Preface

The science of bone replacement has greatly advanced in recent decades, but replacing bone with bone tissue rather than with metallic components remains in early development. The current volume, third in the series *Topics in Bone Biology*, deals with problems inherent in inducing the body cells to accomplish bone tissue repair, to degrade devices introduced to provide initial mechanical support, and to attract and stimulate bone formation. It is therefore logical that Chapter 1, by Hicok and Hedrick, deals with stem cells, i.e., pluripotential cells that may differentiate into cartilage and bone cells. The chapter begins with a description of how stem cells may be harvested; the limitations of autologous, embryonic, and adult stem cells; and the need to expand the harvested cells in culture. The authors then discuss the influences of the body environment on implanted cells and on the scaffolds that need to be introduced. They emphasize the need for adequate oxygenation and for rapid integration with the vascular system of the host/patient. Stem-cell-engineered cartilage is discussed at some length, along with the need for stem-cell-engineered ligaments and tendons. The chapter concludes with an analysis of what needs to be learned to make stem-cell-engineered bone tissue a reality.

In Chapter 2, Gerstenfeld and colleagues review osteogenic growth factors and cytokines, soluble proteins that regulate postnatal bone repair. These molecules are of importance because many are targets of efforts to promote therapeutic bone healing and repair. Molecules discussed are the tumor necrosis factor α (TNF-α) family of cytokines and their role in bone remodeling, the bone morphogenetic proteins (BMPs) and their role in signaling, and angiogenic factors such as the vascular endothelial growth factor (VEGF) and angiopoietin families, with detailed discussion of the role of angiopoietins in bone development and tissue healing. The authors then discuss parathyroid hormone (PTH) and parathyroid hormone-related peptide (PTHrP): the differences between their paracrine and endocrine effects, their signal transduction and nuclear effects, and their effects on endochondral development and bone repair. A concluding section deals with bone healing and the roles played by skeletal stem cells, cytokines, and morphogenetic signals. This chapter, like all the others in this volume, has an extensive reference list.

Transplantation of bone allografts is a common orthopedic practice, but unless great care is taken, the allograft may give rise to infection and its sequelae in the host/patient. Tuan and colleagues Moucha, Renard, Gandhi, and Lin, in Chapter 2, discuss the harvesting and processing of musculoskeletal grafts and the conditions that must be met for the graft to be safe, i.e., not to cause inflammation, disease, or other harm to the host. This means that the medical and social history of the donor must be known in order to avoid complications that might arise, for example, as a result of transmission of the AIDS virus through the donor. The graft itself must be sterilized, and the authors discuss the various possible procedures to achieve this aim. Freezing or gamma-irradiation may weaken the graft, preventing adequate weight bearing initially. Infections due to improperly sterilized grafts include human immunodeficieny virus (HIV), one of the most serious, other viruses such as hepatitis C virus (HCV), and bacteria such as the *Clostridium* species. Factors that may affect performance and mechanical properties of the graft are discussed at the end of the chapter.

Park, Temenoff, and Mikos, in Chapter 4, provide a general discussion of biodegradable implants and the functional characteristics and requirements of such implants. Implants must have high mechanical strength and stiffness if employed in sites subject to high loads, and the chapter discusses various materials suitable for that purpose. Discussed also are nano- and microparticles as means for delivering bioactive molecules to the site, the use of hydrogels to entrap and release drugs, and the kinds of cells that can be embedded in the scaffolds. The implants must be biodegradable and biocompatible, have biological functionality, have suitable mechanical properties, and be composed of appropriate materials, the requirements for which are discussed in detail in the second half of the chapter.

Biodegradable scaffolds are highly desirable, but, as discussed in Chapter 4 and also in Chapters 6 and 7, they are not sufficiently developed for universal use. In Chapter 5, van den Dolder and Jansen summarize results achieved with a nondegradable scaffold made of titanium fiber mesh. Titanium has excellent biocompatibility and, in spongelike form, has been used extensively for tissue-engineering purposes. The authors review in detail the properties that make for biocompatibility of titanium. They then discuss other nondegradable metals, including tantalum and stainless steel. Like biodegradable scaffolds, the nondegradable scaffolds are used to deliver cells or extracellular matrix proteins to the defect site. Van den Dolder and Jansen describe methods of cell seeding and review the effects of matrix proteins on osteoblast differentiation in the titanium fiber mesh scaffolds. The chapter concludes with a review of the cell-based and growth-factor-based approaches to in vivo bone engineering.

The next two chapters describe and review in detail the use of scaffolds in bone tissue engineering. Betz, Yoon, and Fisher, in Chapter 6, discuss the fabrication and properties of polymers used for scaffold construction, including descriptions of curing methods and of the surface and mechanical properties of these scaffolds, as well as their biodegradation and biocompatibility. Polymer entanglement and cross linking, two major curing methods, are described, as is polymer assembly. The chapter describes several conventional fabrication methods (fiber bonding, phase separation, and gas foaming, among others), as well as different types of prototyping, including sheet lamination and laser stereolithography. This is followed by a detailed analysis of the various polyesters and other synthetic polymers and an extensive description of the properties that are desired in scaffold design, as they relate to surface, macrostructure, and mechanical properties and their suitability in terms of biodegradation and biocompatibility.

Chapter 7 deals with injectable scaffolds, which ideally can be used to replace hard or soft tissues. Such materials minimize the need for invasive surgery and thus improve current methods. Migliaresi, Motta, and DiBenedetto discuss the properties that an injectable scaffold must have and then describe injectable scaffolds that are ceramic-based, i.e., hydroxyapatite, tricalcium phosphate, biphasic calcium phosphate, and bioactive glasses. These materials, developed some three decades ago, have porosity, so that cells can be attracted or proteins inserted into the scaffold; the materials therefore must be resorbable. To use these materials, the engineer must impart a setting rate that is not too slow, so that the scaffold assumes mechanical strength rapidly, but that allows the scaffold to be resorbed in a time adequate for replacement of the implant by cells from the host. Soft tissue can be effectively replaced by hydrogel-based scaffolds. The chapter describes the many synthetic and natural hydrogels that have been used for injectable scaffolds. As the authors state, for a scaffold to be injectable, composite technology must be used creatively and the viscoelastic properties of the material must be understood, as must be the effect of the biological environment into which the scaffold is to be placed.

In Chapter 8 on Motion and Bone Regeneration, Ko, Somerman, and An discuss the three stages of bone regeneration—healing, osteogenesis, and osseointegration—and how regenerating bone responds to the signals emitted by limb movement. Bone healing in turn involves three stages—inflammation, reparation, and remodeling—and much of the chapter is devoted to an analysis of how mechanical factors influence bone healing. The authors show the relationships between cellular and organ events, how movement is transduced to the bone cells, and how the resulting intracellular increase in mRNA of protooncogenes and bone matrix proteins in turn affects bone healing and bone repair. A section of the chapter is devoted to distraction osteogenesis, a technique for producing new bone, and its application in principle in dentistry, inasmuch as tooth movement is equivalent to distraction. The final section, on bone and tooth implants, building upon information presented in earlier chapters, analyzes the effects of mechanical loading and bone repair, emphasizing that the correlation depends on the synergy between general boundary conditions and specific bone properties.

In dentistry, functional tooth replacement has become a reality as a result of the development of dental implants. Oates and Cochran, in Chapter 9, describe the bone and periodontal ligament loss frequently encountered in individuals with periodontal disease, a chronic infection. Bone implants have been used, though not always successfully, to stop the fairly extensive resorption of alveolar bone that occurs after tooth extraction. The chapter discusses in detail bone formation around dental implants, methods for speeding the rate of bone healing, how to regenerate bone in areas unsuited for implants, and bone grafting materials. Traditionally implants have been inserted some time after tooth removal, but there is great interest, as pointed out by the authors, in implant therapy very soon after tooth extraction. This may be possible, because healing in the tooth socket does not appear to be significantly affected by implant placement. Because space in the posterior maxilla is limited, implant therapy at that site has been difficult. Sinus augmentation, as described at the end of the chapter, seems to be the solution. The authors conclude by pointing out that further progress in dental practice, as in the recent past, will come from continued progress in bone research.

Computers have found increasing use in two- and three-dimensional design. In the last chapter, Melissa Knothe Tate illustrates the strength of computational modeling to extend experimental findings to the design of implants. An important aspect of modeling is that a given design can be expanded in length or in mechanical properties with the help of the computer, and the resulting expanded design can then be tested. Knothe Tate describes how the theory of poroelasticity has been adapted to bone modeling and how pressure gradients that cause nutrients and waste to be moved to and from cells have become part of the modeling approach. Similarly, the need to take into account cyclic compressive loads in designing bone replacements can be most readily met by appropriate modeling. In the second half of the chapter, the author illustrates in figures and equations the resolution of a variety of design problems. For example, a stochastic model is shown that represents the exact conformation and organization of the pericellular network, as well as reflecting microporosity. Other examples deal with the delivery of drugs to bone, fluid velocity magnitudes in the pericellular space, and the calculated and model-predicted permeability of a specific scaffold. There can be little doubt that computational modeling will find increasing use in implant and scaffold design.

This book appears at a time when functional engineering of bone tissue is ready to play a growing role in orthopedic and orthodontic practice. The editors are grateful to the authors of this book for their critical and timely discussion of this topic and for sharing their perspectives, so important to the many patients in need of bone repair or replacement, whether the very young, athletes, or the elderly. We also thank Springer-UK for their interest, patience, and willingness to publish the needed illustrations.

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