

Does periodontal tissue regeneration really work?

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Periodontitis is an infectious disease that causes destruction of the tooth-attachment apparatus. Untreated periodontitis results in progressive attachment loss that may eventually lead to early tooth loss. Fortunately, research has provided evidence that in most situations chronic periodontal diseases can be treated [reviewed in Ref. (29)]. There is also evidence that periodontally involved teeth have a good chance of survival, provided that therapy, patient compliance and maintenance care are appropriate [reviewed in Ref. (29)]. There are a broad range of treatment options available, but only a few may be regarded as truly regenerative procedures. According to a position paper from the American Academy of Periodontology (29), periodontal regenerative procedures include soft tissue grafts, bone replacement grafts, root biomodifications, guided tissue regeneration, and combinations thereof, for osseous, furcation and recession defects. Regeneration is defined as the reproduction or reconstitution of a lost or injured part of the body in such a way that the architecture and function of the lost or injured tissues are completely restored. The aim of regenerative periodontal therapy is to restore the structure and function of the periodontium. This means that the structure and function of the gingiva, alveolar bone, root cementum and periodontal ligament must be restored (Figs 1 and 2). By contrast, periodontal repair implies healing without restoration of the tooth-attachment apparatus and is often associated with the formation of a long junctional epithelium (Figs 3–5). Detachment of the junctional epithelium from the tooth surface (i.e. the formation of a periodontal pocket), disconnection of periodontal ligament fiber attachment to the root surface via cementum, and bone loss, are hallmarks of periodontitis. New attachment of junctional epithelium to the tooth surface and of connective tissue fibers to the root surface are very critical components of true periodontal regeneration. New connective tissue

attachment requires the formation of new cementum to a previously diseased root surface that was modified following periodontal therapy. Needless to say, in order to increase the attachment function of a tooth, the periodontal connective tissue fibers also have to insert into newly formed bone (Fig. 6). While less concern exists about the new epithelial attachment, new connective tissue attachment is much more critical. Concerns include predictability and the amount of new connective tissue attachment, as well as the strength of the regenerated interface between the treated root surface and the new cementum. As formation of cementum is essential for the attachment of periodontal ligament fibers to the root surface, much research has been devoted to understanding cementogenesis (for reviews, see Refs 3, 7, 9, 26, 30, 61, 62, 81).

Not all studies that claim to have achieved periodontal regeneration have utilized histological techniques. Methods of assessing periodontal regeneration have been reviewed previously (56). Clinically, the outcome of a regenerative periodontal treatment is assessed by clinical parameters (periodontal probing, radiographs and re-entry evaluations). These methods are, however, inappropriate for demonstrating true attachment gain. Histology continues to be the only reliable method of evaluating the efficacy of a therapy aimed at achieving periodontal regeneration. According to the World Workshop in Periodontics of the American Academy of Periodontology (1996), the requirements for a periodontal treatment to be considered a regenerative procedure are as follows: (i) human histology demonstrating new cementum, periodontal ligament and bone coronal to the former defect base; (ii) controlled human clinical trials demonstrating improved clinical probing attachment and bone levels; and (iii) controlled animal histological studies revealing new cementum, periodontal ligament and bone.

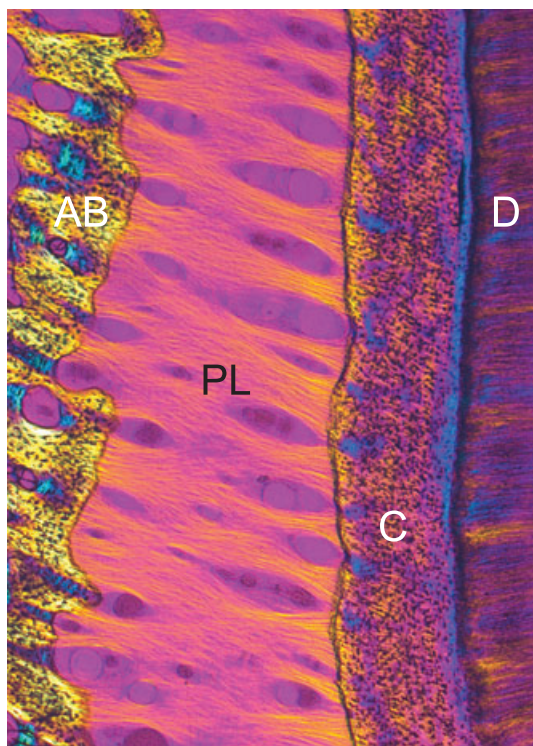


Fig. 1. This micrograph illustrates the periodontal ligament (PL) with its collagen fiber bundles spanning the area between the root covered with cementum (C) and the alveolar bone (AB). D, dentin. (Undecalcified ground section, unstained and viewed under polarized light.)

Well-controlled human histological studies with appropriate controls are very rare. Furthermore, reproduction of results from well-designed, well-controlled and well-conducted animal studies within humans may be difficult. In practical terms we assume that once a regenerative technique has revealed regenerative potential, as evidenced by histology, any positive clinical findings are often automatically equated with periodontal regeneration.

There have been several recent detailed reviews of guided tissue regeneration and therefore this manuscript provides an overview of the current state of the field, stepping back from the details of individual studies in an attempt to answer the question, 'does periodontal tissue regeneration really work?' It also aims to set the scene for two further manuscripts within this volume of *Periodontology 2000* that address novel approaches to cell-based methods of regeneration and tissue engineering.

Scaling and root planing using hand instruments

Scaling and root planing are basic, traditional and effective mechanical methods for treating periodon-

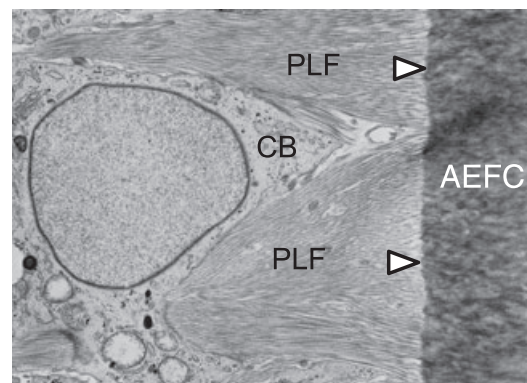


Fig. 2. Transmission electron micrograph illustrating at the mineralization front (arrowheads) the entrance of the periodontal ligament fibers (PLF) into the acellular extrinsic fiber cementum (AEFC). The fiber portions embedded in the mineralized cementum are called Sharpey's fibers. CB, cementoblast.

tal diseases. The aim of scaling and root planing is to remove the bacterial biofilm, calculus and contaminated cementum. Numerous studies have proven the effectiveness of reducing the bacterial load, and thus controlling the subgingival microflora, by scaling and root planing [reviewed in Refs (20, 57)]. Research in animals and in humans (10, 16, 17, 44, 69, 73, 74) indicates that the formation of new connective tissue attachment following scaling and root planing or flap surgery is not predictable. Although some new connective tissue attachment may form, a long junctional epithelium is what predictably establishes itself on the root surface (Fig. 7). Therefore, scaling and root planing cannot be regarded as a regenerative procedure, although its efficacy in treating chronic periodontitis is beyond doubt.

Sonic / ultrasonic scalers and lasers

Lasers or sonic / ultrasonic instruments may be used as an alternative treatment or as an adjunctive treatment to mechanical scaling and root planing. However, findings from a human histological study have failed to show predictable periodontal regeneration following scaling and root planing using ultrasonic instruments. The healing occurred predominantly through a long junctional epithelium, while formation of a new connective tissue attachment occurred only occasionally and was confined to the apical portion of the pockets (69). In a recent systematic review, it was concluded that there is insufficient clinical evidence to support the use of CO₂, neodymium-doped yttrium-aluminum-garnet

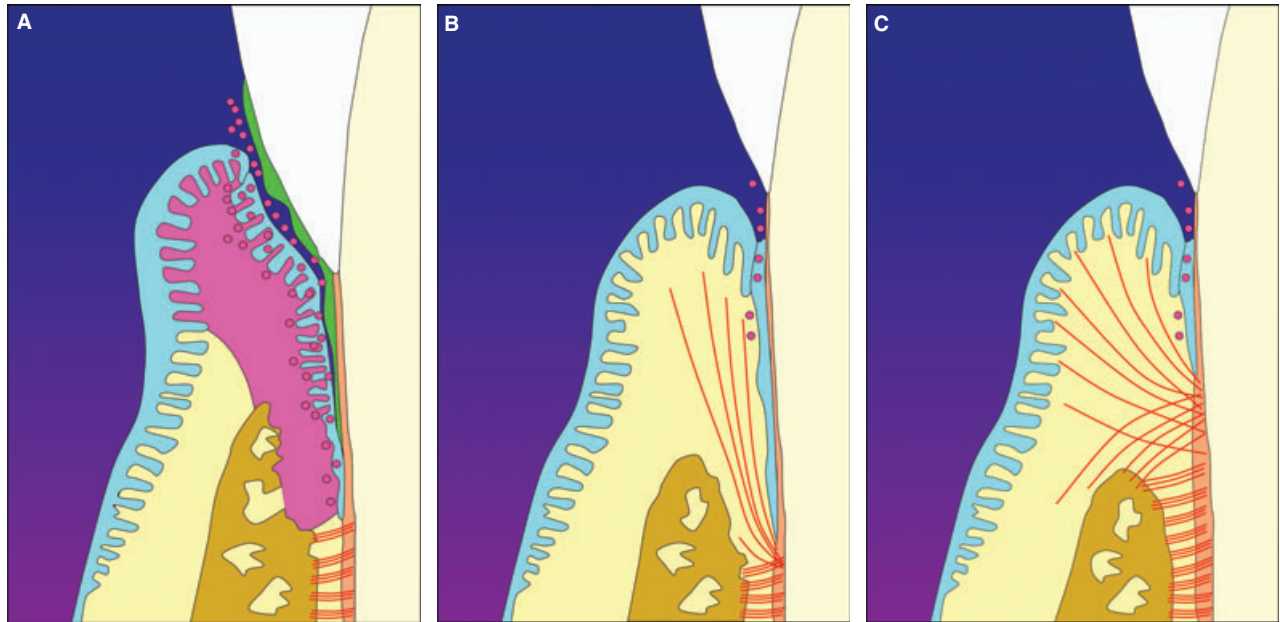


Fig. 3. Schematic drawings illustrating: (A) the inflamed soft tissue region and bone resorption associated with periodontitis (note the loss of both epithelial attachment and connective tissue attachment to the root surface); (B)

periodontal repair, as evidenced by formation of a long junctional epithelium; and (C) periodontal regeneration, as shown by new epithelial and connective tissue attachment to the root.

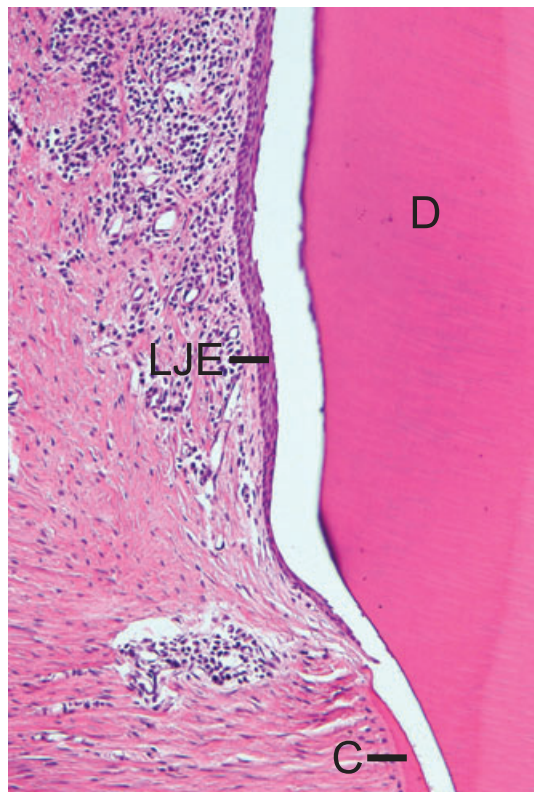


Fig. 4. Light micrograph illustrating formation of a long junctional epithelium (LJE) ending at the coronal-most end of regenerated cementum (C). D, dentin. (Paraffin section stained with hematoxylin and eosin.)

(Nd:YAG), or neodymium-doped yttrium–aluminum–perovskite (Nd:YAP) lasers, or different diode laser wavelengths (63). Only the erbium-doped yttrium–aluminum–garnet (Er:YAG) laser appears to be suitable for the nonsurgical treatment of chronic periodontitis (35, 63). However, there is insufficient evidence to suggest that any specific wavelength of laser is superior to conventional root surface treatment (i.e. root scaling and planing) (21, 63). Regarding histological evidence for periodontal regeneration, only one animal study to date has concluded that both the Er:YAG laser and an ultrasonic device might support the formation of a new connective tissue attachment (64).

The use of Er:YAG laser radiation during periodontal surgery was also evaluated in an animal study by Mizutani et al. (51). Class III furcation defects were experimentally induced in six beagle dogs and randomly treated, using a split-mouth design, with either an Er:YAG laser or hand instruments. The histological analysis 3 months following surgery revealed similar amounts of new connective tissue attachment formation in both groups, but significantly higher bone formation in the laser group. Comparable results were also found in a case report study evaluating, clinically and histologically, the healing following flap surgery and defect debridement with an Er:YAG laser in six patients with one advanced intrabony defect (67). The histologic

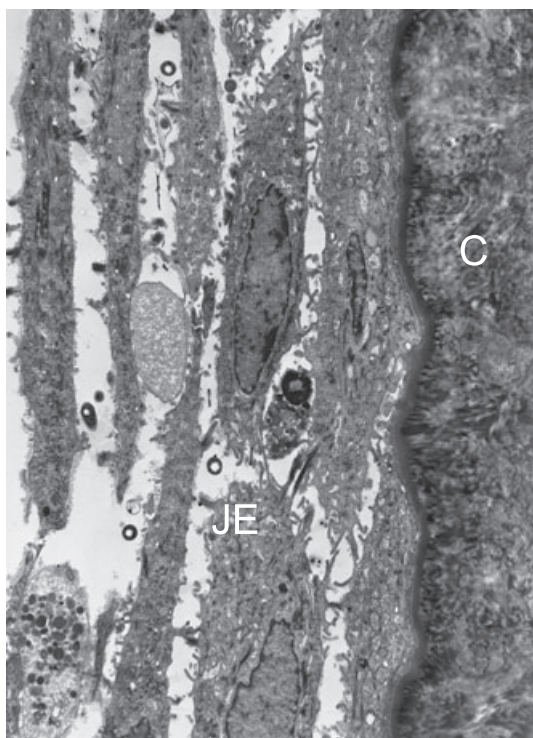


Fig. 5. Transmission electron micrograph showing junctional epithelium (JE) attachment to the cementum (C) layer.

analysis revealed that in four out of the six specimens the healing was mainly characterized by formation of a long junctional epithelium along the instrumented root surface, while cementum formation was only occasionally found and was limited to the most apical part of the defects. Formation of new connective tissue attachment was only found in two out of the six specimens. In one of these two specimens, the new attachment was also accompanied by new bone (67). However, periodontal regeneration at diseased root surfaces was observed following an Nd:YAG laser-assisted new attachment procedure in humans (80).

In conclusion, there are currently insufficient data to support the use of sonic/ultrasonic devices or lasers in promoting periodontal regeneration.

Root surface conditioning

While the aim of root surface debridement is to reduce the amount of bacteria and endotoxins on the root surface, treatment of the root surface with demineralizing agents such as acids or EDTA primarily aims to expose collagen fibrils. To achieve this, the smear layer must be removed and the mineralized component of the superficial layer of

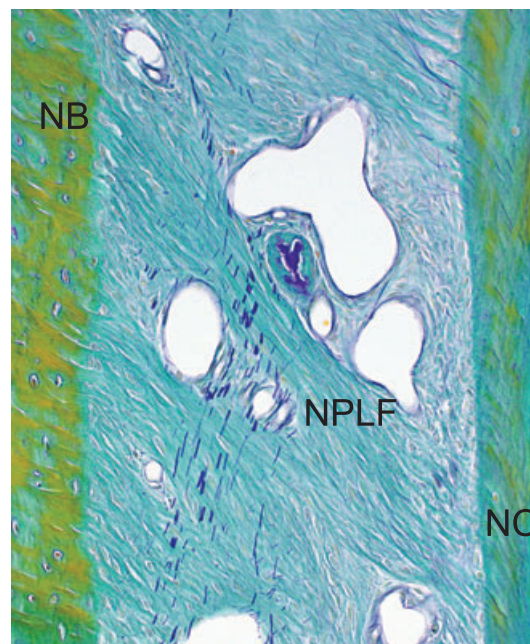


Fig. 6. Light micrograph illustrating true periodontal regeneration as demonstrated by new periodontal ligament fibers (NPLF) inserting into new bone (NB) and new cementum (NC). (Paraffin section, oxone-aldehyde-fuchsin-Halmi stain.)

cementum or dentin needs to be decalcified. The clinical and histological effects of this type of root surface treatment have been discussed previously in excellent reviews (46, 48, 78). The biological concept behind root surface demineralization is to improve blood clot adhesion to exposed collagen fibrils. Stabilization of the coagulum may have a positive effect on wound healing and is regarded as an important contributing factor in achieving periodontal regeneration [reviewed in Ref. (55)]. Mesenchymal cells may preferentially adhere to the blood clot-stabilized root surface and the apical migration of epithelial cells may be reduced. Originally, citric acid was used because of its ability to detoxify the root surface. As reports have shown that treatment with citric acid and phosphoric acid can result in root resorption and ankylosis (1, 47), the chelator EDTA, which possesses a significantly higher pH than acids and is therefore a more gentle agent, appears to be a better choice. Irrespective of the type of demineralizing agent used, it cannot be claimed that demineralization of the root surface *per se* is a regenerative procedure. It may, however, have a positive effect on wound healing and be used as a component of, or a step within, regenerative procedures (e.g. in combination with enamel matrix proteins).

An underestimated issue may be the mechanical strength between the treated root surface and new cementum. Tissue separation between new



Fig. 7. Formation of a long junctional epithelium (LJE) and partial periodontal regeneration, as evidenced by the formation of new cementum (NC) and new bone (NB). The arrowhead points to the apical end of the junctional epithelium, whereas the arrow demarcates the apical border of the defect. This is a section from a monkey tooth 5 months after treatment with Emdogain®. (Paraffin section stained with hematoxylin and eosin.)

cementum and the treated root surface is a very common finding in experimental periodontal regeneration studies [reviewed in Ref. (62)]. As tissue processing for paraffin histology is prone to shrinkage alterations, these tissue gaps are widely believed to represent artifacts. The presence of plaque bacteria in such gaps (Fig. 8), however, suggests that not all gaps are artifactual in nature (8). Moreover, cemento-dentinal tears have been confirmed, by radiographic observations, to be present in periodontally involved teeth and after regenerative periodontal therapy (15, 18, 33, 34, 36, 45, 49, 52), and are associated with rapid periodontal breakdown. Thus, appropriate root surface conditioning may not only provide a biocompatible surface for cell attachment, cell spreading and matrix deposition, but might also improve mechanical interfacial bonding and therefore could be an issue of clinical relevance. It is striking that histology often discloses that root surfaces naturally conditioned by odontoclasts appear to provide a better substrate for new cementum attachment than otherwise modified root surfaces (Fig. 9), as also discussed by Schroeder (62).

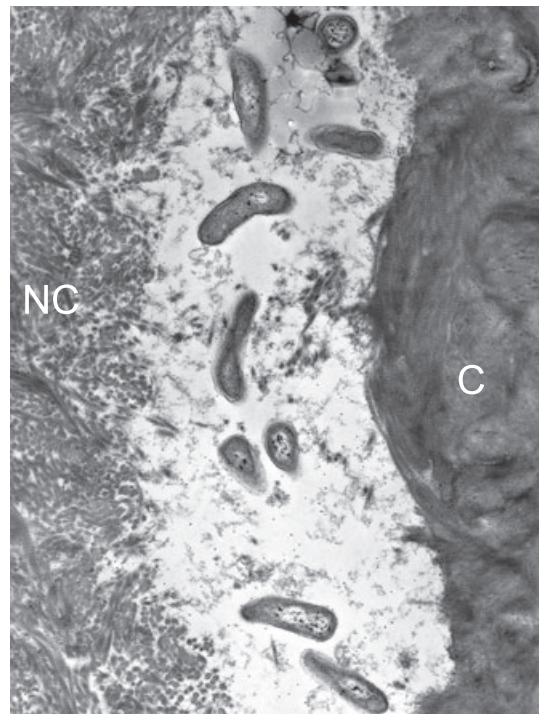


Fig. 8. Transmission electron micrograph illustrating an interfacial gap that formed between the instrumented root surface and new cementum (NC) following regenerative periodontal therapy. Note that the gap between old cementum (C) and new cementum is filled with bacteria.

Bone grafts and bone substitute materials

Autogenous bone, allogeneic bone, xenogeneic bone substitutes and alloplastic materials, hereafter collectively referred to as bone fillers, have all been used with the aim of achieving periodontal regeneration (22, 58, 78). A systematic review has shown that clinical parameters are improved when intrabony and Class II furcation defects are treated with bone fillers (58). The rationale behind the use of bone fillers is to take advantage of one or more of the following properties of such materials, namely osteoconduction, osteoinduction and osteogenesis, induced by transferred cells that are capable of differentiating into osteoblasts (5, 6, 37). Not all three properties apply to every type of bone filler. While the contribution of transferred cells to new tissue formation may be overestimated, osteoconduction is the most powerful property of bone fillers to support new bone. While re-entry surgery or radiographs demonstrate impressive volume gains, the actual ratio of filler material to new bone cannot be determined using these methods. The exact nature of changes occurring around bone fillers in osseous periodontal defects can only be determined by means

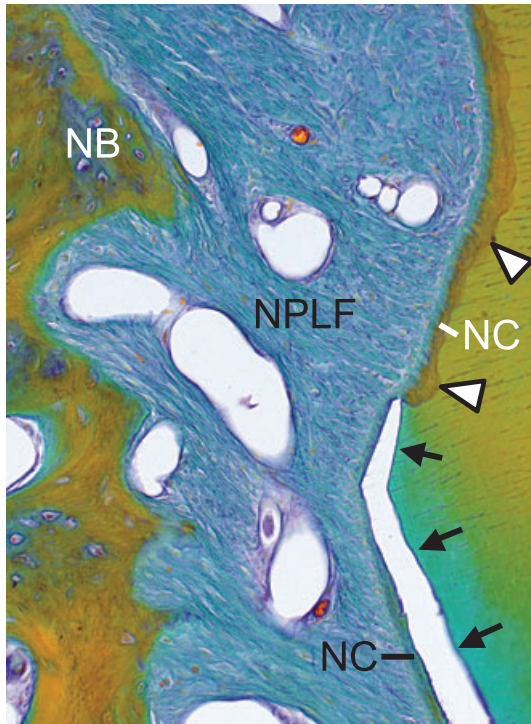


Fig. 9. Light micrograph illustrating new periodontal ligament fibers (NPLF) inserting into both new bone (NB) and new cementum (NC). Note that the thin apical cementum layer became detached from the very smooth-looking dentin surface (arrows). By contrast, there is a tight bonding between the coronal cementum layer and the dentin surface. The latter reveals signs of previous resorptive activity, as evidenced by the presence of Howship's lacunae (arrowheads). (Paraffin section, oxone-aldehyde-fuchsin-Halmi stain.)

of histological evaluation. As in guided bone regeneration, nonosteoinductive bone fillers show deposition of new bone only in proximity to the pre-existing bone (i.e. close to the bone defect margin) (Fig. 10). At a distance from the bone, bone fillers without osteoinductive properties generally show fibrous encapsulation (Fig. 11). It should be noted, however, that material-specific differences seem to exist with regard to the extension of new bone formation from the pre-existing bone. While a bovine-derived xenograft has only occasionally shown fibrous encapsulation (68, 79), both bioactive glass (70) and biphasic calcium phosphate (71) have consistently demonstrated a predominantly fibrous encapsulation.

So far, these observations are limited to bone formation only. With regard to periodontal regeneration, which includes the formation of new connective tissue attachment to the root surface, the available data currently do not look promising. Histologic evidence of new connective tissue attachment is limited.

Regarding autogenous bone, both a long junctional epithelium and some new connective tissue attach-

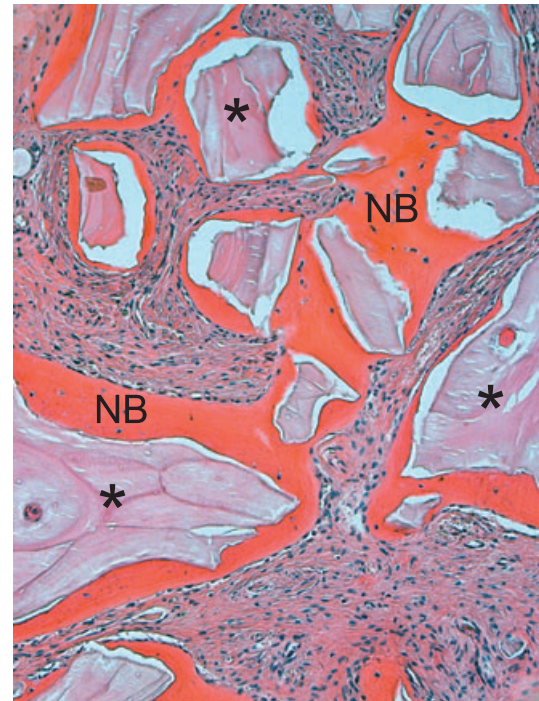


Fig. 10. Light micrograph illustrating new bone (NB) deposited at the periphery of a xenogeneic bone-substitute material (asterisks). Note the bone bridging between neighboring xenograft particles. (Paraffin section stained with hematoxylin and eosin.)

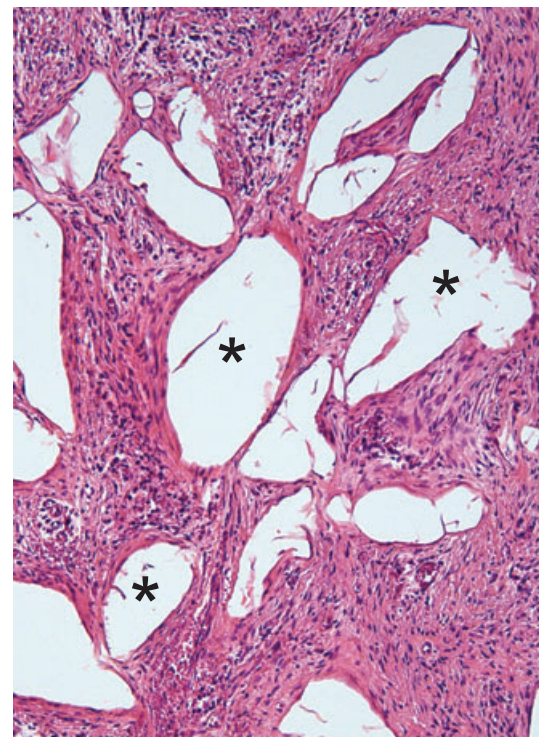


Fig. 11. Light micrograph demonstrating fibrous encapsulation of an alloplastic bone-substitute material (asterisks). There is no new bone formation at all. (Paraffin section stained with hematoxylin and eosin.)

ment are observed [reviewed in Refs (40, 78)]. It may therefore be concluded that histologic evaluation of human and animal studies suggest that the treatment of periodontal osseous defects with autogenous bone grafts lacks predictability and that only limited amounts of new connective tissue attachment form.

Bone allograft materials are generally used as either freeze-dried bone allografts or as demineralized freeze-dried bone allografts. The effects of allogeneic bone grafts on the regeneration of intra-osseous periodontal defects have also been extensively reviewed (22, 40, 78). The conclusions are controversial and range from optimistic to no osteoinductive effects for demineralized freeze-dried bone allografts. Wide variation has been observed in the ability of commercially available demineralized freeze-dried bone allografts preparations to induce new bone formation, which may be related to donor age and to the content of bone-inducing factors in the donor bone (22). Concerning periodontal regeneration, one human histologic study showed that implantation of freeze-dried bone allografts into intrabony periodontal defects resulted in a long junctional epithelium, but no new connective tissue attachment (24). By contrast, the use of demineralized freeze-dried bone allografts resulted in histologic evidence of periodontal regeneration (11, 12). While allografts are widely used in the USA, they are less popular in Europe, partly because of restrictive local regulations within the European Union. The frequently observed resorption may be another reason for reluctant (limited) use of allografts.

Concerning xenogeneic and allogeneic bone substitutes, there is only vague histologic evidence that the formation of new connective tissue attachment is enhanced. As xenografts and allografts were often tested together with a barrier membrane, the often-observed histological evidence of new connective tissue attachment is probably related to the barrier function and not to the supporting materials. Encapsulation in soft connective tissue is a common observation of these bone-substitute materials [reviewed in Ref. (40)].

The basic problem pertaining to all bone filler materials is that a biologic rationale for the regeneration of the periodontium is missing. Bone grafts or bone substitute materials do not possess the ability to regenerate lost connective tissue attachment. The formation of a connective tissue attachment to the root surface may be absent or may not progress beyond what can be achieved with conventional therapy (i.e. open flap surgery alone). The osteoconductive, osteoinductive and/or osteogenic properties

of such materials can at best support new bone formation. Their efficacy is proven in conjunction with barrier membranes in guided bone regeneration procedures (i.e. for augmentation of bone deficiencies or defects to install dental implants). The mechanical membrane support may also be beneficial for guided tissue regeneration approaches around teeth, as the bone-filler particles support the barrier membrane and prevent its collapse into the defect.

Guided tissue regeneration

Guided tissue regeneration is a technique that is based on a solid biologic principle. The rationale behind guided tissue regeneration is to use a physical barrier (barrier membrane or simple membrane) to selectively guide cell proliferation and tissue expansion within tissue compartments [reviewed in Refs (40, 41)] (Fig. 12). The barrier membrane prevents gingival epithelium and connective tissue expansion and favors migration of cells from the periodontal ligament and alveolar bone into the periodontal defect. The foundation for the development of the guided tissue regeneration principle was informed by the realization that the periodontal ligament is of central importance to the regenerative processes of the tooth-attachment apparatus (13, 28, 39, 42, 50, 54). Numerous experimental animal studies have

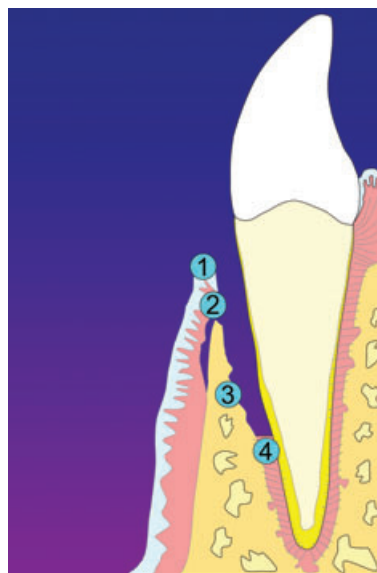


Fig. 12. Schematic drawing illustrating the four compartments from which cells can grow into the periodontal defect and repopulate the root surface after periodontal therapy: (1) oral gingival epithelium; (2) gingival connective tissue; (3) bone from the alveolar process; and (4) periodontal ligament.

proven that this principle leads to periodontal regeneration, and human histology has documented that periodontal regeneration can be achieved [reviewed in Refs (40, 41)]. In the early days, the development of the guided tissue regeneration technique raised hope that lost periodontal tissues can be regenerated in a predictable manner for many defect types. There are, however, some drawbacks. For everyday clinical practice, patient and defect selection may not be as rigorous as in well-designed clinical studies, and the recall schedule is usually less rigorous. Another problem relates to the exposure of membranes to the oral environment and their inevitable contamination with bacteria [reviewed in Ref. (2)]. Nonresorbable membranes are particularly prone to exposure to the oral environment. As a consequence, bacterial contamination and infection may result in delayed wound healing and poor regenerative outcomes. Biodegradable collagen membranes possess a lower risk of exposure and do not need a second surgical procedure for their removal. As collagen membranes possess fewer favorable mechanical properties than nonresorbable membranes, a bone filler is needed to prevent their collapse into the defect area. A recent systematic review came to the conclusion that most preclinical studies have histologically demonstrated periodontal regeneration when grafting materials are combined with barrier membranes (65).

The guided tissue regeneration technique is sensitive and technically demanding. Outcome improvements through the development of new types of barrier membrane (e.g. resorbable collagen membranes, degradable synthetic membranes) may solve some of the reported problems. However, harmful degradation products of synthetic membranes, and difficulties encountered in attempts to seal off the gingival compartment against the space occupied by periodontal ligament and bone without interfering with the very important re-establishment of the junctional epithelium, may hamper such attempts.

Growth / differentiation factors

For many years, research has attempted to use biologically active molecules to achieve periodontal regeneration. Among these molecules are: extracellular matrix proteins and cell-attachment factors; mediators of cell metabolism and activity; and growth / differentiation factors. Growth factors regulate cell proliferation, cell activity, chemotaxis and / or cell differentiation. Numerous growth factors, alone or in

combination, have been tested for periodontal regeneration in animal experiments. Among these are insulin-like growth factors, fibroblast growth factors, epidermal growth factor, platelet-derived growth factors, vascular endothelial growth factor, parathyroid hormone, transforming growth factor- β and bone morphogenetic proteins. In addition, the clinical effectiveness of recombinant human platelet-derived growth factor-BB, platelet-rich plasma and peptide P-15 has been tested for the treatment of intra-osseous and furcation defects (76). A tremendous amount of work has resulted in an enormous number of original articles that have reported upon the efficacy of added growth factors or related bioactive agents in animal and human periodontal defect models. The outcomes of these experiments have been exhaustively presented and discussed in a considerable number of reviews (14, 19, 23, 27, 43, 53, 59, 60, 72). The most promising growth factors appear to be the bone morphogenetic proteins, particularly bone morphogenetic protein-2 and bone morphogenetic protein-7, the same growth factors that are approved and applied in the orthopedic field for hard-to-heal cases (i.e. nonunion, open tibial fractures and spinal fusions), but only when all other treatment options have failed. What can we learn from all these studies and discussions? The translation of knowledge about the functions of bone morphogenetic proteins and other growth factors in embryonic development, tissue formation and homeostasis, and bone healing, into a clinically applicable solution with the aim to regenerate lost periodontal tissues, appears to be very difficult, if not impossible, at the present point in time. Critical issues include: (i) the complexity of the periodontium, which consists of four different tissues; (ii) the use of very high doses of bone morphogenetic proteins; (iii) the ideal carrier has still not been found; and (iv) the enormous costs that are associated with recombinant human bone morphogenetic proteins in relation to relatively small and non-life-threatening periodontal defects for which other treatment options exist.

What can be learned from all of these studies? Despite the fact that very heterogeneous preclinical studies have been performed (i.e. different species, different defect designs, different growth factor doses, single or combined use with other growth factors, different vehicles), most authors concluded that the growth factors evaluated achieved successful periodontal regeneration and it is just a matter of time until their therapeutic application. However, despite a long history of preclinical evaluation with promising results, the routine use of growth factors as

therapeutic agents for periodontal regeneration is not yet a reality. Were preclinical data interpreted too optimistically? Or is it just too simplistic to think that one therapeutically applied growth factor can really restore the complexity of the periodontium?

Enamel matrix proteins

Compared with growth factors such as bone morphogenetic proteins, enamel matrix proteins emerged relatively late as a therapeutic option for periodontal regeneration. Even more surprising is that their entry into the dental practice occurred long before an adequate number of studies was available that allowed a scientifically sound explanation to be provided for the positive effects of enamel matrix proteins on periodontal wound healing and regeneration. Many clinical studies have shown positive effects of an enamel matrix derivative (Emdogain[®], Institute Straumann AG, Basel, Switzerland) for the treatment of periodontitis [e.g. (75)], and many reviews of clinical and histological studies document such beneficial effects (25, 38, 66, 77). Concerning periodontal regeneration, numerous histological studies have shown the formation of new cementum and new bone with inserting

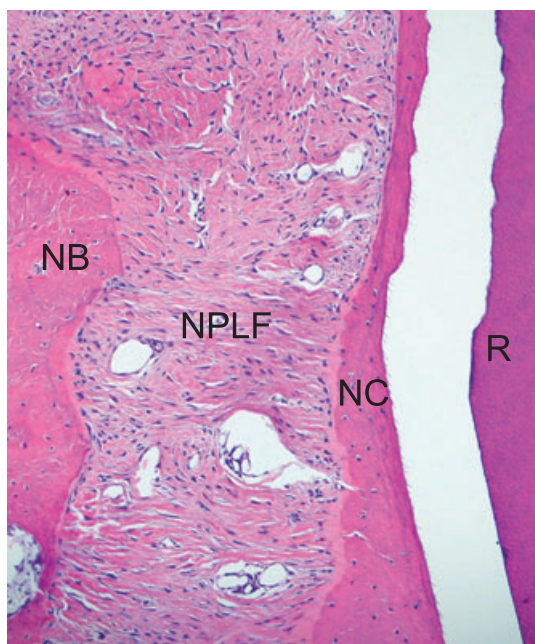


Fig. 13. Light micrograph illustrating periodontal regeneration, as evidenced by formation of new periodontal ligament fibers (NPLF) inserting into both new bone (NB) and new cementum (NC). Detachment of cementum from the treated root (R) surface is a common finding in paraffin sections. (Paraffin section stained with hematoxylin and eosin.)

connective tissue fibers (Fig. 13). Of major interest is the biological concept behind the therapeutic use of enamel matrix proteins for periodontal regeneration. Based on circumstantial evidence, the original idea emerged that there was a causal relationship between enamel matrix proteins and cementogenesis (31, 32). However, such a cause–effect relationship has never been proven experimentally. Over a period of more than a decade, more than 100 nonclinical and non-histological studies formed a basis that allowed the development of a comprehensive picture of what appears to be responsible for supporting periodontal regeneration [reviewed in Ref. (4)]. Overall, these data provide evidence for enamel matrix proteins to support wound healing and new periodontal tissue formation. However, as with any other regenerative technique, patient and defect selection and appropriate recall programs are mandatory for successful outcomes. Furthermore, the clinician's experience and skills, and a biological understanding of periodontal wound healing and regeneration, are certainly of additional advantage.

Conclusions

The answer to the question, 'Does periodontal tissue regeneration really work', may simply be, 'Yes, it does'. As a proof of principle, many histological studies, mainly performed in animals, have provided evidence that various treatment modalities have regenerative potential. However, human studies comparing regenerative procedures with the standard of care alone as a control are lacking. In human studies, usually hopeless (i.e. irrational to treat) teeth are used, because of ethical considerations. It should, however, always be borne in mind that these teeth may possess a considerably lower regenerative potential than less affected or periodontally healthy teeth. Furthermore, the number of treated human teeth scheduled for histological assessment is always at the lower end. Many studies give ample scope for interpretation and sometimes they convey the feeling that a wide margin is left for the imagination. It is not that difficult to find a photo micrograph showing new connective tissue attachment to the root surface. How meaningful are such data, when taking into consideration that other teeth treated in the same way show formation of a long junctional epithelium? Moreover, even in the same treated defect, both periodontal regeneration and repair (i.e. formation of a long junctional epithelium) can occur (Fig. 7). Do histomorphometric

measurements overcome these shortcomings? We very much rely on statistical significance rather than clinical significance. How shall we deal with the fact that a regenerative procedure may produce 0.0 mm of new attachment around one tooth, whereas other teeth show, for the same technique, a broad range from a fraction of a millimeter to a few millimeters? And even if there are statistically significant differences, one question remains: 'Does statistical significance equate to clinical significance?'. Furthermore, in many clinical situations where regenerative techniques are used, despite significant probing depth reduction and gains of clinical attachment, residual defects still remain. Currently, there is limited knowledge on the issue of to what extent such remaining deep sites (i.e. residual pockets) are prone to bacterial recolonization and subsequent deterioration. All these issues need to be discussed and re-evaluated. Better outcome criteria, such as a threshold for what is 'sufficient' new attachment, need to be established for regenerative treatment modalities in order to obtain a seal of approval that is accepted worldwide and subsequently applied.

Our perspective on the current evidence is that regenerative periodontal therapies to date can only restore a fraction of the original tissue volume in extent. Thus, complete periodontal restoration may still be regarded as an illusion. When it comes to predictability and a substantial extent of new attachment formation, there are only a few regenerative techniques available. Guided tissue regeneration and enamel matrix proteins certainly have a regenerative potential. However, these regenerative techniques do not relieve the dentist from his responsibilities. As with so many other sensitive techniques, important aspects to be considered as outcome determining variables include: (i) appropriate patient and defect selection; (ii) correct application of a regenerative device or a technique; and (iii) the dentist's experience and skills. Finally, it is striking to realize how little biology is considered. Minimally invasive surgical techniques for improved wound stabilization and sufficient time for healing should be developed. Finally, it should still be borne in mind that the structural and interactive complexity of periodontal tissues is probably one of the reasons why it is so difficult to regenerate the periodontium.

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