 1989;60:664-674.
3. Cole RT, Crigger M, Bogle G, Egelberg J, Selvig KA. Connective tissue regeneration to periodontally diseased teeth. A histological study. *J Periodontal Res* 1980;15:1-9.
4. Bowers GM, Chadroff B, Carnevale R, et al. Histologic evaluation of new attachment apparatus formation in humans. Part III. *J Periodontol* 1989;60:683-693.
5. Bowers GM, Chadroff B, Carnevale R, et al. Histologic evaluation of new attachment apparatus formation in humans. Part II. *J Periodontol* 1989;60:675-682.
6. Nyman S, Lindhe J, Karring T, Rylander H. New attachment following surgical treatment of human periodontal disease. *J Clin Periodontol* 1982;9:290-296.
7. American Academy of Periodontology. *Glossary of Periodontal Terms*. Chicago: American Academy of Periodontology; 2001.
8. Becker W, Becker BE, Berg L, Prichard J, Caffesse R, Rosenberg E. New attachment after treatment with root isolation procedures: Report for treated Class III and Class II furcations and vertical osseous defects. *Int J Periodontics Restorative Dent* 1988;8(3):8-23.
9. Becker W, Becker BE, Ochsenbein C, et al. A longitudinal study comparing scaling, osseous surgery and modified Widman procedures. Results after one year. *J Periodontol* 1988;59:351-365.
10. Hill RW, Ramfjord SP, Morrison EC, et al. Four types of periodontal treatment compared over two years. *J Periodontol* 1981;52:655-662.
11. Kaldahl WB, Kalkwarf KL, Patil KD, Molvar MP, Dyer JK. Long-term evaluation of periodontal therapy: I. Response to 4 therapeutic modalities. *J Periodontol* 1996;67:93-102.
12. Lindhe J, Westfelt E, Nyman S, Socransky SS, Heijl L, Bratthall G. Healing following surgical/non-surgical treatment of periodontal disease. A clinical study. *J Clin Periodontol* 1982;9:115-128.
13. Pihlstrom BL, McHugh RB, Oliphant TH, Ortiz-Campos C. Comparison of surgical and nonsurgical treatment of periodontal disease. A review of current studies and additional results after 6-1/2 years. *J Clin Periodontol* 1983;10:524-541.
14. Ramfjord SP, Caffesse RG, Morrison EC, et al. Four modalities of periodontal treatment compared over five years. *J Periodontal Res* 1987;22:222-223.
15. Beube F. A radiographic and histologic study on reattachment. *J Periodontol* 1952;23:158-164.
16. Polson AM, Heijl LC. Osseous repair in infrabony periodontal defects. *J Clin Periodontol* 1978;5:13-23.
17. Prichard J. The infrabony technique as a predictable procedure. *J Periodontol* 1957;28:202-216.
18. Stewart H. Partial removal of cementum and decalcification of a tooth in the treatment of pyorrhea alveolaris. *Dent Cosmos* 1899;41:617-626.
19. Stillman PDC. The management of pyorrhea. *Dent Cosmos* 1917;59:405-414. Reply 632-633.
20. Caton J, Zander HA. Osseous repair of an infrabony pocket without new attachment of connective tissue. *J Clin Periodontol* 1976;3:54-58.
21. Caton J, Nyman S. Histometric evaluation of periodontal surgery. I. The modified Widman flap procedure. *J Clin Periodontol* 1980;7:212-223.
22. Caton J, Nyman S, Zander H. Histometric evaluation of periodontal surgery. II. Connective tissue attachment levels after four regenerative procedures. *J Clin Periodontol* 1980;7:224-231.
23. Melcher AH. On the repair potential of periodontal tissues. *J Periodontol* 1976;47:256-260.
24. Ellegaard B, Karring T, Löe H. New periodontal attachment procedure based on retardation of epithelial migration. *J Clin Periodontol* 1974;1:75-88.
25. Fuentes P, Garrett S, Nilveus R, Egelberg J. Treatment of periodontal furcation defects. Coronally positioned flap with or without citric acid root conditioning in Class II defects. *J Clin Periodontol* 1993;20:425-430.
26. Gantes B, Martin M, Garrett S, Egelberg J. Treatment of periodontal furcation defects. II. Bone regeneration in mandibular Class II defects. *J Clin Periodontol* 1988;15:232-239.
27. Garrett S, Martin M, Egelberg J. Treatment of periodontal furcation defects. Coronally positioned flaps versus dura mater membranes in Class II defects. *J Clin Periodontol* 1990;17:179-185.
28. Caton JG, DeFuria EL, Polson AM, Nyman S. Periodontal regeneration via selective cell repopulation. *J Periodontol* 1987;58:546-552.
29. Nyman S, Gottlow J, Lindhe J, Karring T, Wennström J. New attachment formation by guided tissue regeneration. *J Periodontal Res* 1987;22:252-254.
30. Aukhil I. Biology of wound healing. *Periodontol 2000* 2000;22:44-50.
31. Polson AM, Proye MP. Fibrin linkage: A precursor for new attachment. *J Periodontol* 1983;54:141-147.
32. Wikesjö UM, Crigger M, Nilveus R, Selvig KA. Early healing events at the dentin-connective tissue interface. Light and transmission electron microscopy observations. *J Periodontol* 1991;62:5-14.
33. Wikesjö UM, Nilveus RE, Selvig KA. Significance of early healing events on periodontal repair: A review. *J Periodontol* 1992;63:158-165.
34. Egelberg J. Regeneration and repair of periodontal tissues. *J Periodontal Res* 1987;22:233-242.
35. McCulloch CA. Basic considerations in periodontal wound healing to achieve regeneration. *Periodontol 2000* 1993;1:16-25.
36. Pitaru S, McCulloch CA, Narayanan SA. Cellular origins and differentiation control mechanisms during periodontal development and wound healing. *J Periodontal Res* 1994;29:81-94.
37. Karring T, Nyman S, Lindhe J. Healing following implantation of periodontitis-affected roots into bone tissue. *J Clin Periodontol* 1980;7:96-105.
38. Nyman S, Karring T, Lindhe J, Planten S. Healing following implantation of periodontitis-affected roots into gingival connective tissue. *J Clin Periodontol* 1980;7:394-401.
39. Aukhil I, Iglhaut J. Periodontal ligament cell kinetics following experimental regenerative procedures. *J Clin Periodontol* 1988;15:374-382.
40. Aukhil I, Iglhaut J, Suggs C, Schaberg TV, Mandalinich D. An in vivo model to study migration of cells and orientation of connective tissue fibers in simulated periodontal spaces. *J Periodontal Res* 1985;20:392-402.

41. Aukhil I, Pettersson E, Suggs C. Guided tissue regeneration. An experimental procedure in beagle dogs. *J Periodontol* 1986;57:727-734.
42. Aukhil I, Simpson DM, Schaberg TV. An experimental study of new attachment procedure in beagle dogs. *J Periodontal Res* 1983;18:643-654.
43. Bowers GM, Donahue J. A technique for submerging vital roots with associated intrabony defects. *Int J Periodontics Restorative Dent* 1988;8(6):34-51.
44. Iglhaut J, Aukhil I, Simpson DM, Johnston MC, Koch G. Progenitor cell kinetics during guided tissue regeneration in experimental periodontal wounds. *J Periodontal Res* 1988;23:107-117.
45. Gould TR, Melcher AH, Brunette DM. Location of progenitor cells in periodontal ligament of mouse molar stimulated by wounding. *Anat Rec* 1977;188:133-141.
46. Lin WL, McCulloch CA, Cho MI. Differentiation of periodontal ligament fibroblasts into osteoblasts during socket healing after tooth extraction in the rat. *Anat Rec* 1994;240:492-506.
47. Mariotti A, Cochran DL. Characterization of fibroblasts derived from human periodontal ligament and gingiva. *J Periodontol* 1990;61:103-111.
48. Melcher AH. Repair of wounds in the periodontium of the rat. Influence of periodontal ligament on osteogenesis. *Arch Oral Biol* 1970;15:1183-1204.
49. Nojima N, Kobayashi M, Shionome M, Takahashi N, Suda T, Hasegawa K. Fibroblastic cells derived from bovine periodontal ligaments have the phenotypes of osteoblasts. *J Periodontal Res* 1990;25:179-185.
50. Piche JE, Carnes DL Jr, Graves DT. Initial characterization of cells derived from human periodontia. *J Dent Res* 1989;68:761-767.
51. Lang H, Schuler N, Arnhold S, Nolden R, Mertens T. Formation of differentiated tissues in vivo by periodontal cell populations cultured in vitro. *J Dent Res* 1995;74:1219-1225.
52. MacNeil RL, Berry JE, Strayhorn CL, Shigeyama Y, Somerman MJ. Expression of type I and XII collagen during development of the periodontal ligament in the mouse. *Arch Oral Biol* 1998;43:779-787.
53. McCulloch CA, Nemeth E, Lowenberg B, Melcher AH. Paravascular cells in endosteal spaces of alveolar bone contribute to periodontal ligament cell populations. *Anat Rec* 1987;219:233-242.
54. Melcher AH, McCulloch CA, Cheong T, Nemeth E, Shiga A. Cells from bone synthesize cementum-like and bone-like tissue in vitro and may migrate into periodontal ligament in vivo. *J Periodontal Res* 1987;22:246-247.
55. Ogiso B, Hughes FJ, Melcher AH, McCulloch CA. Fibroblasts inhibit mineralised bone nodule formation by rat bone marrow stromal cells in vitro. *J Cell Physiol* 1991;146:442-450.
56. Nohutcu RM, Somerman MJ, McCauley LK. Dexamethasone enhances the effects of parathyroid hormone on human periodontal ligament cells in vitro. *Calcif Tissue Int* 1995;56:571-577.
57. Saito S, Rosol TJ, Saito M, Ngan PW, Shanfeld J, Davidovitch Z. Bone-resorbing activity and prostaglandin E produced by human periodontal ligament cells in vitro. *J Bone Miner Res* 1990;5:1013-1018.
58. Giniger MS, Norton L, Sousa S, Lorenzo JA, Bronner F. A human periodontal ligament fibroblast clone releases a bone resorption inhibition factor in vitro. *J Dent Res* 1991;70:99-101.
59. Boyko GA, Melcher AH, Brunette DM. Formation of new periodontal ligament by periodontal ligament cells implanted in vivo after culture in vitro. A preliminary study of transplanted roots in the dog. *J Periodontal Res* 1981;16:73-88.
60. Ramakrishnan PR, Lin WL, Sodek J, Cho MI. Synthesis of noncollagenous extracellular matrix proteins during development of mineralized nodules by rat periodontal ligament cells in vitro. *Calcif Tissue Int* 1995;57:52-59.
61. Wang HL, MacNeil RL. Guided tissue regeneration. Absorbable barriers. *Dent Clin North Am* 1998;42:505-522.
62. Reynolds MA, Aichelmann-Reidy ME, Branch-Mays GL, Gunsolley JC. The efficacy of bone replacement grafts in the treatment of periodontal osseous defects. A systematic review. *Ann Periodontol* 2003;8:227-265.
63. Dragoo MR, Sullivan HC. A clinical and histological evaluation of autogenous iliac bone grafts in humans. I. Wound healing 2 to 8 months. *J Periodontol* 1973;44:599-613.
64. Schallhorn RG. Eradication of bifurcation defects utilizing frozen autogenous hip marrow implants. *J Ont Dent Assoc* 1968;45:18-22.
65. Schallhorn RG. The use of autogenous hip marrow biopsy implants for bony crater defects. *J Periodontol* 1968;39:145-147.
66. Schallhorn RG, Hiatt WH, Boyce W. Iliac transplants in periodontal therapy. *J Periodontol* 1970;41:566-580.
67. Burnette EW Jr. Fate of an iliac crest graft. *J Periodontol* 1972;43:88-90.
68. Schallhorn RG, Hiatt WH. Human allografts of iliac cancellous bone and marrow in periodontal osseous defects. II. Clinical observations. *J Periodontol* 1972;43:67-81.
69. Froum SJ, Ortiz M, Witkin RT, Thaler R, Scopp IW, Stahl SS. Osseous autografts. III. Comparison of osseous coagulum-bone blend implants with open curetage. *J Periodontol* 1976;47:287-294.
70. Froum SJ, Thaler R, Scopp IW, Stahl SS. Osseous autografts. II. Histological responses to osseous coagulum-bone blend grafts. *J Periodontol* 1975;46:656-661.
71. Hiatt WH, Schallhorn RG. Intraoral transplants of cancellous bone and marrow in periodontal lesions. *J Periodontol* 1973;44:194-208.
72. Nabers C, O'Leary T. Autogenous bone transplants in the treatment of osseous defects. *J Periodontol* 1965:36:5-14.
73. Renvert S, Garrett S, Schallhorn RG, Egelberg J. Healing after treatment of periodontal intraosseous defects. III. Effect of osseous grafting and citric acid conditioning. *J Clin Periodontol* 1985;12:441-455.
74. Rosenberg MM. Free osseous tissue autografts as a predictable procedure. *J Periodontol* 1971;42:195-209.
75. Froum SJ, Thaler R, Scopp IW, Stahl SS. Osseous autografts. I. Clinical responses to bone blend or hip marrow grafts. *J Periodontol* 1975;46:515-521.
76. Haggerty PC, Maeda I. Autogenous bone grafts: A revolution in the treatment of vertical bone defects. *J Periodontol* 1971;42:626-641.

77. Hawley CE, Miller J. A histologic examination of a free osseous autograft. Case report. *J Periodontol* 1975;46: 289-293.
78. Hiatt WH, Schallhorn RG, Aaronian AJ. The induction of new bone and cementum formation. IV. Microscopic examination of the periodontium following human bone and marrow allograft, autograft and nongraft periodontal regenerative procedures. *J Periodontol* 1978;49:495-512.
79. Nabers CL, O'Leary TJ. Autogenous bone grafts: Case report. *Periodontics* 1967;5:251-253.
80. Listgarten MA, Rosenberg MM. Histological study of repair following new attachment procedures in human periodontal lesions. *J Periodontol* 1979;50:333-344.
81. Moskow BS, Karsh F, Stein SD. Histological assessment of autogenous bone graft. A case report and critical evaluation. *J Periodontol* 1979;50:291-300.
82. American Academy of Periodontology. Tissue banking of bone allografts used in periodontal regeneration (position paper). *J Periodontol* 2001;72:834-838.
83. Altiere ET, Reeve CM, Sheridan PJ. Lyophilized bone allografts in periodontal intraosseous defects. *J Periodontol* 1979;50:510-519.
84. Blumenthal N, Steinberg J. The use of collagen membrane barriers in conjunction with combined demineralized bone-collagen gel implants in human infrabony defects. *J Periodontol* 1990;61:319-327.
85. Rummelhart JM, Mellonig JT, Gray JL, Towle HJ. A comparison of freeze-dried bone allograft and demineralized freeze-dried bone allograft in human periodontal osseous defects. *J Periodontol* 1989;60:655-663.
86. Evans GH, Yukna RA, Sepe WW, Mabry TW, Mayer ET. Effect of various graft materials with tetracycline in localized juvenile periodontitis. *J Periodontol* 1989;60:491-497.
87. Mabry TW, Yukna RA, Sepe WW. Freeze-dried bone allografts combined with tetracycline in the treatment of juvenile periodontitis. *J Periodontol* 1985;56:74-81.
88. Mellonig JT. Decalcified freeze-dried bone allograft as an implant material in human periodontal defects. *Int J Periodontics Restorative Dent* 1984;4(6):40-55.
89. Oreamuno S, Lekovic V, Kenney EB, Carranza FA Jr, Takei HH, Prokic B. Comparative clinical study of porous hydroxyapatite and decalcified freeze-dried bone in human periodontal defects. *J Periodontol* 1990;61:399-404.
90. Quintero G, Mellonig JT, Gambill VM, Pelleu GB Jr. A six-month clinical evaluation of decalcified freeze-dried bone allografts in periodontal osseous defects. *J Periodontol* 1982;53:726-730.
91. Pearson GE, Rosen S, Deporter DA. Preliminary observations on the usefulness of a decalcified, freeze-dried cancellous bone allograft material in periodontal surgery. *J Periodontol* 1981;52:55-59.
92. Urist MR, Iwata H. Preservation and biodegradation of the morphogenetic property of bone matrix. *J Theor Biol* 1973;38:155-167.
93. Urist MR. Bone: Formation by autoinduction. *Science* 1965;150:893-899.
94. Reddi AH, Huggins CB. Influence of geometry of transplanted tooth and bone on transformation of fibroblasts. *Proc Soc Exp Biol Med* 1973;143:634-637.
95. Becker W, Becker BE, Caffesse R. A comparison of demineralized freeze-dried bone and autologous bone to induce bone formation in human extraction sockets. *J Periodontol* 1994;65:1128-1133 (erratum 1995;66:309).
96. Becker W, Lynch SE, Lekholm U, et al. A comparison of ePTFE membranes alone or in combination with platelet-derived growth factors and insulin-like growth factor-I or demineralized freeze-dried bone in promoting bone formation around immediate extraction socket implants. *J Periodontol* 1992;63:929-940.
97. Becker W, Urist MR, Tucker LM, Becker BE, Ochsenbein C. Human demineralized freeze-dried bone: Inadequate induced bone formation in athymic mice. A preliminary report. *J Periodontol* 1995;66:822-828.
98. Schwartz Z, Mellonig JT, Carnes DL Jr, et al. Ability of commercial demineralized freeze-dried bone allograft to induce new bone formation. *J Periodontol* 1996;67: 918-926.
99. Shigeyama Y, D'Errico JA, Stone R, Somerman MJ. Commercially-prepared allograft material has biological activity in vitro. *J Periodontol* 1995;66:478-487.
100. Somerman MJ. Is there a role for DFDBA in periodontal regenerative therapy? (editorial) *J Periodontol* 1996;67: 946-948.
101. Schwartz Z, Somers A, Mellonig JT, et al. Ability of commercial demineralized freeze-dried bone allograft to induce new bone formation is dependent on donor age but not gender. *J Periodontol* 1998;69:470-478.
102. Meffert RM, Thomas JR, Hamilton KM, Brownstein CN. Hydroxylapatite as an alloplastic graft in the treatment of human periodontal osseous defects. *J Periodontol* 1985;56:63-73.
103. Yukna RA, Cassingham RJ, Caudill RF, et al. Six month evaluation of Calcitite (hydroxyapatite ceramic) in periodontal osseous defects. *Int J Periodontics Restorative Dent* 1986;6(3):34-45.
104. Yukna RA, Harrison BG, Caudill RF, Evans GH, Mayer ET, Miller S. Evaluation of durapatite ceramic as an alloplastic implant in periodontal osseous defects. II. Twelve month reentry results. *J Periodontol* 1985; 56:540-547.
105. Yukna RA, Mayer ET, Amos SM. 5-year evaluation of durapatite ceramic alloplastic implants in periodontal osseous defects. *J Periodontol* 1989;60:544-551.
106. Baldock WT, Hutchens LH Jr, McFall WT Jr, Simpson DM. An evaluation of tricalcium phosphate implants in human periodontal osseous defects of two patients. *J Periodontol* 1985;56:1-7.
107. Snyder AJ, Levin MP, Cutright DE. Alloplastic implants of tricalcium phosphate ceramic in human periodontal osseous defects. *J Periodontol* 1984;55:273-277.
108. Yukna RA. HTR polymer grafts in human periodontal osseous defects. I. 6-month clinical results. *J Periodontol* 1990;61:633-642.
109. Yukna RA. Clinical evaluation of HTR polymer bone replacement grafts in human mandibular Class II molar furcations. *J Periodontol* 1994;65:342-349.
110. Shepard WK, Bohat O, Joseph CE, LoPiccolo P, Bernick S. Human clinical and histological responses to a Calcitite implant in intraosseous lesions. *Int J Periodontics Restorative Dent* 1986;6(3):46-63.
111. Stahl SS, Froum S. Histological evaluation of human intraosseous healing responses to the placement of tricalcium phosphate ceramic implants. I. Three to eight months. *J Periodontol* 1986;57:211-217.
112. Sapkos SW. The use of Periograf in periodontal defects. Histologic findings. *J Periodontol* 1986;57:7-13.

113. Kenney EB, Lekovic V, Sa Ferreira JC, Han T, Dimitrijevic B, Carranza FA Jr. Bone formation within porous hydroxylapatite implants in human periodontal defects. *J Periodontol* 1986;57:76-83.
114. Carranza FA Jr, Kenney EB, Lekovic V, Talamante E, Valencia J, Dimitrijevic B. Histologic study of healing of human periodontal defects after placement of porous hydroxylapatite implants. *J Periodontol* 1987;58:682-688.
115. Stahl SS, Froum SJ, Tarnow D. Human clinical and histologic responses to the placement of HTR polymer particles in 11 intrabony lesions. *J Periodontol* 1990;61:269-274.
116. Barnett JD, Mellonig JT, Gray JL, Towle HJ. Comparison of freeze-dried bone allograft and porous hydroxylapatite in human periodontal defects. *J Periodontol* 1989;60:231-237.
117. Bowen JA, Mellonig JT, Gray JL, Towle HT. Comparison of decalcified freeze-dried bone allograft and porous particulate hydroxyapatite in human periodontal osseous defects. *J Periodontol* 1989;60:647-654.
118. Froum SJ, Weinberg MA, Tarnow D. Comparison of bioactive glass synthetic bone graft particles and open debridement in the treatment of human periodontal defects. A clinical study. *J Periodontol* 1998;69:698-709.
119. Ong MM, Eber RM, Korsnes MI, et al. Evaluation of a bioactive glass alloplast in treating periodontal intrabony defects. *J Periodontol* 1998;69:1346-1354.
120. Hench LL, Wilson J. Surface-active biomaterials. *Science* 1984;226:630-636.
121. Lovelace TB, Mellonig JT, Meffert RM, Jones AA, Nummikoski PV, Cochran DL. Clinical evaluation of bioactive glass in the treatment of periodontal osseous defects in humans. *J Periodontol* 1998;69:1027-1035.
122. Anderegg CR, Alexander DC, Freidman M. A bioactive glass particulate in the treatment of molar furcation invasions. *J Periodontol* 1999;70:384-387.
123. Hall EE, Meffert RM, Hermann JS, Mellonig JT, Cochran DL. Comparison of bioactive glass to demineralized freeze-dried bone allograft in the treatment of intrabony defects around implants in the canine mandible. *J Periodontol* 1999;70:526-535.
124. Yukna RA, Evans GH, Aichelmann-Reidy MB, Mayer ET. Clinical comparison of bioactive glass bone replacement graft material and expanded polytetrafluoroethylene barrier membrane in treating human mandibular molar Class II furcations. *J Periodontol* 2001;72:125-133.
125. Zamet JS, Darbar UR, Griffiths GS, et al. Particulate bioglass as a grafting material in the treatment of periodontal intrabony defects. *J Clin Periodontol* 1997;24:410-418.
126. Nevins ML, Camelo M, Nevins M, et al. Human histologic evaluation of bioactive ceramic in the treatment of periodontal osseous defects. *Int J Periodontics Restorative Dent* 2000;20:458-467.
127. Spector M. Anorganic bovine bone and ceramic analogs of bone mineral as implants to facilitate bone regeneration. *Clin Plast Surg* 1994;21:437-444.
128. Mellonig JT. Human histologic evaluation of a bovine-derived bone xenograft in the treatment of periodontal osseous defects. *Int J Periodontics Restorative Dent* 2000;20:19-29.
129. Older LB. The use of heterogenous bovine bone implants in the treatment of periodontal pockets. An experimental study in humans. *J Periodontol* 1967;38:539-549.
130. Pietruska MD. A comparative study on the use of Bio-Oss and enamel matrix derivative (Emdogain) in the treatment of periodontal bone defects. *Eur J Oral Sci* 2001;109:178-181.
131. Richardson CR, Mellonig JT, Brunsvold MA, McDonnell HT, Cochran DL. Clinical evaluation of Bio-Oss: A bovine-derived xenograft for the treatment of periodontal osseous defects in humans. *J Clin Periodontol* 1999;26:421-428.
132. Camelo M, Nevins M, Lynch S. Periodontal regeneration with an autogenerous bone-Bio-Oss composite graft and a Bio-Gide membrane. *Int J Periodontics Restorative Dent* 2001;21:109-119.
133. Paolantonio M, Scarano A, Di Placido G. Periodontal healing in humans using anorganic bovine bone and bovine peritoneum-derived collagen membrane: A clinical and histologic case report. *Int J Periodontics Restorative Dent* 2001;21:505-515.
134. Nevins M, Camelo M, Lynch S. Evaluation of periodontal regeneration following grafting intrabony defects treated with Bio-Oss collagen: A human histologic report. *Int J Periodontics Restorative Dent* 2003;23:9-17.
135. Hallman M, Lundgren S, Sennerby L. Histologic analysis of clinical biopsies taken 6 months and 3 years after maxillary sinus floor augmentation with 80% bovine hydroxyapatite and 20% autogenous bone mixed with fibrin glue. *Clin Implant Dent Relat Res* 2001;3:87-96.
136. Maiorana C, Santoro F, Rabagliati M, Salina S. Evaluation of the use of iliac cancellous bone and anorganic bovine bone in the reconstruction of the atrophic maxilla with titanium mesh: A clinical and histologic investigation. *Int J Oral Maxillofac Implants* 2001;16:427-432.
137. Yildirim M, Spiekermann H, Handt S, Edelhoff D. Maxillary sinus augmentation with the xenograft Bio-Oss and autogenous intraoral bone for qualitative improvement of the implant site: A histologic and histomorphometric clinical study in humans. *Int J Oral Maxillofac Implants* 2001;16:23-33.
138. Valentini P, Abensur D, Wenz B, Peetz M, Schenk R. Sinus grafting with porous bone mineral (Bio-Oss) for implant placement: A 5-year study on 15 patients. *Int J Periodontics Restorative Dent* 2000;20:245-253.
139. Maiorana C, Redemagni M, Rabagliati M, Salina S. Treatment of maxillary ridge resorption by sinus augmentation with iliac cancellous bone, anorganic bovine bone, and endosseous implants: A clinical and histologic report. *Int J Oral Maxillofac Implants* 2000;15:873-878.
140. Hurzeler MB, Quinones CR, Kirsch A, et al. Maxillary sinus augmentation using different grafting materials and dental implants in monkeys. Part I. Evaluation of anorganic bovine-derived bone matrix. *Clin Oral Implants Res* 1997;8:476-486.
141. Valentini P, Abensur D. Maxillary sinus floor elevation for implant placement with demineralized freeze-dried bone and bovine bone (Bio-Oss): A clinical study of

20 patients. *Int J Periodontics Restorative Dent* 1997;17: 232-241.
142. Sogal A, Tofe AJ. Risk assessment of bovine spongiform encephalopathy transmission through bone graft material derived from bovine bone used for dental applications. *J Periodontol* 1999;70:1053-1063.
143. Weihl CC, Roos RP. Creutzfeldt-Jakob disease, new variant Creutzfeldt-Jakob disease, and bovine spongiform encephalopathy. *Neurol Clin* 1999;17:835-859.
144. Human transmissible spongiform encephalopathies. *Can Commun Dis Rep* 1999;25:1-3,6-7.
145. Asher DM, Padilla AM, Pocchiari M. WHO consultation on diagnostic procedures for transmissible spongiform encephalopathies: Need for reference reagents and reference panels. Geneva, Switzerland, 22-23 March 1999. *Biologicals* 1999;27:265-272.
146. Wenz B, Oesch B, Horst M. Analysis of the risk of transmitting bovine spongiform encephalopathy through bone grafts derived from bovine bone. *Biomaterials* 2001;22:1599-1606.
147. Roos RP. Controlling new prion diseases. *N Engl J Med* 2001;344:1548-1551.
148. Murphy K, Gunsolley J. Guided tissue regeneration for the treatment of periodontal intrabony and furcation defects. A systematic review. *Ann Periodontol* 2003;8: 266-302.
149. Nyman S, Gottlow J, Karring T, Lindhe J. The regenerative potential of the periodontal ligament. An experimental study in the monkey. *J Clin Periodontol* 1982;9: 257-265.
150. Gottlow J, Nyman S, Karring T. Maintenance of new attachment gained through guided tissue regeneration. *J Clin Periodontol* 1992;19:315-317.
151. Handelsman M, Davarpanah M, Celletti R. Guided tissue regeneration with and without citric acid treatment in vertical osseous defects. *Int J Periodontics Restorative Dent* 1991;11:350-363.
152. Cortellini P, Prato GP. Guided tissue regeneration with a rubber dam: A five-case report. *Int J Periodontics Restorative Dent* 1994;14:8-15.
153. Salama H, Rigotti F, Gianserra R, Seibert J. The utilization of rubber dam as a barrier membrane for the simultaneous treatment of multiple periodontal defects by the biologic principle of guided tissue regeneration: Case reports. *Int J Periodontics Restorative Dent* 1994;14:16-33.
154. Schultz AJ, Gager AH. Guided tissue regeneration using an absorbable membrane (polyglactin 910) and osseous grafting. *Int J Periodontics Restorative Dent* 1990;10:8-17.
155. Lekovic V, Kenney EB, Carranza FA, Martignoni M. The use of autogenous periosteal grafts as barriers for the treatment of Class II furcation involvements in lower molars. *J Periodontol* 1991;62:775-780.
156. Black BS, Gher ME, Sandifer JB, Fucini SE, Richardson AC. Comparative study of collagen and expanded polytetrafluoroethylene membranes in the treatment of human Class II furcation defects. *J Periodontol* 1994; 65:598-604.
157. Blumenthal NM. A clinical comparison of collagen membranes with ePTFE membranes in the treatment of human mandibular buccal Class II furcation defects. *J Periodontol* 1993;64:925-933.
158. Chen CC, Wang HL, Smith F, Glickman GN, Shyr Y, O'Neal RB. Evaluation of a collagen membrane with and without bone grafts in treating periodontal intrabony defects. *J Periodontol* 1995;66:838-847.
159. Chung KM, Salkin LM, Stein MD, Freedman AL. Clinical evaluation of a biodegradable collagen membrane in guided tissue regeneration. *J Periodontol* 1990;61: 732-736.
160. Wang HL, O'Neal RB, Thomas CL, Shyr Y, MacNeil RL. Evaluation of an absorbable collagen membrane in treating Class II furcation defects. *J Periodontol* 1994;65:1029-1036.
161. Yukna CN, Yukna RA. Multi-center evaluation of bioabsorbable collagen membrane for guided tissue regeneration in human Class II furcations. *J Periodontol* 1996;67:650-657.
162. Laurell L, Falk H, Fornell J, Johard G, Gottlow J. Clinical use of a bioresorbable matrix barrier in guided tissue regeneration therapy. Case series. *J Periodontol* 1994;65:967-975.
163. Polson AM, Garrett S, Stoller NH, et al. Guided tissue regeneration in human furcation defects after using a biodegradable barrier: A multi-center feasibility study. *J Periodontol* 1995;66:377-385.
164. Vernino AR, Jones FL, Holt RA, Nordquist RE, Brand JW. Evaluation of the potential of a polylactic acid barrier for correction of periodontal defects in baboons: A clinical and histologic study. *Int J Periodontics Restorative Dent* 1995;15:84-101.
165. Bouchard P, Giovannoli JL, Mattout C, Davarpanah M, Etienne D. Clinical evaluation of a bioabsorbable regenerative material in mandibular Class II furcation therapy. *J Clin Periodontol* 1997;24:511-518.
166. Caffesse RG, Mota LF, Quiñones CR, Morrison EC. Clinical comparison of resorbable and non-resorbable barriers for guided periodontal tissue regeneration. *J Clin Periodontol* 1997;24:747-752.
167. Garrett S, Polson AM, Stoller NH, et al. Comparison of a bioabsorbable GTR barrier to a non-absorbable barrier in treating human Class II furcation defects. A multicenter parallel design randomized single-blind trial. *J Periodontol* 1997;68:667-675.
168. Christgau M, Bader N, Schmalz G, Hiller KA, Wenzel A. GTR therapy of intrabony defects using 2 different bioresorbable membranes: 12-month results. *J Clin Periodontol* 1998;25:499-509.
169. De Leonardis D, Garg AK, Pedrazzoli V, Pecora GE. Clinical evaluation of the treatment of Class II furcation involvement with bioabsorbable barriers alone or associated with demineralized freeze-dried bone allografts. *J Periodontol* 1999;70:8-12.
170. Stoller NH, Johnson LR, Garrett S. Periodontal regeneration of a Class II furcation defect utilizing a bioabsorbable barrier in a human. A case study with histology. *J Periodontol* 2001;72:238-242.
171. Cortellini P, Pini Prato G, Tonetti MS. Periodontal regeneration of human infrabony defects. II. Re-entry procedures and bone measures. *J Periodontol* 1993;64: 261-268.
172. Becker W, Becker BE. Treatment of mandibular 3-wall intrabony defects by flap debridement and expanded polytetrafluoroethylene barrier membranes. Long-term

evaluation of 32 treated patients. *J Periodontol* 1993; 64(Suppl. 11):1138-1144.
173. Selvig KA, Kersten BG, Wikesjö UM. Surgical treatment of intrabony periodontal defects using expanded polytetrafluoroethylene barrier membranes: Influence of defect configuration on healing response. *J Periodontol* 1993;64:730-733.
174. Guillemin MR, Mellonig JT, Brunsvold MA. Healing in periodontal defects treated by decalcified freeze-dried bone allografts in combination with ePTFE membranes. I. Clinical and scanning electron microscope analysis. *J Clin Periodontol* 1993;20:528-536.
175. Laurell L, Gottlow J, Zybutz M, Persson R. Treatment of intrabony defects by different surgical procedures. A literature review. *J Periodontol* 1998;69:303-313.
176. Pontoriero R, Lindhe J, Nyman S, Karring T, Rosenberg E, Sanavi F. Guided tissue regeneration in degree II furcation-involved mandibular molars. A clinical study. *J Clin Periodontol* 1988;15:247-254.
177. Anderegg CR, Martin SJ, Gray JL, Mellonig JT, Gher ME. Clinical evaluation of the use of decalcified freeze-dried bone allograft with guided tissue regeneration in the treatment of molar furcation invasions. *J Periodontol* 1991;62:264-268.
178. Schallhorn RG, McClain PK. Combined osseous composite grafting, root conditioning, and guided tissue regeneration. *Int J Periodontics Restorative Dent* 1988;8(4):8-31.
179. Wallace SC, Gellin RG, Miller MC, Mishkin DJ. Guided tissue regeneration with and without decalcified freeze-dried bone in mandibular Class II furcation invasions. *J Periodontol* 1994;65:244-254.
180. Evans GH, Yukna RA, Gardiner DL, Cambre KM. Frequency of furcation closure with regenerative periodontal therapy. *J West Soc Periodontol Periodontal Abstr* 1996;44:101-109.
181. Garrett S, Gantes B, Zimmerman G, Egelberg J. Treatment of mandibular Class III periodontal furcation defects. Coronally positioned flaps with and without expanded polytetrafluoroethylene membranes. *J Periodontol* 1994;65:592-597.
182. Mellonig JT, Seamons BC, Gray JL, Towle HJ. Clinical evaluation of guided tissue regeneration in the treatment of grade II molar furcation invasions. *Int J Periodontics Restorative Dent* 1994;14:254-271.
183. Metzler DG, Seamons BC, Mellonig JT, Gher ME, Gray JL. Clinical evaluation of guided tissue regeneration in the treatment of maxillary Class II molar furcation invasions. *J Periodontol* 1991;62:353-360.
184. Pontoriero R, Lindhe J, Nyman S, Karring T, Rosenberg E, Sanavi F. Guided tissue regeneration in the treatment of furcation defects in mandibular molars. A clinical study of degree III involvements. *J Clin Periodontol* 1989;16: 170-174.
185. Nowzari H, Matian F, Slots J. Periodontal pathogens on polytetrafluoroethylene membrane for guided tissue regeneration inhibit healing. *J Clin Periodontol* 1995;22:469-474.
186. Machtei EE, Dunford R, Grossi SG, Genco RJ. Gingival recession and exposure of barrier membrane: Effect on guided tissue regeneration of Class II furcation defects. *Int J Periodontics Restorative Dent* 1995;15:590-599.
187. Novaes AB Jr, Gutierrez FG, Francischetto IF, Novaes AB. Bacterial colonization of the external and internal sulci and of cellulose membranes at time of retrieval. *J Periodontol* 1995;66:864-869.
188. Teparat T, Solt CW, Claman LJ, Beck FM. Clinical comparison of bioabsorbable barriers with non-resorbable barriers in guided tissue regeneration in the treatment of human intrabony defects. *J Periodontol* 1998;69:632-641.
189. Weltman R, Trejo PM, Morrison E, Caffesse R. Assessment of guided tissue regeneration procedures in intrabony defects with bioabsorbable and non-resorbable barriers. *J Periodontol* 1997;68:582-590.
190. Wang HL, O'Neal RB, MacNeil LM. Regenerative treatment of periodontal defects utilizing a bioresorbable collagen membrane. *Pract Periodontics Aesthet Dent* 1995;7:59-66.
191. Steinberg AD, LeBreton G, Willey R, Mukherjee S, Lipowski J. Extravascular clot formation and platelet activation on variously treated root surfaces. *J Periodontol* 1986;57:516-522.
192. Postlethwaite AE, Seyer JM, Kang AH. Chemotactic attraction of human fibroblasts to type I, II, and III collagens and collagen-derived peptides. *Proc Natl Acad Sci* (USA) 1978;75:871-875.
193. Bunyaratavej P, Wang HL. Collagen membranes: A review. *J Periodontol* 2001;72:215-229.
194. Becker W, Becker BE, Mellonig J, et al. A prospective multi-center study evaluating periodontal regeneration for Class II furcation invasions and intrabony defects after treatment with a bioabsorbable barrier membrane: 1-year results. *J Periodontol* 1996;67:641-649.
195. Caton J, Greenstein G, Zappa U. Synthetic bioabsorbable barrier for regeneration in human periodontal defects. *J Periodontol* 1994;65:1037-1045.
196. Christgau M, Schmalz G, Reich E, Wenzel A. Clinical and radiographical split-mouth study on resorbable versus non-resorbable GTR membranes. *J Clin Periodontol* 1995;22:306-315.
197. Hugoson A, Ravald N, Fornell J, Johard G, Teiwik A, Gottlow J. Treatment of Class II furcation involvements in humans with bioresorbable and nonresorbable guided tissue regeneration barriers. A randomized multi-center study. *J Periodontol* 1995;66:624-634.
198. Lindhe J, Pontoriero R, Berglundh T, Araujo M. The effect of flap management and bioresorbable occlusive devices in GTR treatment of degree III furcation defects. An experimental study in dogs. *J Clin Periodontol* 1995;22:276-283.
199. Vernino AR, Ringeisen TA, Wang HL, et al. Use of biodegradable polylactic acid barrier materials in the treatment of grade II periodontal furcation defects in humans. Part I: A multicenter investigative clinical study. *Int J Periodontics Restorative Dent* 1998;18:572-585.
200. Vernino AR, Wang HL, Rapley J, et al. The use of biodegradable polylactic acid barrier materials in the treatment of grade II periodontal furcation defects in humans. Part II: A multicenter investigative surgical study. *Int J Periodontics Restorative Dent* 1999;19:56-65.
201. Bogle G, Garrett S, Stoller NH, et al. Periodontal regeneration in naturally occurring Class II furcation defects

in beagle dogs after guided tissue regeneration with bioabsorbable barriers. *J Periodontol* 1997;68:536-544.
202. Robert PM, Frank RM. Periodontal guided tissue regeneration with a new resorbable polylactic acid membrane. *J Periodontol* 1994;65:414-422.
203. Jepsen S, Heinz B, Kermanie MA, Jepsen K. Evaluation of a new bioabsorbable barrier for recession therapy: A feasibility study. *J Periodontol* 2000;71: 1433-1440.
204. Matarasso S, Cafiero C, Coraggio F, Vaia E, de Paoli S. Guided tissue regeneration versus coronally repositioned flap in the treatment of recession with double papillae. *Int J Periodontics Restorative Dent* 1998;18: 444-453.
205. Harris RJ. A comparison of 2 root coverage techniques: Guided tissue regeneration with a bioabsorbable matrix style membrane versus a connective tissue graft combined with a coronally positioned pedicle graft without vertical incisions. Results of a series of consecutive cases. *J Periodontol* 1998;69:1426-1434.
206. Harris RJ. A comparative study of root coverage obtained with guided tissue regeneration utilizing a bioabsorbable membrane versus the connective tissue with partial-thickness double pedicle graft. *J Periodontol* 1997;68:779-790.
207. Mattson JS, Gallagher SJ, Jabro MH. The use of 2 bioabsorbable barrier membranes in the treatment of interproximal intrabony periodontal defects. *J Periodontol* 1999;70:510-517.
208. Yamaoka SB, Mellonig JT, Meffert RM, Arnold RM, Nummikoski PV, Mealey BL. Clinical evaluation of demineralized-unicortical-ilium-strips for guided tissue regeneration. *J Periodontol* 1996;67:803-815.
209. Yukna RA. Placement of hydroxyapatite-coated implants into fresh or recent extraction sites. *Dent Clin North Am* 1992;36:97-115.
210. Galgut PN. Oxidized cellulose mesh used as a biodegradable barrier membrane in the technique of guided tissue regeneration. A case report. *J Periodontol* 1990;61:766-768.
211. Sottosanti J. Calcium sulfate: A biodegradable and biocompatible barrier for guided tissue regeneration. *Compendium* 1992;13:226-228,230,232-224.
212. Aichelmann-Reidy ME, Heath C, Reynolds MA. Clinical evaluation of calcium sulfate in combination with demineralized freeze-dried bone allograft for the treatment of human intraosseous defects. *J Periodontol* 2004;75:340-347.
213. Oates T, Robinson M, Gunsolley J. Surgical therapies for the treatment of gingival recession. A systematic review. *Ann Periodontol* 2003;8:303-320.
214. Caffesse RG, Smith BA, Duff B, Morrison EC, Merrill D, Becker W. Class II furcations treated by guided tissue regeneration in humans: Case reports. *J Periodontol* 1990;61:510-514.
215. Eickholz P, Kim TS, Holle R. Guided tissue regeneration with non-resorbable and biodegradable barriers: 6 months results. *J Clin Periodontol* 1997;24:92-101.
216. Pontoriero R, Nyman S, Lindhe J, Rosenberg E, Sanavi F. Guided tissue regeneration in the treatment of furcation defects in man. *J Clin Periodontol* 1987;14: 618-620.
217. Pontoriero R, Lindhe J. Guided tissue regeneration in the treatment of degree III furcation defects in maxillary molars. *J Clin Periodontol* 1995;22:810-812.
218. Mehlbauer MJ, Greenwell H, Nouneh I, et al. Improved closure rate of Class III furcations using a layered GTR technique. *Int J Periodontics Restorative Dent* 2000;20: 285-295.
219. Pontoriero R, Lindhe J. Guided tissue regeneration in the treatment of degree II furcations in maxillary molars. *J Clin Periodontol* 1995;22:756-763.
220. Cortellini P, Bowers GM. Periodontal regeneration of intrabony defects: An evidence-based treatment approach. *Int J Periodontics Restorative Dent* 1995;15:128-145.
221. Cortellini P, Carnevale G, Sanz M, Tonetti MS. Treatment of deep and shallow intrabony defects. A multicenter randomized controlled clinical trial. *J Clin Periodontol* 1998;25:981-987.
222. Cortellini P, Pini Prato G, Tonetti MS. Periodontal regeneration of human infrabony defects. I. Clinical measures. *J Periodontol* 1993;64:254-260.
223. Cortellini P, Pini Prato G, Tonetti MS. Periodontal regeneration of human intrabony defects with titanium reinforced membranes. A controlled clinical trial. *J Periodontol* 1995;66:797-803.
224. Cortellini P, Pini Prato G, Tonetti MS. Periodontal regeneration of human intrabony defects with bioresorbable membranes. A controlled clinical trial. *J Periodontol* 1996;67:217-223.
225. Gouldin AG, Fayad S, Mellonig JT. Evaluation of guided tissue regeneration in interproximal defects. II. Membrane and bone versus membrane alone. *J Clin Periodontol* 1996;23:485-491.
226. Trejo PM, Weltman R, Caffesse R. Treatment of intraosseous defects with bioabsorbable barriers alone or in combination with decalcified freeze-dried bone allograft: A randomized clinical trial. *J Periodontol* 2000;71:1852-1861.
227. Batista EL Jr, Novaes AB Jr, Simonpietri JJ, Batista FC. Use of bovine-derived anorganic bone associated with guided tissue regeneration in intrabony defects. Six-month evaluation at re-entry. *J Periodontol* 1999;70:1000-1007.
228. Mellado JR, Salkin LM, Freedman AL, Stein MD. A comparative study of ePTFE periodontal membranes with and without decalcified freeze-dried bone allografts for the regeneration of interproximal intraosseous defects. *J Periodontol* 1995;66:751-755.
229. Paolantonio M. Combined periodontal regenerative technique in human intrabony defects by collagen membrane and anorganic bovine bone. A controlled clinical study. *J Periodontol* 2002;73:158-166.
230. Cortellini P, Clauser C, Prato GP. Histologic assessment of new attachment following the treatment of a human buccal recession by means of a guided tissue regeneration procedure. *J Periodontol* 1993;64:387-391.
231. Roccuzzo M, Lungo M, Corrente G, Gandolfo S. Comparative study of a bioresorbable and a non-resorbable membrane in the treatment of human buccal gingival recessions. *J Periodontol* 1996;67:7-14.
232. Shieh AT, Wang HL, O'Neal R, Glickman GN, MacNeil RL. Development and clinical evaluation of a root coverage procedure using a collagen barrier membrane. *J Periodontol* 1997;68:770-778.

233. Lee E-J, Meraw S, Oh T-J, Giannobile W, Wang H-L. Utilizing type I collagen membrane for the treatment of gingival recession: A histomorphometric analysis. *J Periodontol* 2002;73:781-790.
234. Pini Prato G, Clauser C, Cortellini P, Tinti C, Vincenzi G, Pagliaro U. Guided tissue regeneration versus mucogingival surgery in the treatment of human buccal recessions. A 4-year follow-up study. *J Periodontol* 1996;67:1216-1223.
235. Wang HL, Bunyaratavej P, Labadie M, Shyr Y, MacNeil RL. Comparison of 2 clinical techniques for treatment of gingival recession. *J Periodontol* 2001;72:1301-1311.
236. al-Hamdan K, Eber R, Sarment D, Kowalsky C, Wang H. Guided tissue regeneration-based root coverage: Meta-analysis. *J Periodontol* 2003;74:1520-1533.
237. Özcan G, Kurtis B, Balos K. Combined use of root conditioning, fibrin-fibronectin system and a collagen membrane to treat a localized gingival recession: A 10-case report. *J Marmara Univ Dent Fac* 1997;2:588-598.
238. Wang H, Kimble K, Eber R. Utilization of bone grafts for the enhancement of a GTR-based root coverage procedure: A pilot case study. *Int J Periodontics Restorative Dent* 2002;22:119-127.
239. Kimble K, Eber R, Soehren S, Shyr Y, Wang H. Treatment of gingival recession using a collagen membrane with or without the use of demineralized freeze-dried bone allograft for space maintenance. *J Periodontol* 2004;75:210-220.
240. Baldi C, Pini-Prato G, Pagliaro U, et al. Coronally advanced flap procedure for root coverage. Is flap thickness a relevant predictor to achieve root coverage? A 19-case series. *J Periodontol* 1999;70:1077-1084.
241. Selvig KA, Kersten BG, Chamberlain AD, Wikesjö UM, Nilveus RE. Regenerative surgery of intrabony periodontal defects using ePTFE barrier membranes: Scanning electron microscopic evaluation of retrieved membranes versus clinical healing. *J Periodontol* 1992; 63:974-978.
242. Nowzari H, Slots J. Microorganisms in polytetrafluoroethylene barrier membranes for guided tissue regeneration. *J Clin Periodontol* 1994;21:203-210.
243. Machtei EE, Cho MI, Dunford R, Norderyd J, Zambon JJ, Genco RJ. Clinical, microbiological, and histological factors which influence the success of regenerative periodontal therapy. *J Periodontol* 1994;65:154-161.
244. Machtei EE, Dunford RG, Norderyd OM, Zambon JJ, Genco RJ. Guided tissue regeneration and anti-infective therapy in the treatment of Class II furcation defects. *J Periodontol* 1993;64:968-973.
245. Machtei EE. The effect of membrane exposure on the outcome of regenerative procedures in humans: A meta-analysis. *J Periodontol* 2001;72:512-516.
246. Tonetti MS, Pini-Prato G, Cortellini P. Effect of cigarette smoking on periodontal healing following GTR in infrabony defects. A preliminary retrospective study. *J Clin Periodontol* 1995;22:229-234.
247. Trombelli L, Kim CK, Zimmerman GJ, Wikesjö UM. Retrospective analysis of factors related to clinical outcome of guided tissue regeneration procedures in intrabony defects. *J Clin Periodontol* 1997;24:366-371.
248. Anderegg CR, Metzler DG, Nicoll BK. Gingiva thickness in guided tissue regeneration and associated recession at facial furcation defects. *J Periodontol* 1995;66:397-402.
249. Andersson B, Bratthall G, Kullendorff B, Grondahl K, Rohlin M, Attstrom R. Treatment of furcation defects. Guided tissue regeneration versus coronally positioned flap in mandibular molars: A pilot study. *J Clin Periodontol* 1994;21:211-216.
250. Goldman HM, Smukler H. Controlled surgical stimulation of periosteum. *J Periodontol* 1978;49:518-522.
251. Ritsila V, Alhopuro S, Rintala A. Bone formation with free periosteum. An experimental study. *Scand J Plast Reconstr Surg* 1972;6:51-56.
252. Martin M, Gantes B, Garrett S, Egelberg J. Treatment of periodontal furcation defects. I. Review of the literature and description of a regenerative surgical technique. *J Clin Periodontol* 1988;15:227-231.
253. Stahl SS, Froum SJ. Healing of human suprabony lesions treated with guided tissue regeneration and coronally anchored flaps. Case reports. *J Clin Periodontol* 1991;18:69-74.
254. Gantes BG, Synowski BN, Garrett S, Egelberg JH. Treatment of periodontal furcation defects. Mandibular Class III defects. *J Periodontol* 1991;62:361-365.
255. Register AA, Burdick FA. Accelerated reattachment with cementogenesis to dentin, demineralized in situ. I. Optimum range. *J Periodontol* 1975;46:646-655.
256. Register AA, Burdick FA. Accelerated reattachment with cementogenesis to dentin, demineralized in situ. II. Defect repair. *J Periodontol* 1976;47:497-505.
257. Daly CG. Anti-bacterial effect of citric acid treatment of periodontally diseased root surfaces in vitro. *J Clin Periodontol* 1982;9:386-392.
258. Garrett JS, Crigger M, Egelberg J. Effects of citric acid on diseased root surfaces. *J Periodontal Res* 1978; 13:155-163.
259. Crigger M, Bogle G, Nilveus R, Egelberg J, Selvig KA. The effect of topical citric acid application on the healing of experimental furcation defects in dogs. *J Periodontal Res* 1978;13:538-549.
260. Klinge B, Nilveus R, Kiger RD, Egelberg J. Effect of flap placement and defect size on healing of experimental furcation defects. *J Periodontal Res* 1981;16:236-248.
261. Stahl SS, Froum SJ, Kushner L. Healing responses of human intraosseous lesions following the use of debridement, grafting and citric acid root treatment. II. Clinical and histologic observations: One year post-surgery. *J Periodontol* 1983;54:325-338.
262. Albair WB, Cobb CM, Killoy WJ. Connective tissue attachment to periodontally diseased roots after citric acid demineralization. *J Periodontol* 1982;53:515-526.
263. Kersten BG, Chamberlain AD, Khorsandi S, Wikesjö UM, Selvig KA, Nilveus RE. Healing of the intrabony periodontal lesion following root conditioning with citric acid and wound closure including an expanded PTFE membrane. *J Periodontol* 1992;63:876-882.
264. Moore JA, Ashley FP, Waterman CA. The effect on healing of the application of citric acid during replaced flap surgery. *J Clin Periodontol* 1987;14:130-135.
265. Terranova VP, Franzetti LC, Hic S, et al. A biochemical approach to periodontal regeneration: Tetracycline treatment of dentin promotes fibroblast adhesion and growth. *J Periodontal Res* 1986;21:330-337.

266. Blomlof J, Blomlof L, Lindskog S. Effect of different concentrations of EDTA on smear removal and collagen exposure in periodontitis-affected root surfaces. *J Clin Periodontol* 1997;24:534-537.
267. Blomlof J, Jansson L, Blomlof L, Lindskog S. Root surface etching at neutral pH promotes periodontal healing. *J Clin Periodontol* 1996;23:50-55.
268. Caffesse RG, Kerry GJ, Chaves ES, et al. Clinical evaluation of the use of citric acid and autologous fibronectin in periodontal surgery. *J Periodontol* 1988;59:565-569.
269. Mariotti A. Efficacy of clinical root surface modifiers in the treatment of periodontal disease. A systematic review. *Ann Periodontol* 2003;8:205-226.
270. Ripamonti U, Heliotis M, van den Heever B, Reddi AH. Bone morphogenetic proteins induce periodontal regeneration in the baboon (*Papio ursinus*). *J Periodontal Res* 1994;29:439-445 (erratum 1995;30:149-151).
271. Bowers G, Felton F, Middleton C, et al. Histologic comparison of regeneration in human intrabony defects when osteogenin is combined with demineralized freeze-dried bone allograft and with purified bovine collagen. *J Periodontol* 1991;62:690-702.
272. King GN, King N, Hughes FJ. Effect of two delivery systems for recombinant human bone morphogenetic protein-2 on periodontal regeneration in vivo. *J Periodontal Res* 1998;33:226-236.
273. Kinoshita A, Oda S, Takahashi K, Yokota S, Ishikawa I. Periodontal regeneration by application of recombinant human bone morphogenetic protein-2 to horizontal circumferential defects created by experimental periodontitis in beagle dogs. *J Periodontol* 1997;68:103-109.
274. Ripamonti U, Reddi AH. Tissue engineering, morphogenesis, and regeneration of the periodontal tissues by bone morphogenetic proteins. *Crit Rev Oral Biol Med* 1997;8:154-163.
275. Sigurdsson TJ, Tatakis DN, Lee MB, Wikesjö UM. Periodontal regenerative potential of space-providing expanded polytetrafluoroethylene membranes and recombinant human bone morphogenetic proteins. *J Periodontol* 1995;66:511-521.
276. Giannobile WV, Ryan S, Shih MS, Su DL, Kaplan PL, Chan TC. Recombinant human osteogenic protein-1 (OP-1) stimulates periodontal wound healing in Class III furcation defects. *J Periodontol* 1998;69:129-137.
277. Howell TH, Fiorellini JP, Paquette DW, Offenbacher S, Giannobile WV, Lynch SE. A Phase I/II clinical trial to evaluate a combination of recombinant human platelet-derived growth factor-BB and recombinant human insulin-like growth factor-I in patients with periodontal disease. *J Periodontol* 1997;68:1186-1193.
278. Howell TH, Fiorellini J, Jones A, et al. A feasibility study evaluating rhBMP-2/absorbable collagen sponge device for local alveolar ridge preservation or augmentation. *Int J Periodontics Restorative Dent* 1997;17:124-139.
279. Talwar R, Di Silvio L, Hughes FJ, King GN. Effects of carrier release kinetics on bone morphogenetic protein-2-induced periodontal regeneration in vivo. *J Clin Periodontol* 2001;28:340-347.
280. American Academy of Periodontology. The potential role of growth and differentiation factors in periodontal regeneration (position paper). *J Periodontol* 1996;67:545-553.
281. Heden G. A case report study of 72 consecutive Emdogain-treated intrabony periodontal defects: Clinical and radiographic findings after 1 year. *Int J Periodontics Restorative Dent* 2000;20:127-139.
282. Heijl L, Heden G, Svardstrom G, Ostgren A. Enamel matrix derivative (EMDOGAIN) in the treatment of intrabony periodontal defects. *J Clin Periodontol* 1997;24:705-714.
283. Pontoriero R, Wennstrom J, Lindhe J. The use of barrier membranes and enamel matrix proteins in the treatment of angular bone defects. A prospective controlled clinical study. *J Clin Periodontol* 1999;26:833-840.
284. Rasperini G, Ricci G, Silvestri M. Surgical technique for treatment of infrabony defects with enamel matrix derivative (Emdogain): 3 case reports. *Int J Periodontics Restorative Dent* 1999;19:578-587.
285. Zetterstrom O, Andersson C, Eriksson L, et al. Clinical safety of enamel matrix derivative (EMDOGAIN) in the treatment of periodontal defects. *J Clin Periodontol* 1997;24:697-704.
286. Hirooka H. The biologic concept for the use of enamel matrix protein: True periodontal regeneration. *Quintessence Int* 1998;29:621-630.
287. Sallum EA, Casati MZ, Caffesse RG, Funis LP, Nociti Junior FH, Sallum AW. Coronally positioned flap with or without enamel matrix protein derivative for the treatment of gingival recessions. *Am J Dent* 2003;16:287-291.
288. Cattaneo V, Rota C, Silvestri M, et al. Effect of enamel matrix derivative on human periodontal fibroblasts: Proliferation, morphology and root surface colonization. An in vitro study. *J Periodontal Res* 2003;38:568-574.
289. Donos N, Glavind L, Karring T, Sculean A. Clinical evaluation of an enamel matrix derivative in the treatment of mandibular degree II furcation involvement: A 36-month case series. *Int J Periodontics Restorative Dent* 2003;23:507-512.
290. Cochran DL, Jones A, Heijl L, Mellonig JT, Schoolfield J, King GN. Periodontal regeneration with a combination of enamel matrix proteins and autogenous bone grafting. *J Periodontol* 2003;74:1269-1281.
291. Watanabe K, Kikuchi M, Okumura M, Kadosawa T, Fujinaga T. Efficacy of enamel matrix protein applied to spontaneous periodontal disease in two dogs. *J Vet Med Sci* 2003;65:1007-1010.
292. Newman SA, Coscia SA, Jotwani R, Iacono VJ, Cutler CW. Effects of enamel matrix derivative on *Porphyromonas gingivalis*. *J Periodontol* 2003;74:1191-1195.
293. McGuire MK, Cochran DL. Evaluation of human recession defects treated with coronally advanced flaps and either enamel matrix derivative or connective tissue. Part 2: Histological evaluation. *J Periodontol* 2003;74:1126-1135.
294. McGuire MK, Nunn M. Evaluation of human recession defects treated with coronally advanced flaps and either enamel matrix derivative or connective tissue. Part 1: Comparison of clinical parameters. *J Periodontol* 2003;74:1110-1125.
295. Cattaneo V, Rota C, Silvestri M, et al. Effect of enamel matrix derivative on human periodontal fibroblasts:

Proliferation, morphology and root surface colonization. An in vitro study. *J Periodontal Res* 2003;38:568-574.
296. Petinaki E, Nikolopoulos S, Castanas E. Low stimulation of peripheral lymphocytes, following in vitro application of Emdogain. *J Clin Periodontol* 1998;25:715-720.
297. Barrett EJ, Kenny DJ. Optimization of post-replantation healing for avulsed permanent teeth in children. *Ont Dent* 1999;76:23-27.
298. Dobbs WE. Emdogain. *Northwest Dent* 1999;78(5):27-29.
299. Sculean A, Chiantella GC, Miliauskaite A, Brecx M, Arweiler NB. Four-year results following treatment of intrabony periodontal defects with an enamel matrix protein derivative: A report of 46 cases. *Int J Periodontics Restorative Dent* 2003;23:345-351.
300. Berry JE, Zhao M, Jin Q, Foster BL, Viswanathan H, Somerman MJ. Exploring the origins of cementoblasts and their trigger factors. *Connect Tissue Res* 2003;44 (Suppl. 1):97-102.
301. Cochran DL, King GN, Schoolfield J, Velasquez-Plata D, Mellonig JT, Jones A. The effect of enamel matrix proteins on periodontal regeneration as determined by histological analyses. *J Periodontol* 2003;74:1043-1055.
302. Gutierrez MA, Mellonig JT, Cochran DL. Evaluation of enamel matrix derivative as an adjunct to non-surgical periodontal therapy. *J Clin Periodontol* 2003;30:739-745.
303. Yuan K, Chen CL, Lin MT. Enamel matrix derivative exhibits angiogenic effect in vitro and in a murine model. *J Clin Periodontol* 2003;30:732-738.
304. Gurpinar A, Onur MA, Cehreli ZC, Tasman F. Effect of enamel matrix derivative on mouse fibroblasts and marrow stromal osteoblasts. *J Biomater Appl* 2003;18:25-33.
305. Sculean A, Reich E, Chiantella GC, Brecx M. Treatment of intrabony periodontal defects with an enamel matrix protein derivative (Emdogain): A report of 32 cases. *Int J Periodontics Restorative Dent* 1999;19:157-163.
306. Sculean A, Donos N, Windisch P, et al. Healing of human intrabony defects following treatment with enamel matrix proteins or guided tissue regeneration. *J Periodontal Res* 1999;34:310-322.
307. Heden G, Wennström J, Lindhe J. Periodontal tissue alterations following Emdogain treatment of periodontal sites with angular bone defects. A series of case reports. *J Clin Periodontol* 1999;26:855-860.
308. Pontoriero R, Wennström J, Lindhe J. The use of barrier membranes and enamel matrix proteins in the treatment of angular bone defects. A prospective controlled clinical study. *J Clin Periodontol* 1999;26:833-840.
309. Mellonig JT. Enamel matrix derivative for periodontal reconstructive surgery: Technique and clinical and histologic case report. *Int J Periodontics Restorative Dent* 1999;19:8-19.
310. Maycock J, Wood SR, Brookes SJ, Shore RC, Robinson C, Kirkham J. Characterization of a porcine amelogenin preparation, EMDOGAIN, a biological treatment for periodontal disease. *Connect Tissue Res* 2002; 43:472-476.
311. Kalpidis CD, Ruben MP. Treatment of intrabony periodontal defects with enamel matrix derivative: A literature review. *J Periodontol* 2002;73:1360-1376.
312. Chen L, Cha J, Guiha R, Bouwsma OJ. Root coverage with enamel matrix derivatives. *Compend Contin Educ Dent* 2002;23:797-800,802,804 passim.
313. Sculean A, Windisch P, Keglevich T, Fabi B, Lundgren E, Lyngstadaas PS. Presence of an enamel matrix protein derivative on human teeth following periodontal surgery. *Clin Oral Investig* 2002;6:183-187.
314. Sculean A, Junker R, Donos N, Berakdar M, Brecx M, Dunker N. Immunohistochemical evaluation of matrix molecules associated with wound healing following regenerative periodontal treatment in monkeys. *Clin Oral Investig* 2002;6:175-182.
315. Peretz B. Research on enamel matrix proteins: A model for the intensity and dynamics in dental research (in Hebrew). *Refuat Hapeh Vehashinayim* 2002;19:93.
316. Parodi R, Liuzzo G, Patrucco P, et al. Use of Emdogain in the treatment of deep intrabony defects: 12-month clinical results. Histologic and radiographic evaluation. *Int J Periodontics Restorative Dent* 2000;20:584-595.
317. Yukna RA, Mellonig JT. Histologic evaluation of periodontal healing in humans following regenerative therapy with enamel matrix derivative. A 10-case series. *J Periodontol* 2000;71:752-759.
318. Sculean A, Windisch P, Chiantella GC. Human histologic evaluation of an intrabony defect treated with enamel matrix derivative, xenograft, and GTR. *Int J Periodontics Restorative Dent* 2004;24:326-333.
319. Francetti L, Del Fabbro M, Basso M, Testori T, Weinstein R. Enamel matrix proteins in the treatment of intrabony defects. A prospective 24-month clinical trial. *J Clin Periodontol* 2004;31:52-59.
320. Craig RG, Kallur SP, Inoue M, Rosenberg PA, LeGeros RZ. Effect of enamel matrix proteins on the periodontal connective tissue-material interface after wound healing. *J Biomed Mater Res* 2004;69A:180-187.
321. Parashis A, Andronikaki-Faldami A, Tsiklakis K. Clinical and radiographic comparison of three regenerative procedures in the treatment of intrabony defects. *Int J Periodontics Restorative Dent* 2004;24:81-90.
322. Parodi R, Santarelli GA, Gasparetto B. Treatment of intrabony pockets with Emdogain: Results at 36 months. *Int J Periodontics Restorative Dent* 2004;24:57-63.
323. Sakallioglu U, Acikgoz G, Ayas B, Kirtiloglu T, Sakallioglu E. Healing of periodontal defects treated with enamel matrix proteins and root surface conditioning–an experimental study in dogs. *Biomaterials* 2004;25:1831-1840.
324. Boyan BD, Weesner TC, Lohmann CH, et al. Porcine fetal enamel matrix derivative enhances bone formation induced by demineralized freeze dried bone allograft in vivo. *J Periodontol* 2000;71:1278-1286.
325. Scheyer ET, Velasquez-Plata D, Brunsvold MA, Lasho DJ, Mellonig JT. A clinical comparison of a bovine-derived xenograft used alone and in combination with enamel matrix derivative for the treatment of periodontal osseous defects in humans. *J Periodontol* 2002;73:423-432.
326. Velasquez-Plata D, Scheyer ET, Mellonig JT. Clinical comparison of an enamel matrix derivative used alone or in combination with a bovine-derived xenograft for the treatment of periodontal osseous defects in humans. *J Periodontol* 2002;73:433-440 (erratum 2002;73:684).
327. Cardaropoli G, Leonhardt AS. Enamel matrix proteins in the treatment of deep intrabony defects. *J Periodontol* 2002;73:501-504.

328. Giannobile W, Somerman M. Growth and amelogenin-like factors in periodontal wound healing. A systematic review. *Ann Periodontol* 2003;8:193-204.
329. Gestrelius S, Andersson C, Lidstrom D, Hammarstrom L, Somerman M. In vitro studies on periodontal ligament cells and enamel matrix derivative. *J Clin Periodontol* 1997;24:685-692.
330. Hoang AM, Oates TW, Cochran DL. In vitro wound healing responses to enamel matrix derivative. *J Periodontol* 2000;71:1270-1277.
331. Lyngstadaas SP, Lundberg E, Ekdahl H, Andersson C, Gestrelius S. Autocrine growth factors in human periodontal ligament cells cultured on enamel matrix derivative. *J Clin Periodontol* 2001;28:181-188.
332. Tokiyasu Y, Takata T, Saygin E, Somerman M. Enamel factors regulate expression of genes associated with cementoblasts. *J Periodontol* 2000;71:1829-1839.
333. Wennström JL, Lindhe J. Some effects of enamel matrix proteins on wound healing in the dento-gingival region. *J Clin Periodontol* 2002;29:9-14.
334. Yukna RA, Callan DP, Krauser JT, et al. Multi-center clinical evaluation of combination anorganic bovine-derived hydroxyapatite matrix (ABM)/cell binding peptide (P-15) as a bone replacement graft material in human periodontal osseous defects. 6-month results. *J Periodontol* 1998;69:655-663.
335. Qian JJ, Bhatnagar RS. Enhanced cell attachment to anorganic bone mineral in the presence of a synthetic peptide related to collagen. *J Biomed Mater Res* 1996;31:545-554.
336. Bhatnagar RS, Qian JJ, Wedrychowska A, Sadeghi M, Wu YM, Smith N. Design of biomimetic habitats for tissue engineering with P-15, a synthetic peptide analogue of collagen. *Tissue Eng* 1999;5:53-65.
337. Lallier TE, Yukna R, St. Marie S, Moses R. The putative collagen binding peptide hastens periodontal ligament cell attachment to bone replacement graft materials. *J Periodontol* 2001;72:990-997.
338. Yukna RA, Krauser JT, Callan DP, Evans GH, Cruz R, Martin M. Multi-center clinical comparison of combination anorganic bovine-derived hydroxyapatite matrix (ABM)/cell binding peptide (P-15) and ABM in human periodontal osseous defects: 6-month results. *J Periodontol* 2000;71:1671-1679.
339. Yukna RA, Krauser JT, Callan DP, Evans GH, Cruz R, Martin M. Thirty-six month follow-up of 25 patients treated with combination anorganic bovine-derived hydroxyapatite matrix (ABM)/cell-binding peptide (P-15) bone replacement grafts in human infrabony defects. I. Clinical findings. *J Periodontol* 2002;73:123-128.
340. Yukna R, Salinas TJ, Carr RF. Periodontal regeneration following use of ABM/P-15: A case report. *Int J Periodontics Restorative Dent* 2002;22:146-155.