Introductory Chapter

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The fields of medicine and dentistry continue to develop in an ever-changing environment, with day-to-day innovations and discoveries. Among the many procedures that have to be implemented in the course of medical and dental therapy, guided bone repair and regeneration present vast challenges to the science, art and practice of reconstituting the shape and function of damaged skeletal structures.

Bone is a specialized connective tissue that is characterized mainly by its mineralized organic matrix. The bone matrix is composed of collagenous and non-collagenous proteins. Within this matrix, calcium and phosphate ions are laid down, ultimately to form hydroxyapatite. In most parts of the skeleton, bone formation occurs during embryogenesis, by the initial deposition of cartilaginous templates that are subsequently replaced by bone, a process referred to as *endochondral* bone formation. In the cranial vault, in the diaphysis of long bones, and in the alveolar processes of the maxilla and of the mandible, bone is primarily formed within fibrous connective tissue; this is termed *intramembranous* bone formation.

Mature bones are made up of mineralized tissue and bone marrow. The mineralized compartment comprises an outer smooth, compact portion, the cortical bone, and an inner spongy part, the trabecular bone, in the proportion, by weight, of about 80% to 20%. The cellular component of the mineralized bone tissue, including osteoblasts, osteocytes and osteoclasts, is located within and upon the cortical and the trabecular bone. This composition and structure of bone allows it to resist load, to protect vulnerable organs, such as the central nervous system, and to support functional organs, like the teeth.

As bone is a specialized connective tissue, *osteoblasts* rather than fibroblasts are the cells primarily responsible for its formation. They are located on bone surfaces, where they actively deposit organic bone matrix and control its mineralization. Osteoblasts are the direct descendants of osteoprogenitor cells (Kneser et al., 2006; Buckwalter & Hunziker, 1996; Heinegard & Oldberg, 1989), and they differentiate either into *bone lining cells* or into *osteocytes*. Among other activities, osteocytes participate in the regulation of blood-calcium homeostasis and in signalling mechanical loading to other cells within the bone. Since osteoblasts are fully differentiated stable cells that lack the ability either to migrate or to proliferate, new bone formation is entirely dependent on the presence of *osteoprogenitors,*

which are undifferentiated mesenchymal cells that can migrate to target sites, proliferate and differentiate into osteoblasts.

It has been suggested that osteoprogenitor cells may be designated as *determined* or as *inducible osteogenic precursor cells* (Friedenstein 1973). The *determined* osteoprogenitor cells are located in the bone marrow, in the endosteum and in the periosteum, and they possess the capacity to proliferate and to differentiate into osteoblasts. The *inducible* osteogenic precursor cells (e.g. myoblasts or adipocytes), present in other organs and tissues, may differentiate into bone-forming cells when exposed to specific stimuli. The main source of osteoprogenitor cells is considered to be the *pericyte*, a stellate perivascular cell.

The differentiation of osteoblasts from osteoprogenitor cells is dependent upon the release of, or the presence of factors that induce or promote bone growth, among them bone growth factors and bone growth proteins, as well as insulin-like growth factor, platelet-derived growth factor, and fibroblast growth factor.

Bone formation and remodelling are consistently associated with bone resorption that is initiated and maintained by *osteoclasts,* which are multinucleated cells originating from haematopoietic precursor cells. The processes of modelling and remodelling of bone start shortly after bone formation, by resorption and apposition of new mineralized tissue resulting in changes in bone architecture and morphology. It is believed that changes brought about by bone modelling are induced by functional demands, such as muscle tension and external loads, while remodelling occurs within the bone as an ongoing maintenance process.

Experimental observations show that primary (woven) bone that appears to be more amorphous and has a low load-bearing capacity is the first to be formed in areas of bone regeneration. Woven bone is gradually replaced by lamellar bone with a structure that is more resistant to stress in general, and to functional loading in particular.

Bone is one of a few tissues that possess spontaneous regenerative capacity; but spontaneous regeneration is limited, and falls far short of the ideal ultimate goal of therapeutic reconstruction, which is complete restoration of tissues or organs that have been damaged or removed, to their original normal structure, architecture, size and function.

In the oral cavity, for example, the periodontal attachment apparatus is an organ that comprises alveolar bone, periodontal ligament and cementum. If the periodontal attachment apparatus is disrupted by inflammatory disease such as periodontitis, or by trauma, or by surgical damage, spontaneous healing is achieved mainly by repair, i.e., fibrous tissue replaces the lost tissues (Le *et al.* 2005). The capacity of alveolar bone to regenerate has been shown to improve significantly in the presence of growth factors, which are natural biological mediators that significantly increase cellular chemo-attraction, proliferation and differentiation by regulating essential cellular events (Giannobile 1996). Once growth factors bind to surface receptors of specific target cells, they induce the activation of genes that change cellular activity and phenotype (Anusaksathien & Giannobile 2002; Schilephake 2002; Ripamonti *et al.* 2005).

This book is divided into three sections: chapters 1-5 deal mainly with regenerative tissue engineering, chapters 6-10 with different techniques of enhancing and supporting bone

regeneration, and chapters 11-14 concentrate on biotechnology, and on recent advances and new approaches in developing biomaterials for bone regeneration.

Regenerative tissue engineering (RTE) may be defined as a process of combining living cells with biocompatible scaffolds to generate a biological substitute capable of sustaining itself and of integrating with functional native tissue (Chapter 1). RTE addresses the discrepancy between available transplantable donor tissues and the anatomical need.

Optimized methods have improved the function and maturation of engineered cellular constructs to produce new ones with clinically useful, near-native tissue properties. Following any bone injury, a healing cascade is triggered to restore the tissue's original state. This reaction occurs in the three phases of inflammation, repair, and remodelling. Initially, the inflammatory phase follows the formation of a blood clot arising from blood flowing and cells migrating into the site of injury from the borders of the injury. These cells include fibroblasts and inflammatory cells, such as macrophages, monocytes, lymphocytes, etc., which, together with ingrowing blood vessels that are a source of pericytes, promote new formation of collagen fibers and osteoid, forming a soft callus. This process starts within hours to a few days after bone injury and continues for about 4-8 weeks, while ossification of the callus and the formation of unorganized woven bone may take an additional 2-4 months. This progression of healing events establishes a basis for formulation of the principles of guided bone regeneration and distraction osteogenesis (Chapters 6–9).

The restructuring of woven bone is responsive to muscular activity and to mechanical stresses (Kneser et al. 2006). In the dental environment, for instance, restructuring of bone is observed around teeth and dental implants which transfer functional and occlusal forces to their anchoring bone.

The range over which healing, followed by spontaneous regeneration of bone may occur is, however, of limited potential. If the zone of damage exceeds a certain critical size, a bone defect may not self-repair, in which case guided bone regeneration using tissue barriers, autologous bone grafts, allografts, xenografts or alloplasts may provide a partial solution (Chapters 11-14). The following terms are defined for the sake of clarity:

- *Autografts* - human bone is harvested from the recipient of the graft himself or herself. This is currently considered by many as being the gold standard for bone grafting.
- *Allografts* - human bone for grafting harvested from donors usually unrelated to the recipient. Such grafts do not have the recipient-compatible immunogenic properties of autografts, thus increasing the risk of rejection (Mankin et al., 2005). Allografts are generally osteoconductive, although some are osteoinductive, depending somewhat upon the source of the bone and the technique of preparation.
- *Xenografts* - deproteinized bone grafts prepared from species other than human that contain only the hydroxyapatite matrix of bone. Xenografts are osteoconductive.
- *Alloplasts* - synthetic grafts made of biocompatible and/or bioactive materials, such as ceramics, bioglasses or calcium sulphate. Some alloplastic materials have the potential to be used as carriers of growth factors, thereby improving their osteoconductive and osteoinductive properties.

The potential of regenerative tissue engineering (RTE) has attracted much interest in the field of bone research. Current studies on RTE focus mainly on stem cells. The human body

has many different types of cells, each specialized for a distinct rôle. The cells are committed to specific lineages and functions, for example, cardiomyocytes in the heart, chondrocytes in cartilage, and osteoblasts in bone. Cells are assessed for their possible utility for tissue engineering, mainly by their rate of proliferation and by their potential for differentiation, both of which depend upon the speed at which the individual cells divide as well as on the cell line's capability of developing into specific lineages, in our case, an osteogenic lineage. For the engineered tissue to mirror the native tissue, it is essential for the cells to expand at a specific rate and to differentiate towards the desired lineage.

Stem cells are multipotent, not lineage-specific, with the potential to differentiate into many kinds of specialized daughter cells. Adult stem cells can be harvested from various tissues of the body and can then be cultured *in vitro*, where they can be directed to provide a potentially unlimited supply of tissue. Stem cell-based bone tissue engineering is founded upon the potential of multipotent postnatal stem cells to participate in the regenerative healing of bone defects. Postnatal stem cells can be isolated from bone marrow, from adipose tissue, from muscle, from dental pulp tissue, from oral mucosa and from umbilical cord (Zuk et al., 2001; Miura et al., 2003; Schugar et al., 2009). It is noteworthy that in spite of the fact that embryonic stem cells are considered to be the gold standard in RTE , postnatal bone marrow-derived mesenchymal stem cells are the most researched and the most frequently used.

Clinically, most efforts to increase bone volume have focused on procedures that exploit spontaneous bone regeneration. The introduction of dental implant therapy, and the well established need for adequate bone volume at the implant site, in order to foster a favourable long-term prognosis for dental implants (Lekholm 1986) have dramatically increased interest in the development of implant sites.

Four approaches to the augmentation of bone volume have been described: a. *osteoinduction*, using appropriate growth factors (Urist 1965 ; Reddi 1981); b. *osteoconduction*, using grafting materials that serve as scaffolds for new bone growth (Buch *et al*. 1986; Reddi *et al*. 1987); c. *distraction osteogenesis*, by which bone growth is induced between the fragments at a surgically created bone fracture when the fragments are pulled apart in a slow, controlled manner. (Ilizarov 1989a,b); d. *guided bone regeneration*, which allows selective growth of bone tissue into a space maintained by tissue barriers (Dahlin *et al*. 1988, 1991**a,b**; Kostopoulos & Karring 1994; Nyman & Lang 1994). The purpose of all these procedures is to deal with the problem of localized lack of bone volume resulting from congenital, post-traumatic, postsurgical or pathological defects in various parts of the skeleton (Chapters 6-10).

Guided-tissue regeneration (GTR) was introduced into dental clinical practice soon after it became understood that the alveolar bone and the periodontal ligament can be sources of progenitor cells for the regenerative repair of adjacent periodontal lesions (Melcher 1970, 1976). Karring et al. (1980) and Nyman et al. (1980) formulated the basic principles of GTR over three decades ago. These are as follows: under certain conditions, cells that originate from a tissue adjacent to a delimited space are able to grow into that space and to form new tissue identical to their tissue of origin. In order to allow exclusive migration into, and population of such a space by a specific tissue, cells of that tissue must be given preferential access to the space. This is achieved by preventing access of cells from neighbouring dissimilar tissues by means of tissue barriers, commonly referred to as membranes.

For detailed discussion of the rationale and techniques of contemporary GBR procedures and the biotechnology associated with resorbable collagen bio-barriers, the reader is referred to Chapters 6 and 7. There is a wide variety of available resorbable and non-resorbable tissue barrier materials, including polytetrafluoroethylene (PTFE), expanded PTFE (e-PTFE), polyglactin 910, polylactic acid, polyglycolic acid, polyorthoester, polyurethane, polyhydroxybutyrate, calcium sulfate, freeze-dried fascia lata and freeze-dried dura mater allografts, titanium micro-mesh, and titanium foil.

Collagen membranes are generally to be preferred to other barrier materials because they possess all the essential properties required in a bio-barrier, including biocompatibility, cell occlusiveness, integration into the host tissues, space-making capacity, and also clinical manageability and ease of application.

To secure the space necessary for bone regeneration in GBR procedures, tissue barrier membranes need to be supported, or they will collapse owing to peripheral pressure, thus possibly reducing or completely eliminating the space that had been designated for potential bone growth and regeneration. Although membrane-stiffeners, or a wide range of membrane-supporting materials have been claimed successfully to fulfill the necessary requirements for membrane support, there is an ongoing search for new materials, both osseoinductive and osseoconductive, to be placed under the membrane (Chapters 11-14). The current consensus is that the optimal osteoconductive membrane-supporting material is one that interferes least with the spontaneous bone growth replacing the submembranous clot of blood. Taking this a step further, however, it may well be that with advances in engineered bone regeneration, future materials will promote bone growth, perhaps to the extent that tissue barriers may become unnecessary.

The main limitation of current guided bone regeneration procedures is that reliance is placed upon bone's spontaneous regenerative capacity, which suffices only for defects of limited size. Furthermore, the problem of stabilization of the volume of regenerated bone is a major limiting factor in bony defects of this nature, especially when lateral and, even more so, vertical bone loss is to be treated. Other measures, such as block grafts or distraction osteogenesis, may be more suitable for those cases.

The effectiveness of bone grafts depends on their osteoinductivity and osteoconductivity as well as on their biomechanical properties (Khan et al., 2005). Synthetic block grafts have recently been added to the range of available allografts: these grafts provide sizable, stable scaffolds that encourage new bone formation originating from any bone that is in direct contact with the graft material (Chapter 10). Therefore, while autologous block grafts still remain the gold standard, allograft and alloplast blocks reduce morbidity by obviating the need for harvesting bone blocks from the patient's iliac crest, fibula, ribs, calvaria or mandible (Burchardt, 1983).

Distraction osteogenesis (DO) may offer a viable alternative when size or volume of a bone defect exceeds the capacity of grafting successfully to replace the missing tissue. DO is a surgical technique by which, through the appropriate application of traction to the bone, the intrinsic capacity of bone to regenerate is directed towards lengthening or altogether replacing segments of bone. DO allows the spontaneous *de novo* formation of native bone without bone grafts. It may be considered a type of *in vivo* bone tissue engineering and may be superior to other techniques in certain cases. The current status, future developments and applications of DO are discussed in Chapters 8 and 9.

A number of extrinsic, local or systemic factors may affect bone mass, volume, structure and density, thereby influencing skeletal function. Among these, osteopenia, osteoporosis, diabetes mellitus, smoking and periodontal disease are frequently mentioned in the context of the jaws. This subject is not discussed separately in this book since data on the influence of those conditions on bone regeneration and on osseointegration in the setting of oral and orthopaedic implants are limited, neither is there any agreement on whether or not they should be regarded as contraindications for implant placement (Shernoff et al., 1994; Farzad et al., 2002).

In view of the increasing clinical application of bone regenerative procedures to dental implant site development, the relationship between such procedures and general health conditions has attracted considerable interest. However, no conclusive data are available with respect to bone augmentation procedures in patients suffering from those systemic diseases or conditions referred to above, including smoking, or in those with poor compliance in bacterial plaque control, any of which can have the effect of impairing tissue healing.

On the other hand, in patients who have lost their teeth owing to periodontal disease, implant procedures had greater rates of failure and more complications, than implant procedures in patients in whom periodontal disease had not been the primary reason for tooth loss (Mengel et al., 2001; Hardt et al., 2002; Karoussis et al., 2003; Wennstrom et al., 2004).

References

Anusaksathien, O. & Giannobile, W.V. (2002). Growth factor delivery to re-engineer periodontal tissues. *Current Pharmaceutical Biotechnology* 3, 129–139.

Buch, F., Albrektsson, T. & Herbst, E. (1986). The bone growth chamber for quantification of electrically induced osteogenesis. *Journal of Orthopedic Research* 4, 194–203.

Buckwalter, J., & Hunziker, E. (1996, Dec). Healing of bones, cartilages, tendons, and ligaments: a new era. *Lancet* 348 Suppl 2: sII18, 21-28.

Burchardt, H. (1983). The biology of bone graft repair. Clin Orthop Relat Res, 28-42.

Dahlin, C., Linde, A., Gottlow, J. & Nyman, S. (1988). Healing of bone defects by guided tissue regeneration. *Plastic and Reconstructive Surgery* 81, 672–677.

Dahlin, C., Alberius, P. & Linde, A. (1991a). Osteopromotion for cranioplasty. An experimental study in rats using a membrane technique. *Journal of Neurosurgery* 74 (3), 487–491.

Dahlin, C., Andersson, L. & Linde, A. (1991b). Bone augmentation at fenestrated implants by an osteopromotive membrane technique. A controlled clinical study. *Clinical Oral Implants Research* 2, 159–165.

Farzad, P., Andersson, L. & Nyberg, J. (2002). Dental implant treatment in diabetic patients. *Implant Dentistry* 11,262–267.

Friedenstein, A.J. (1973). Determined and inducible osteogenic precursor cells. In: *Hand Tissue Growth Repair and Remineralisation. Ciba Foundation Symposium. New series* 11,169–181.

Giannobile, W.V. (1996). Periodontal tissue engineering by growth factors. *Bone* 19, 23S-37S.

Hardt CR, Gröndahl K, Lekholm U, Wennström JL. (2002) Outcome of implant therapy in relation to experienced loss of periodontal bone support: a retrospective 5- year study. Clin Oral Implants Res. 13,488-94.

Heinegard, D., & Oldberg, A. (1989, Jul). Structure and biology of cartilage and bone matrix noncollagenous macromolecules. *FASEB J* 3(9), 2042-2051.

Ilizarov, G.A. (1989a). The tension-stress effect on the genesis and growth of tissues: Part I. The influence of stability of fixation and soft tissue preservation. *Clinical Orthopaedics* 238, 249–281.

Ilizarov, G.A. (1989b). The tension-stress effect on the genesis and growth of tissues: Part II. The influence of the rate and frequency of distraction. *Clinical Orthopaedics* 239, 263–285.

Karoussis IK, Salvi GE, Heitz-Mayfield LJ, Brägger U, Hämmerle CH, Lang NP. (2003) Long-term implant prognosis in patients with and without a history of chronic periodontitis: a 10-year prospective cohort study of the ITI Dental Implant System. Clin Oral Implants Res. 14,329-39.

Khan, M., Sahibzada, A., Khan, M., Sultan, S., Younas, M., & Khan, A. (2005, Apr-Jun). Outcome of plating, bone grafting and shortening of non-union humeral diaphyseal fracture. *Journal of Ayub Medical College Abbottabed*, 17(2), 44-46.

Karring, T., Nyman, S. & Lindhe, J. (1980). Healing following implantation of periodontitis affected roots into bone tissue. *Journal of Clinical Periodontology* 7, 96–105.

Kneser, U., Schaefer, D., Polykandriotis, E., & Horch, R. (2006, Jan-Mar). Tissue engineering of bone: the reconstructive surgeon's point of view. *Journal of Cellular and Molecular Medicine*, 10(1), 7-19.

Kostopoulos, L. & Karring, T. (1994). Augmentation of the rat mandible using guided tissue regeneration. *Clinical Oral Implants Research* 5, 75–82.

Le, A.D., Basi, D.L. & Abubaker, A.O. (2005). Wound healing:fi ndings of the 2005 AAOMS Research Summit. *Journal of Oral and Maxillofacial Surgery* 63, 1426–1435.

Lekholm *U.* (1986) Osseointegrated implants in clinical practice. J Oral Implantol. 1986;12(3):357-64

Lugero, G.G., de Falco Caparbo, V., Guzzo, M.L., Konig, B., Jr. & Jorgetti, V. (2000). Histomorphometric evaluation of titanium implants in osteoporotic rabbits. *Implant Dentistry* 9, 303–309.

Mankin, H., Hornicek, F., & Raskin, K. (2005, Mar). Infection in massive bone allografts. *Clinical Orthopedics and Related Research* (432), 210-216.

Mengel R, Schröder T, Flores-de-Jacoby L.(2001) Osseointegrated implants in patients treated for generalized chronic periodontitis and generalized aggressive periodontitis: 3- and 5-year results of a prospective long-term study. J Periodontol. 2001 Aug;72(8):977-89

Melcher AH. (1970) Repair of wounds in the periodontium of the rat. Influence of periodontal ligament on osteogenesis. Arch Oral Biol. 1970 Dec;15(12):1183-204.

Melcher AH (1976) On the repair potential of periodontal tissues. Journal of Periodontology; 47(5):256-60.

Miura, M., Gronthos, S., Zhao, M., Lu, B., Fisher, L. W., Robey, P. G., & Shi, S. (2003). SHED: stem cells from human exfoliated deciduous teeth. *Proceeds of the National Academy of Science USA*, 100(10), 5807-5812.

Nyman, S., Karring, T., Lindhe, J. & Planten, S. (1980). Healing following implantation of periodontitis affected roots into gingival connective tissue. *Journal of Clinical Periodontology* 7, 394–401.

Nyman, S.R. & Lang, N.P. (1994). Guided tissue regeneration and dental implants. *Periodontology 2000* 4, 109–118.

Reddi, A.H. (1981). Cell biology and biochemistry of endochondral bone development. *Collagen Related Research* 1,209–226.

Reddi, A.H., Weintroub, S. & Muthukumaran, N. (1987). Biologic principles of bone induction. *Orthopedic Clinics of North America* 18, 207–212.

Ripamonti, U., Herbst, N.N. & Ramoshebi, L.N. (2005). Bone morphogenetic proteins in craniofacial and periodontal tissue engineering: experimental studies in the nonhuman primate Papio ursinus. *Cytokine and Growth Factor Review* 16, 357–368.

Schilephake, H. (2002). Bone growth factors in maxillofacial skeletal reconstruction. *International Journal of Oral & Maxillofacial Surgery* 31, 469–484.

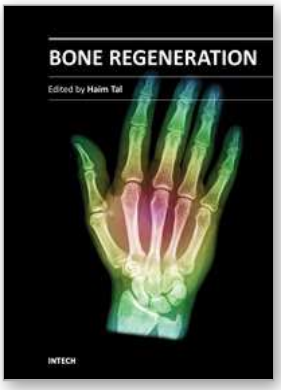
Schugar, R., Chireleison, S., Wescoe, K., Schmidt, B., Askew, Y., Nance, J., Deasy, B. (2009). High harvest yield, high expansion, and phenotype stability of CD146 mesenchymal stromal cells from whole primitive human umbilical cord tissue. *Journal of Biomedicine & Biotechnology*, 789526.

Shernoff, A.F., Colwell, J.A. & Bingham, S.F. (1994). Implants for type II diabetic patients: interim report. VA Implants in Diabetes Study Group. *Implant Dentistry* 3, 183–185.

Urist, M.R. (1965). Bone: formation by autoinduction. *Science* 150, 893–899.

Wennström JL, Ekestubbe A, Gröndahl K, Karlsson S, Lindhe J. (2004). Oral rehabilitation with implant-supported fixed partial dentures in periodontitis-susceptible subjects. A 5-year prospective study. J Clin Periodontology 31,713-24.

Zuk, P., Zhu, M., Mizuno, H., Huang, J., Futrell, J., Katz, A., Hedrick, M. (2001). Multilineage cells from human adipose tissue: implications for cell-based therapies. *Tissue Enginering*, 7, 211-228.



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Bone is a specialized connective tissue, most prominently characterized by its mineralized organic matrix that imparts the physical properties that allow bone tissue to resist load, to support functional organs, and to protect highly sensitive body parts. Bone loss and bone damage may occur as a result of genetic conditions, infectious diseases, tumours, and trauma. Bone healing and repair, involves integrative activity of native tissues and living cells, and lends itself to the incorporation of naturally derived or biocompatible synthetic scaffolds, aimed at replacing missing or damaged osseous tissues. There are several modalities of bone regeneration including tissue engineering, guided bone regeneration, distraction ontogenesis, and bone grafting. This book concentrates on such procedures that may well be counted among the recent outstanding breakthroughs in bone regenerative therapy.

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