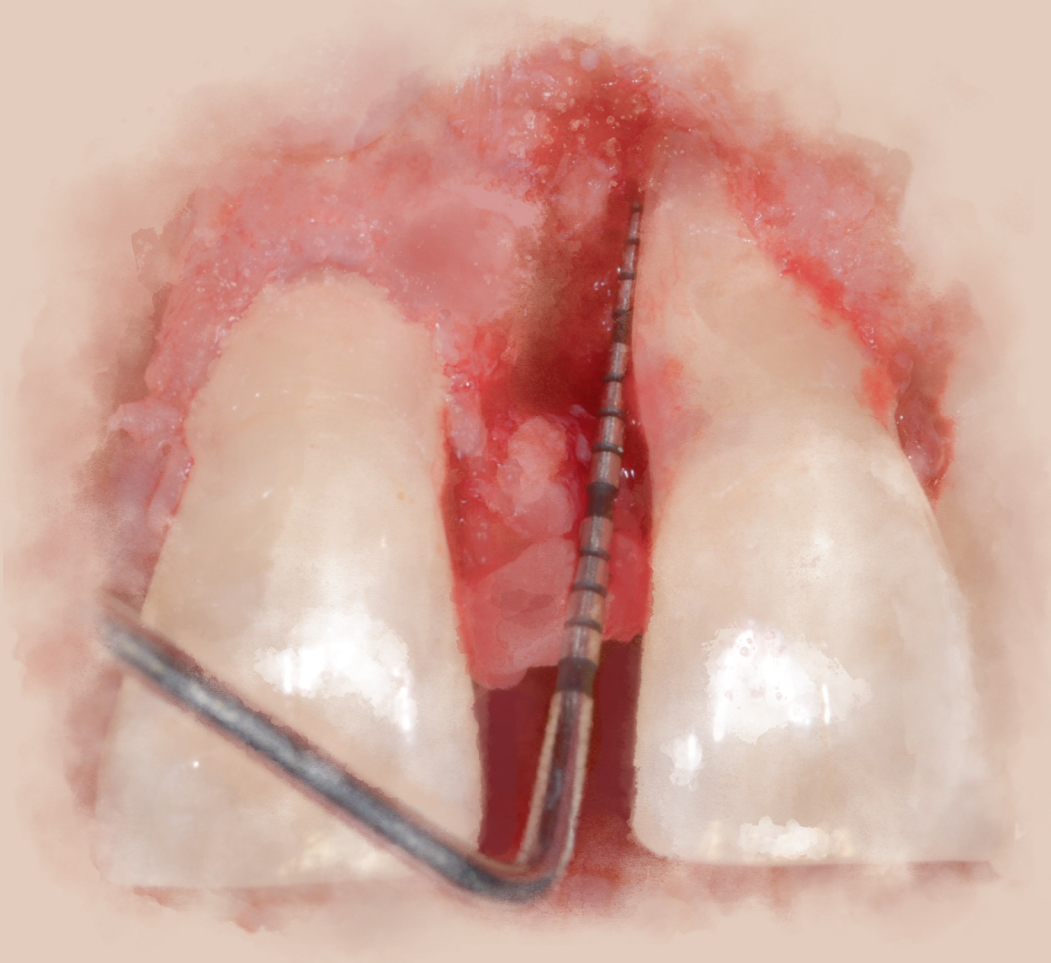
SIMPLIFIED REGENERATIVE PROCEDURES

for Intraosseous Defects

Edited by
Leonardo Trombelli, DDS, PhD



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To my mentor, Prof Giorgio Calura, with gratitude

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FOREWORD

It is always a great satisfaction when you are asked to write a foreword of a good book. This is especially true when the book expands our scientific culture and promotes the training of our students and professionals. Frequently, these books introduce new knowledge or new technologies. However, it is less frequent for a book to be purposely focused on training students and professionals on surgical procedures. This atlas focuses on evidence-based education and in acquiring relevant professional competencies in the surgical treatment of specific periodontal lesions (ie, intraosseous defects). The information provided is clear, well organized, and very practical, but at the same time it is rigorous and up to date with current knowledge, comprehensively covering the fundamentals of periodontal regeneration and the use of the different technologies. It particularly focuses on simplified surgical procedures aimed to attain the best possible regenerative outcomes with minimal invasiveness.

The author, Prof Leonardo Trombelli, has dedicated many years of his professional life to studying and researching successful long-term periodontal therapy and specifically the use of regenerative surgical interventions to improve the prognosis of periodontally affected teeth. He has published essential scientific articles that provide the basis for this book. His contribution to this work clearly demonstrates not only his excellent scientific background but also the teaching abilities that are needed to produce a book such as this, with scientific rigor and at the same time with practical relevance for students and professionals. Moreover, the many contributors in this work are not only well respected in Italy but also in Europe and beyond.

In summary, this book is clear and well written and provides very useful and relevant content to support dentists and periodontists in learning how to apply modern periodontal surgical interventions to achieve regeneration in teeth that have lost periodontal attachment as a consequence of periodontitis.

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PREFACE

Man should be as eager to simplify his life as he is to complicate it.
–Henri-Louis Bergson

For 20 years, in collaboration with the whole research group at the Research Centre for the Study of Periodontal and Peri-Implant Diseases, University of Ferrara, we have been making a great effort in trying to find diagnostic and therapeutic solutions that could optimize endpoints while making clinical processes and pathways easier for practitioners and students. We started back in 2007 with a simplified method to access deep intraosseous defects (the *single-flap approach*, or SFA, that will be extensively described in this book). Then, in 2008, we introduced the Smart Lift technique—a simplified, standardized method to perform sinus elevations with a minimally invasive transcrestal surgical procedure (a method that has been extensively investigated and published on for more than 10 years). In 2009, we reported on a simplified method to assess the periodontal risk profile of the patient, based on five straightforward parameters that have been shown to be linked to the progression of periodontal breakdown. And more recently, in 2018, we published on a simplified method for horizontal bone augmentation, which is based on the creation of a periosteal pouch that acts as an osteogenic, space-providing membrane for bone grafting (the subperiosteal peri-implant augmented layer, or SPAL technique).

The development of simplified procedures has been a main focus of my career for two main reasons. First, I want to provide the profession with simple, straightforward, innovative solutions that may bring clinicians closer to procedures that are otherwise neglected because of their potential complexity. In search of simplified diagnostic and treatment procedures, we targeted those that are mostly perceived as successful only when performed by the talented and gifted hands of a few select colleagues. I am well aware that spreading the use of simplified procedures among dental professionals means amplifying the number of patients who may benefit from them. The second reason is related to my mission as a university faculty member. Teaching simple procedures can help the great majority of students to reach a high level of competence in a reasonable amount of time with a fast learning curve.

These two reasons represent the main driving force that brought me to write this book. With the large number of photographs and videos of many different clinical cases, the textbook has been designed as a sort of tutorial for both graduate students and practitioners who want to expand their knowledge and technical skill in the nonsurgical and surgical treatment of deep intraosseous defects, very common lesions in patients with Stage III and IV periodontitis. In particular, the SFA is thoroughly described with a step-by-step approach, starting from the analysis of diagnostic and prognostic patient/defect characteristics to the selection of surgical instruments, choice of flap design, methods for root debridement and

conditioning, use of appropriate regenerative technologies, description of suitable suture techniques for different flap designs, and the short- and long-term postsurgery care. A multitude of clinical cases are illustrated in great detail in order to provide a wide range of scenarios and conditions where the SFA can be easily and successfully applied.

In conclusion, I wish to acknowledge all the coauthors who have contributed to make this textbook a unique, up-to-date manual on regenerative procedures: Anton Sculean, Dieter Bosshardt, and Raluca Cosgarea, who have thoroughly described the fundamental principles of periodontal regeneration; Mario Aimetti, Giulia Mariani, and Federica Romano, who described novel nonsurgical approaches; and Roberto Farina for his talented help with the surgical chapter. A special thanks to Anna Simonelli, who spent a great amount of her postgraduate education and PhD program coordinating and monitoring a massive amount of clinical research on the SFA. Without her precious work, this textbook would have never reached such a level of quality and completeness. Also, I want to express my sincere gratitude to Quintessence Publishing, who from the very first moment has strongly and convincingly believed in this challenging editorial project. Last but not least, I want to thank my family: my wife, Cristina, and my children Emma and Andrea for their continuous, silent, and patient support.

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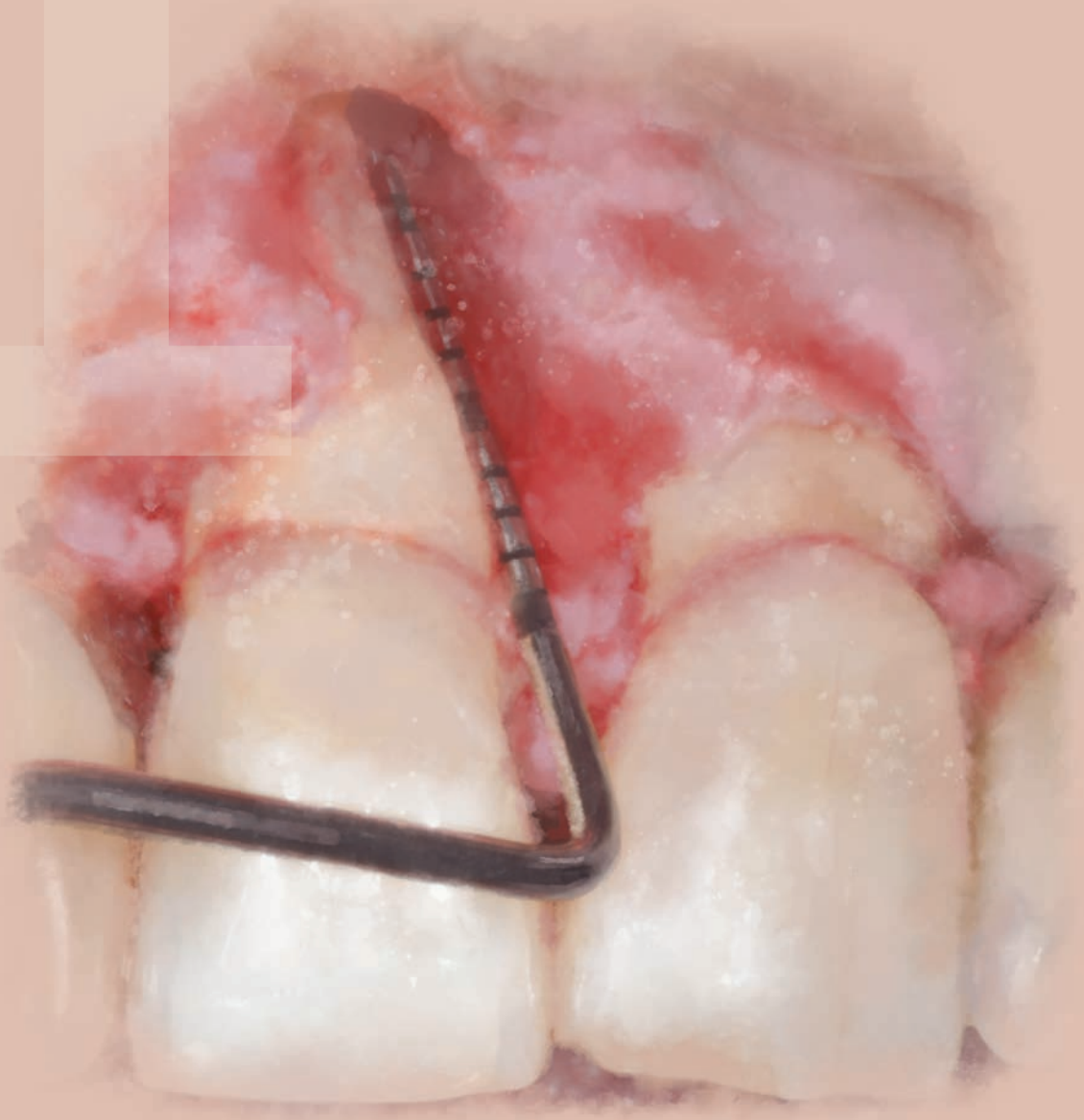

INTRODUCTION

Leonardo Trombelli, DDS, PhD
Roberto Farina, DDS, PhD, MSc
Anna Simonelli, DDS, PhD

WHY A TEXTBOOK ON THE TREATMENT OF INTRAOSSEOUS DEFECTS?

The prevalence of intraosseous defects in adults was investigated on dried skulls[1] as well as through clinical[2,3] and radiographic assessments.[4–8] At the patient level, the presence of at least one intraosseous defect was detected with an incidence ranging between 25.5% and 51% in samples representative of the general population or specific age cohorts,[1,6,7] between 18% and 23% in patients seeking dental care,[4,8] and of 45.1% in a periodontally compromised cohort.[2] A retrospective study revealed that intraosseous lesions are at high risk of further progression, and they may lead to tooth loss if left untreated.[9] Papapanou and Wennström[9] retrospectively recorded the bone level changes as well as tooth loss over a 10-year period at tooth sites with intraosseous defects in individuals not treated with systematic periodontal therapy. The results demonstrated an increased frequency of tooth loss and bone loss with increasing depth of the intraosseous defect. In particular, the proportion of teeth lost between the 1- and 10-year examinations was 22%, 46%, and 68% for teeth with a defect depth of 2 mm, 2.5 to 4 mm, and ≥ 4.5 mm, respectively.

These observations reinforce the need for:

- A proper diagnosis of the intraosseous defect, which represents a common lesion in patients affected by Stage III and IV periodontitis.
- An appropriate treatment of the lesion that may successfully revert those conditions (probing depth [PD] ≥ 5 mm associated with bleeding on probing [BOP]) conducive to progressive attachment/bone loss.

WHY A TEXTBOOK ON REGENERATIVE PROCEDURES?

The ideal outcome of the surgical treatment of a deep intraosseous defect is the regeneration of the tooth attachment apparatus destroyed by the process of periodontitis. From a histologic point of view, periodontal regeneration implies the formation of periodontal ligament fibers inserted into newly formed cementum and bone.[10] Data from human histologic studies have provided evidence that periodontal regeneration may be accomplished by using different regenerative technologies, including membranes and biologic agents[11–15] (see chapter 2).

Extensive clinical data have shown that compared with nonregenerative treatment, the surgical regenerative treatment of deep intraosseous lesions may result in a considerable improvement of probing parameters following the tissue maturation phase.[16–21] From a clinical point of view, periodontal regeneration may result in a substantial increase in clinical attachment level (CAL) gain (of at least 3 mm) and relevant bone fill of the intraosseous component of the lesion together with a maintainable, stable probing depth (ie, PD ≤ 4 mm in absence of BOP).

Sculean et al[22] published the results of a 10-year follow-up after the regenerative treatment of 38 intraosseous periodontal defects with different regenerative treatments: enamel matrix derivative (EMD), guided tissue regeneration (GTR), combination EMD and GTR, and open flap debridement (OFD). After treatment, all patients were placed in a 3-month supportive periodontal care program. At 1 year, a significantly greater CAL gain was achieved in the regeneration groups (ie, GTR, EMD, or combination) compared to OFD controls, and this was maintained substantially unvaried for a 10-year period.

A 20-year follow-up after regenerative treatment of intraosseous defects was recently reported in a cohort of 45 patients.[23] Defects were treated with three different modalities: GTR with modified papilla preservation flap, GTR with conventional access flap, and access flap alone without membrane. All patients were enrolled in a supportive periodontal care program with 3-month recalls. At both 1-year and 20-year reevaluation, a significantly better CAL gain and PD reduction was obtained by the two GTR treatments than the access flap. Moreover, the access flap surgery was associated with a greater disease recurrence.[23]

Collectively, available data seem to support the use of regenerative devices to ensure better short- and long-term outcomes than mere surgical debridement at deep intraosseous defects.

WHY A TEXTBOOK ON SIMPLIFIED TREATMENT PROCEDURES?

Despite decades of well-established nonsurgical and surgical protocols and techniques, the treatment of deep intraosseous lesions still represents a challenge for clinicians. There is a perception that the regenerative treatment of an intraosseous lesion is both technically sensitive and costly, with limited outcome predictability in the hands of the average operator (ie, not specially trained or highly skilled). This perception is likely due to aspects related to debridement of any lesions via a "closed" approach (see chapter 3) and those associated with the difficulty in performing a correct flap design and suturing technique as well as in selecting the appropriate regenerative

technology. The purpose of this textbook is to present simplified procedures that may overcome these issues, at least in part, when treating an intraosseous defect.

The term *simplify* means the act of making something less complex. In the present textbook, we define a procedure aimed at improving the clinical conditions of a deep intraosseous lesion (in terms of substantial clinical and histologic attachment gain and bone fill, reduction of the PD to a maintainable condition, and limited to no postsurgery recession) as *simplified* when characterized by more favorable conditions for the patient and/or the clinical operator. Although the terms *simplification* and *minimal invasiveness* may appear as synonyms when referring to periodontal treatment, in our perspective *simplification* implies a substantially broader concept.

For the operator, a simplified procedure has the following characteristics[24]:

- Limited surgical equipment
- An easy-to-learn technique
- Limited need for additional treatments or devices (through the maximization of the inherent healing potential of the treated lesion)

For the patient, a simplified procedure should have a reduced impact on the following[24]:

- Posttreatment daily activities
- Posttreatment pain and discomfort (also reducing the required compliance for posttreatment regimens)
- Preexisting esthetics

For both patient and operator, a simplified procedure should reduce both treatment costs and chairside time needed for both treatment administration and follow-up visits.[24] This also results in fewer treatment costs.

Nonsurgical therapy as a standalone treatment always represents a "simplified" procedure, particularly when compared with surgical approaches. Among the available surgical options, simplified surgical procedures share a common technical aspect (ie, the elevation of a single flap on the buccal or palatal/lingual aspect), leaving the tissues on the opposite side intact. In this respect, this textbook will focus in detail on a novel surgical approach—the single-flap approach—that was first introduced in 2007[25] and repeatedly validated by different randomized clinical trials thereafter (see chapter 4). The single-flap approach was shown to be at least as effective as traditional papilla preservation techniques when evaluated either as a standalone protocol or in combination with regenerative devices.

The main goal of this textbook is to show the effectiveness of simplified surgical procedures to treat challenging intraosseous lesions. The authors' ambition is to teach how clinicians may achieve substantial treatment outcomes associated with minimal esthetic impairment and a more tolerable postoperative course.

Simplifying both the nonsurgical and surgical treatment phases will achieve the following outcomes:

- Reshape the learning curve, thus increasing the generalizability of treatment outcomes
- Improve patient access to care by limiting biologic and economic costs

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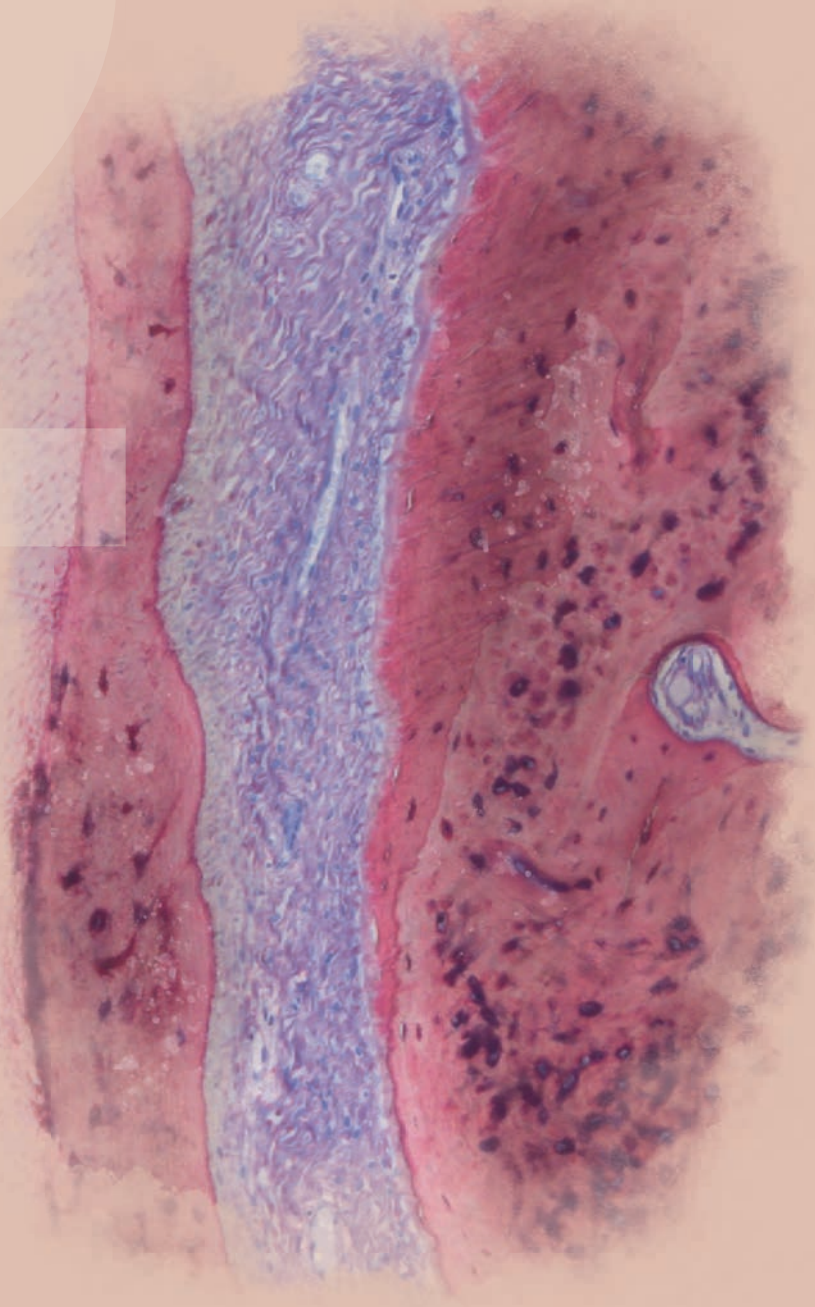

FUNDAMENTALS IN PERIODONTAL REGENERATION

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Dieter D. Bosshardt, PhD
Leonardo Trombelli, DDS, PhD
Anton Sculean, DMD, Dr hc, MSc

PRINCIPLES OF PERIODONTAL WOUND HEALING

Based on histologic observations, the healing process of a mucogingival flap at a tooth surface resembles that of epidermal wound healing.[1] This is characterized by an initial adhesion/adsorption of a fibrin clot to the wound margins, followed by early and late phases of inflammation, then formation of granulation tissue and a matrix. The final step of wound healing is tissue remodeling[2,3] (Fig 2-1). As opposed to epidermal wound healing (ie, epidermal incisions or excisions) where the opposing wound margins are two vascular gingival/mucosal margins, periodontal wound healing is different because healing occurs between a vascular surface (ie, epithelium, connective tissue) and an avascular, rigid, mineralized surface (ie, cementum or dentin). Additionally, tissue resources for the healing process derive from the mucogingival flap, the alveolar bone, and the periodontal ligament (PDL).

The periodontal healing process is initiated by adsorption/adhesion of plasma proteins (ie, blood-derived proteins) onto the exposed root surface at the time of flap closure, resulting in clot formation at the tooth-mucogingival interface.[4] This clot has a dual role as protection for the denuded tissues and as a provisional matrix for the consequent cell migration.[2] In the early phase of inflammation, which follows within hours after incision, inflammatory cells (ie, neutrophils and monocytes) colonize onto the root surface, cleansing the wound area from necrotic debris and bacteria via phagocytosis, enzymes, and toxic oxygen products. A few days later, macrophages invade the wound, and the late phase of inflammation begins. Macrophages sustain the release of various growth factors and cytokines, which in turn stimulate migration of various cells from the circumscribing tissues (fibroblasts, endothelial cells, etc), forming a cell-rich granulation tissue. This undergoes maturation and remodeling: fibroblasts replace the initial provisional matrix with a new matrix rich in collagen, and a connective tissue attachment is established by day 7. However,

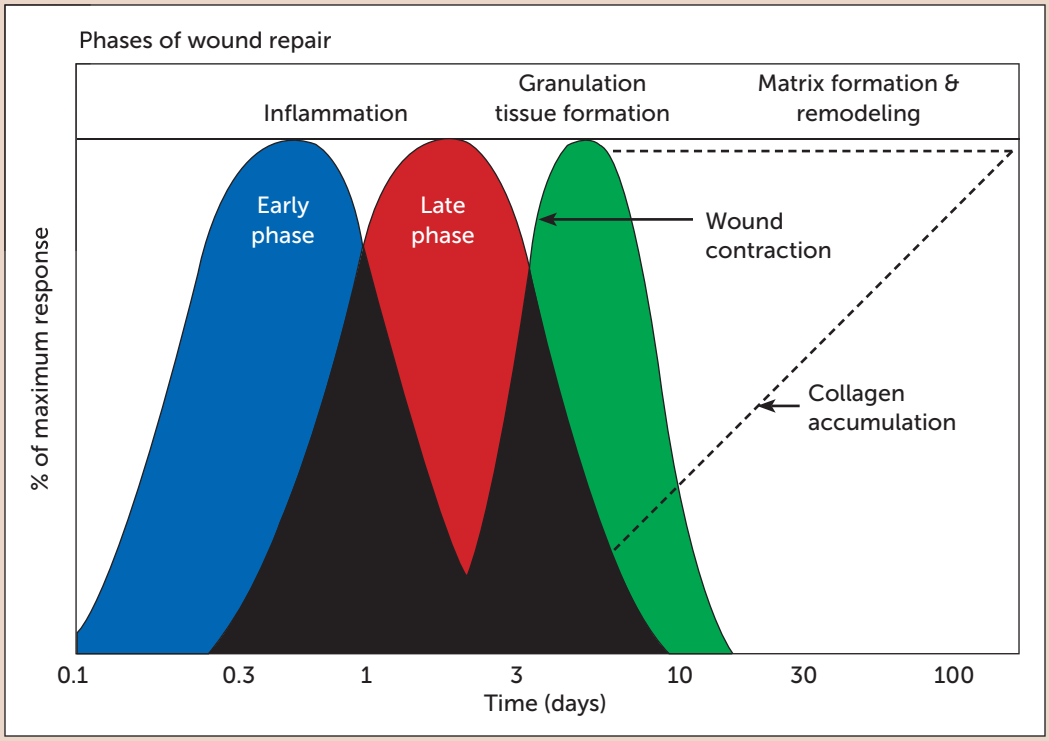

Fig 2-1 Phases of epidermal incisional wound healing, including an early (ie, within hours) and a late (ie, within days) phase of inflammation dominated by polymorphonuclear neutrophils and macrophages, respectively. The magnitude of wound contraction parallels the phase of granulation tissue formation. Collagen accumulation is first observed during the phase of granulation tissue formation, continuing through the phase of matrix formation and remodeling (courtesy of Dr Richard AF Clark).

depending on the wound size and the cell resources of the surrounding area, a fibrin clot may still be observed at the maturation stage. These observations underline the importance of allowing adhesion/adsorption of plasma proteins onto the root surface undisturbed to form new connective tissue attachment/periodontal regeneration.[1,4]

Epithelial versus connective tissue attachment

The type of healing—regeneration or repair/scar formation—is determined by the maturation of the granulation tissue in the periodontal wound.[5] This depends on the available cell types and signals that stimulate the migration of these cells into the granulation tissue.[5]

Healing in the form of periodontal repair is characterized by a long junctional epithelium (ie, epithelial attachment) between the mucogingival flap and the tooth surface (Fig 2-2). Additionally, a fibrous encapsulation (ie, collagen adhesion) may sometimes be observed with collagen fibrils coming in close vicinity to the root surface and forming a physicochemical attachment.[6] In other situations, the exposed root surface may present repair cementum (intrinsic fiber cementum), and parts of the exposed tooth structure may be replaced with connective tissue initiating root resorption or may be replaced by bone

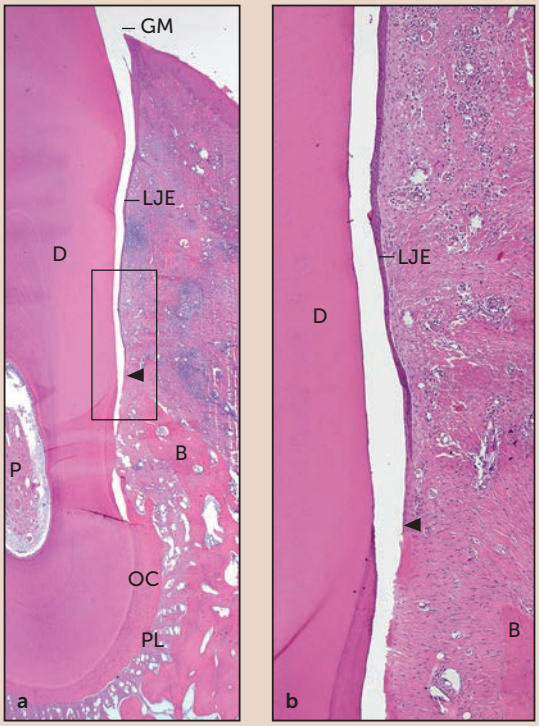

Fig 2-2 Micrographs at low *(a)* and high *(b)* magnifications illustrating the formation of a long junctional epithelium (LJE), when no periodontal regenerative therapy was applied. The *arrowhead* marks the apical end of the junctional epithelium. B, bone; D, dentin; GM, gingival margin; OC, old cementum; P, dental pulp; PL, periodontal ligament.

resulting in ankylosis.[7] Nonetheless, when newly formed collagen fibers are functionally oriented in newly formed cementum (cellular/acellular mixed/extrinsic fiber cementum), healing results in periodontal regeneration.

Early histologic studies pointed out the importance of an adhering fibrin clot to the root surface and its subsequent maturation to prevent an epithelial downgrowth and promote a connective tissue attachment.[8,9] In this sense, histologic experiments in critical-size defects in dogs (5-mm supra-alveolar periodontal defects) showed that an initial contamination of the root surface with heparin rather inhibits the formation/adhesion/adsorption of a fibrin clot and leads to healing with a long junctional epithelium.[10] Nonetheless, it was observed in further animal studies that wound-stabilizing measures like the use of a macropouros polylactic acid (PLA) matrix or an occlusive expanded polytetrafluoroethylene (ePTFE) barrier membrane to divert wound-rupturing forces inhibited the downgrowth of epithelial cells and sustained the maturation of the fibrin clot into a viable connective tissue attachment.[11,12] Thus, the formation, adhesion, and adsorption of a fibrin clot and its integrity against physiologic and/or wound-rupturing forces are critical for its maturation into connective tissue and therefore play a key role in periodontal healing via connective tissue attachment.[8,11,12] In the early healing phase, wound stability is assured by the passive adaptation of the flap and by suturing. Strategically placed holding and closing sutures

have to overcome wound-rupturing tensile forces to ensure primary intention healing until wound maturation (14 days as shown in animal experiments for limited periodontal dehiscence defects).[8] Early suture removal or other traumatic postsurgical procedures (eg, mechanical tooth brushing, periodontal dressings) may interfere with the structural integrity of the wound.[1]

In 1976, Melcher was the first to hypothesize that the cells that initially adhere to the root surface determine the type of the new attachment.[13] In histologic studies, Karring et al not only confirmed this theory but also showed that the PDL has an enormous regenerative potential and further that it is the only structure with the capacity to regenerate the lost periodontal attachment.[14] When cells originating from the PDL are the first to repopulate the previously contaminated root surface, periodontal regeneration seems to occur predictably.[15–17] These research findings therefore suggested that using a barrier to block migration of cells originating from the mucogingival flap may allow the regeneration of lost periodontal tissues; thus, the concept of guided tissue regeneration (GTR) was born.

In this context, further histologic animal experiments evaluated the regenerative potential of PDL in various settings using the critical-size supra-alveolar periodontal defect model and different types of ePTFE membranes.[11,18–20] When the defects treated with ePTFE membranes were evaluated after 4 weeks of healing, bone regeneration was only detectable at sites where the membrane provided space. At 4 weeks of healing, neither cementum nor functionally oriented periodontal attachment could be observed. Moreover, at the sites where the membrane collapsed or wound failure occurred (eg, membrane exposure, infection, necrosis), no regeneration of any tissue could be observed.[11] However, in a subsequent study with a space-providing ePTFE membrane and an 8-week healing period, regeneration of all periodontal tissues (ie, alveolar bone, cementum, and functionally oriented PDL fibers) was noted on the entire exposed root surface. Limited regeneration of periodontal tissues was also observed in cases with membrane collapse or at control sites (no membrane), but inflammation and necrosis occurred at sites with membrane exposure.[18] Thus, it seems crucial to ensure wound healing by primary intention and space provision for a healing and regeneration period of at least 8 weeks to regenerate the lost periodontium.

Another histologic study in dogs treated surgically created periodontal defects with a space-providing nonobstructive gold mesh and showed that osteogenesis occurred even when occlusion of the gingival tissue was not assured.[21] A study testing a structurally reinforced space-providing macroporous ePTFE membrane and a semi-occlusive ePTFE membrane was performed in critical-size supra-alveolar periodontal defects, resulting in comparable significant regeneration of cementum, alveolar bone, and a functionally oriented PDL for both membrane types.[19] Nonetheless, 50% of the sites treated with the occlusive membrane experienced membrane exposure and wound failure, while those treated with the macroporous membrane remained submerged during the entire healing period. Therefore, it can be concluded that the use of a macroporous membrane may support flap survival during the healing period by enhancing vascularization.[19,20,22]

Enhancement of periodontal wound healing/regeneration has additionally been investigated by evaluating the use of agents that modify the root surface. In vitro studies used acidic or chelating agents for root surface demineralization or for the removal of bacterial endotoxins or the smear layer after root instrumentation, leading to exposure of the dentin tubules and the collagen matrix[23–26] and an enhanced adsorption/adhesion of the

fibrin clot to the root surface.[27–29] Surface demineralization showed enhanced formation of new attachment compared with control sites in experimental animal studies,[9,30,31] but this effect has not been observed in clinical studies.[32–34] Moreover, wound healing in the form of a new connective tissue attachment and regeneration of all periodontal tissue (ie, alveolar bone, cementum, functionally oriented PDL) has been shown to be possible without removal of the smear layer or the exposure of the dentin collagen matrix and its growth factors.[17–20,22]

Taken together, observations from experimental studies point out the pivotal role of primary intention healing and space provision with barrier membranes without the need of tissue occlusion (ie, use of macroporous membranes) for achieving periodontal regeneration. Secondly, despite the positive effect of root surface biomodifying agents on fibrin clot adhesion/adsorption, their clinical use remains questionable.

BIOLOGIC CONCEPTS IN GTR

The concept of GTR was developed based on the early hypothesis by Melcher in 1976 and early animal experiments of Ellegaard et al[35,36] and Nielsen et al[37] suggesting that periodontal regeneration is induced by the cells originating from the PDL and not from the alveolar bone as previously believed.[13] As previously mentioned, this hypothesis was then confirmed in experimental studies by Karring et al.[14] Finally, in the early 1990s, it was definitively proven that the progenitor cells for regeneration of PDL derive from the PDL alone: in experimental studies in monkeys, formation of new PDL with inserting collagen fibers into new cementum and bone was observed after 12 months of healing when dental implants were inserted in alveolar bone in contact with root tips. Opposed to this, when implants were inserted just in bone, osseointegration (ie, implant surface in direct contact with bone) was obtained instead.[38–40]

Several further experimental studies investigated and confirmed the hypothesis that new attachment can be predictably achieved during healing by preventing the ingrowth of gingival connective tissue and epithelium to the root area, thus giving exclusivity to cells originating from the PDL.[18,41–48] In one of these studies in monkeys, cell-occlusive barrier membranes (cellulose acetate laboratory filter or ePTFE) were used to cover roots that had been previously infected (plaque accumulation for 6 months) and mechanically treated by scaling and root planing (SRP). In this study, significantly more new attachment was gained on the root surfaces covered with a membrane than the control sites that were not covered, which additionally showed signs of root resorption. However, bone was formed in both groups.[46]

A series of experimental studies on discriminating supra-alveolar defects in dogs were performed in 1991, demonstrating that undisturbed adhesion and maturation of a blood clot to the root surface is critical to attain periodontal regeneration. This ensures sufficient space for the periodontal tissue to regenerate and mature free of infection.[49] Thus, membranes have a rather protective role for the blood clot and wound maturation (ie, space provision, protection against tensile forces).

GTR was also shown to be successful in achieving predictable periodontal regeneration in experimental studies on clinical models for the treatment of intrabony[42,43,48,50] (Fig 2-3),

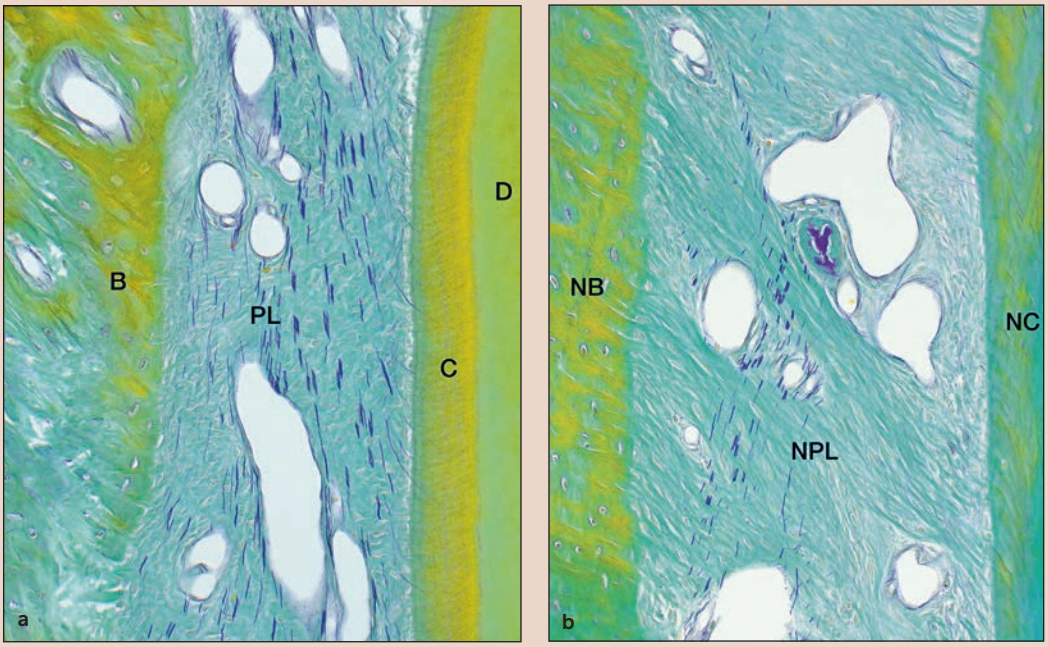

Fig 2-3 Light micrographs. *(a)* The genuine periodontal attachment with bone (B), periodontal ligament (PL), and cementum (C). *(b)* True periodontal regeneration with new attachment as demonstrated by new periodontal ligament (NPL) and fibers inserting into both new bone (NB) and new cementum (NC) after a regenerative GTR therapy with a bioresorbable membrane in a monkey tooth. D, dentin.

supra-alveolar,[18] recession,[44,45,51–59] and furcation-type defects.[41,47] Additionally, several reports provided human histologic evidence for the efficiency of GTR in regenerating lost periodontium (new cementum, new PDL, varying amounts of new alveolar bone) at sites affected by periodontitis and treated with SRP[17,60–63] (Fig 2-4).

The use of membranes in GTR

GTR was initially performed using nonresorbable membranes. Early reports evaluating the potential of various kinds of barrier membranes (eg, rubber dam, resin-ionomer) to regenerate periodontal tissues in intrabony defects showed only limited success.[64–66] It was therefore concluded that a membrane should be biocompatible, ensure tissue integration and space provisions, and be easy to clinically apply for periodontal regeneration to be predictably achieved.[67,68]

GTR was first shown to be successful in regenerating lost periodontal tissues in humans in a histologic study where teflon membranes (cellulose acetate laboratory filter called Millipore) were used to cover periodontally affected teeth after open flap debridement (OFD). The membranes were fixed to prevent any contact between the epithelium and

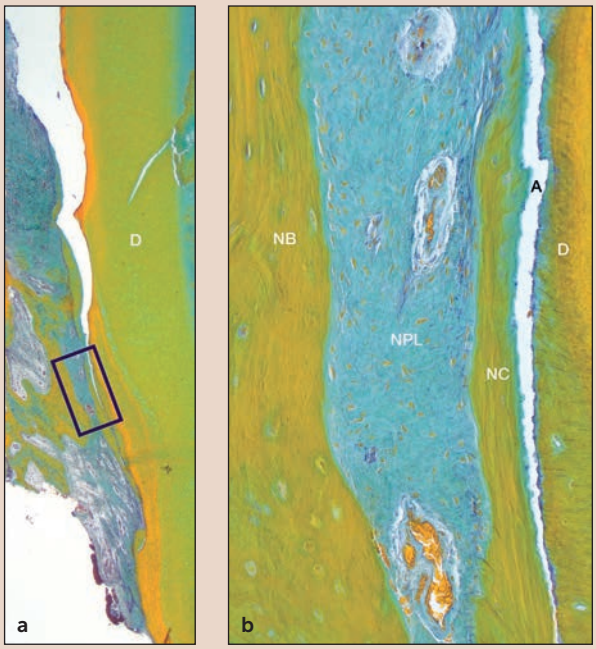

Fig 2-4 Micrographs at low *(a)* and high *(b)* magnifications illustrating periodontal regeneration on a human tooth after GTR therapy as demonstrated by the presence of new bone (NB), new periodontal ligament (NPL), and new cementum (NC) with inserting collagen fibers. A, artifact; D, dentin.

the gingival connective tissue and the root surfaces.[17] Later on, ePTFE (teflon) membranes were successfully used to regenerate lost periodontal tissues in various types of periodontal defects in both animal[11,42–43,45,46,69] and human studies.[50,56,61,70–72]

Despite successful regeneration with nonresorbable membranes, using them requires removal 4 to 6 weeks after implantation, which in turn may compromise the new regenerated tissue. A second surgical intervention is associated with bone resorption,[73] and wound healing by primary intention may not always be accomplished because it is not always possible to fully cover the newly formed periodontal tissues. In such cases, a 1.8- to 2.1-mm loss of clinical attachment level (CAL) was observed within 1 year after the second surgery.[74,75]

Considering these limitations of nonresorbable membranes, the use of synthetic (eg, oxidized cellulose mesh, calcium sulfate, polyurethanes)[76–79] or natural barrier resorbable membranes (human cadaveric dura mater, Cargile bovine membranes, laminar bone strips, type I and III porcine collagen)[80–83] have been implemented in GTR with various degrees of periodontal regeneration. Most investigated were membranes derived from collagen type I, PLA, and polyglycolic acid (PGA). The resorption process of collagen membranes relies on the enzymatic activity of the polymorphonuclear leucocytes and macrophages that infiltrate the wound during wound healing.[68,84] Additionally, PLA and

PGA membranes hydrolyze, and their degradation products are metabolized in the citric cycle.[85] However, timing is critical for these membranes to retain their physicochemical characteristics and their barrier function. For collagen membranes, this depends on the degree of collagen crosslinking; for PGA and PLA membranes, it depends on the relative concentration of the acids. Generally, a barrier function of at least 2 months should be assured.[86] Nonetheless, inferior outcomes for CAL gain and bone fill were obtained with these membranes in wide defects, where a longer period is likely required for regeneration than is needed with narrow defects.[87]

Several experimental[88–93] and human histologic studies[62,63,94] have predictably attained periodontal regeneration in various types of periodontal defects. These results have been confirmed clinically in further studies. In a systematic review and meta-analysis comparing the clinical efficiency after 6 months of GTR as opposed to OFD alone, a statistically significant added benefit for the use of ePTFE, polymeric, and collagen membranes was observed for CAL gain (1.61 mm, 0.92 mm, 0.95 mm) and PD reduction (1.41 mm, 0.89 mm, 1.06 mm), with no statistically significant differences among membranes.[95] Several studies report the long-term stability of clinical results after GTR with various types of resorbable membranes: PLA/citric acid ester copolymer,[96] polyglactin-910,[97] PLA/PGA,[98] and nonresorbable membranes.[57,99–101]

The role of grafting materials in periodontal regeneration

Bone grafts were introduced in periodontal regenerative therapy with the scope to enhance the regeneration of new bone, new PDL, and new root cementum either by osteoneogenesis (by releasing bone-forming cells), by osteoconduction (playing a role as a scaffold for bone formation), or by osteoinduction (by releasing bone-inducing substances). Grafts investigated for this purpose are divided according to their origin into autogenous grafts (derived from the same individual), allogeneic grafts (allografts, same species but different individuals), xenogeneic grafts (xenografts, from another species), and alloplastic materials (synthetic or anorganic material).

Autogenous grafts

Autogenous grafts are intended to maintain living cells that induce osteogenesis or osteoconduction. They can be divided in intra- and extraoral grafts depending on their origin. Despite the histologically proven regeneration of PDL, cementum, and alveolar bone in animal and human studies,[102–105] these grafts are not used in periodontal regenerative therapy because of the high rate of root resorption and ankylosis.[102–103]

Intraoral autogenous grafts are harvested from the retromolar mandibular region, edentulous space, chin area, and maxillary tuberosities. These grafts are gradually resorbed and replaced by new bone. Nonetheless, in a recent systematic review on human histologic studies, some of the included studies reported an encapsulation in bone or connective tissue and not complete resorption.[106] Controversial results for periodontal regeneration have been reported in human histologic studies: some reported complete to partial regeneration of the PDL, cementum, and alveolar bone,[107–110] while others noted a healing by means of long junctional epithelium.[111–113] Variable degrees of periodontal regeneration were also reported in a recent systematic review[106] where only 5 of the 10 included studies reported complete

periodontal regeneration.[103,108,109,112,114] The others reported either partial regeneration and long junctional epithelium[110,111,113] or only long junctional epithelium.[115,116] Sculean et al[106] reported a residual defect depth of 3 mm and a new cementum and bone formation length of 1.9 mm (results from two studies).

Allografts

Allografts are an alternative to autogenous grafts. These do not require harvesting from a second surgical site and the associated risk of patient morbidity. Allografts derive from the same species (ie, humans) but are from a different individual (genetically different origin). Despite the rigorous processing of allografts, these still bear the risk of disease transmission and antigenicity. Two types of allograft have been investigated for the use in periodontal regenerative therapy: mineralized freeze-dried bone allograft (FDBA) and decalcified or demineralized freeze-dried bone allograft (DFDBA).

Although FDBA is supposed to promote regeneration through osteoconduction,[117] it was histologically shown to induce healing via long junctional epithelium with no periodontal regeneration.[118] Moreover, in a randomized controlled clinical trial, the use of FDBA in intrabony defects brought no additional improvement in terms of CAL gain or defect fill compared with OFD alone.[119]

DFDBA was shown to be osteogenic due to its bone morphogenetic proteins (BMPs), which are capable of inducing new bone formation.[120,121] Despite the fact that experimental studies showed no signs of periodontal regeneration,[122,123] DFDBA led to regeneration of all periodontal tissues in a human histologic study.[124,125] Moreover, two of the seven included studies in a recent systematic review[87] reported almost compete periodontal regeneration,[126,127] while six reported partial periodontal regeneration combined with formation of long junctional epithelium,[110,113,124–126,128] and only one study reported healing by long junctional epithelium alone.[129] These results corroborate those from several clinical studies that support the effective use of DFDBA in intrabony defects, reporting superior outcomes for CAL gain and defect fill compared with OFD alone.[130,131] Moreover, in a study evaluating the efficacy of autolysed antigen-extracted allogeneic bone for a longer observation period (ie, over 3 years), the statistically significantly higher amount of bone and CAL gain obtained 6 months postoperatively could be maintained up to 3 years (2.0 ± 0.7 mm vs 0.8 ± 0.5 mm).[130]

Xenografts

Bovine-derived xenografts (BDXs) were evaluated for periodontal regeneration in several animal and human histologic studies (Figs 2-5 to 2-7). Human histologic studies using BDX with and without a bioresorbable collagen membrane in intrabony defects resulted in the formation of new cellular cementum with functionally oriented inserting collagen fibers (PDL) on periodontally compromised root surfaces after 6 and 8 months.[80,132] Moreover, BDX particles were surrounded by newly formed bonelike tissue. In another study, BDX combined with collagen was shown to be efficient in treating human intrabony defects; after 9 months of healing, the biopsies provided evidence for formation of new cementum, new PDL, and new alveolar bone.[133] Comparable clinical results were reported by other authors for BDX and DFDBA in the treatment of intrabony defects[134] (see Figs 2-6 and 2-7).

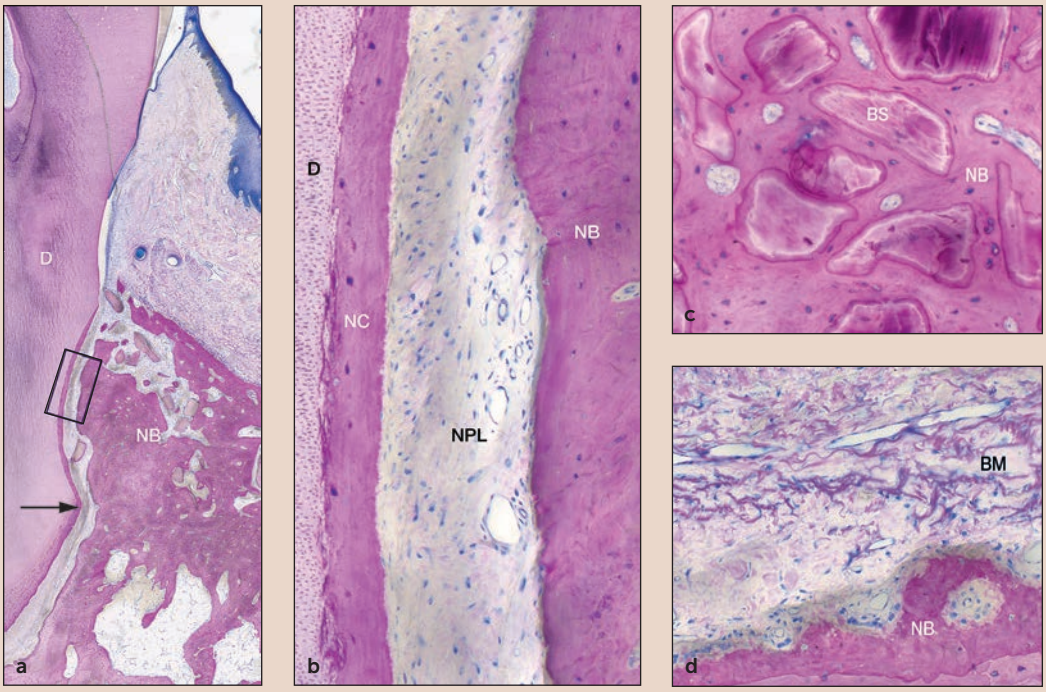

Fig 2-5 Light micrographs demonstrating periodontal regeneration in a dog tooth using the principle of GTR with a particulate xenogeneic bone substitute and a collagen barrier membrane. *(a)* Overview of the defect on the root surface. *(b)* Detail showing periodontal regeneration with new cementum (NC), new periodontal ligament (NPL), and new bone (NB). *(c)* Complete incorporation of the bone substitute (BS) particles in newly formed bone. *(d)* Residual collagen barrier membrane (BM) is present next to the surface of new bone. D, dentin.

Xenografts of coralline origin have also been investigated for periodontal regeneration. The natural coral can either be transformed into nonresorbable porous hydroxyapatite (HA) or into resorbable calcium carbonate. Controlled clinical trials showed better clinical outcomes (eg, probing depth [PD] reduction, CAL gain, defect fill) after grafting intrabony defects with coralline derivates compared with control sites,[135,136] and clinical outcomes were comparable with FDBA and DFDBA.[137,138] However, animal and human histologic studies revealed healing with a long junctional epithelium, encapsulation of the graft particles in connective tissue, and no periodontal regeneration.[139–141] These results are in line with those reported in the systematic review by Sculean et al.[106] Three of five studies reporting human histologic and histomorphometric results showed periodontal regeneration.[142–144] In an additional study, healing was described as a combination of periodontal regeneration and long junctional epithelium.[130] The only study that treated intrabony defects with coralline HA did not report any information related to the type of healing.[134] New bone was observed in direct contact with the graft particles in all studies. However, in some cases, the graft particles were observed encapsulated in connective tissue.