

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 pro-

cedures, 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 bone³⁷ 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 review⁶² 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 supra-crestal 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 chips⁷² 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 paper⁸² 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 bone⁹¹ 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 diseases¹⁰¹ 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: non-porous hydroxyapatite (HA), hydroxyapatite cement, porous hydroxyapatite (replamineform), beta tricalcium phosphate, PMMA and HEMA polymer (a cal-

cium 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 non-resorbable 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 DFDBA¹²¹ 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 spongiform 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 study¹⁴⁹ 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 filter⁶ 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 FDBA¹⁷⁷ or composite grafts of autogenous intraoral grafts and tricalcium phosphate and/or DFDBA¹⁷⁸ 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 varieties 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 study²¹² 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 review¹⁴⁸ 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 furcation 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% ($\pm 11.3\%$) root coverage with 100% root coverage at 33.1% ($\pm 20.4\%$) 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 max-

illary Class III defects^{8,217,218} and maxillary Class II defects.^{183,219} An early study²¹⁶ 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 group²¹⁷ 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 non-resorbable) 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 intrabony defect during GTR treatment may be unnecessary. Nonetheless, both procedures (GTR or GTR plus bone grafts) are proven effective in treating periodontal intrabony 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 species²⁴² 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 level²⁴³ 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 mm¹⁷⁵ 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 studies²⁵⁻²⁷ 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 surface²⁵⁷ 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 grafts⁷³ 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, with-

out 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 formation⁹³ 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 evi-

dence 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 DFDBA³³⁴ 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, non-resorbable or bioabsorbable, to control the cell and tis-

sue 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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