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# Preface

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## Why This Volume?

The title of this volume reads like an oxymoron. After all, it is well known that, whether animal or human, adults do not spontaneously regenerate any of their organs that have been lost to accidental trauma or to surgery. If mammals could somehow regenerate organs such as the skin of a hand lost to a burn or a breast lost to mastectomy, scars should not fill the anatomical site of the lost organ; instead, a regrown organ should emerge. If regeneration were possible, treatments might also be developed for potentially lethal degenerative conditions such as a scarred heart muscle or a cirrhotic liver.

The concept of induced organ regeneration in adults is relatively new. The deliberate modification of healing to achieve regrowth of lost tissue structures does not follow directly from current mainstream paradigms of biological research. The first tentative recognition that the healing process could be modified to induce regeneration of the dermis, a tissue that does not spontaneously regenerate in adults, appeared in reports published in the early 1980s. Eventually, other organs, including peripheral nerves and the eye conjunctiva, were induced to regenerate in anatomical wounds known to be incapable of supporting spontaneous regeneration. The data on induced regeneration are scattered in a variety of journals, book chapters, abstracts, and theses. It is time to marshal the extensive evidence. This is the main reason for writing this volume.

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## Generic Methodology

The emphasis throughout this volume is on systematic development of the viewpoint that regeneration is an instance of synthesis of tissues and organs. Although somewhat self-evident, this proposition has been hardly employed. It has three simple consequences. The first is the requirement for a special kind of experimental reactor, free of tissues that do not spontaneously regenerate. The second calls for meticulous physicochemical and biological characterization of the end products of such a reaction. The third requires the use of appropriate nondiffusible regulators in the experimental reactor. These insoluble matrices induce adult cells to abandon

their normal proclivity in closing up adult wounds in exchange for synthesizing physiological tissues.

This approach appears to be independent of the organ under study. It is developed in substantial depth during the first several chapters by limiting the discussion to just two organs that are quite different from each other, namely, skin and peripheral nerves. The conclusions from this analysis apply to either organ with roughly equal strength. This intriguing result clearly suggests a generic methodology for synthesis of other organs.

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## **In Vitro or In Vivo?**

Many researchers in tissue engineering have preferred to carry an organ synthesis in vitro as extensively as possible before implanting the resulting construct in an experimental animal model. The methodology developed in this volume applies whether the bulk of the synthetic process is being carried in vitro or in vivo. Irrespective of whether the organ being synthesized in vitro is in advanced state of completion or is simply a matrix seeded with cells, it is still necessary to eventually implant it by inflicting a traumatic (surgical) injury at the correct anatomical site. Once more, the implantation site can be construed as an experimental reactor and the process of remodeling or regeneration that follows can be looked at as a synthetic process. In short, the methodology of organ synthesis developed in this volume should apply in a large variety of protocols used in tissue and organ synthesis.

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## **Who Should Benefit by Reading This Volume?**

A second reason for writing this volume is the need for a single-author textbook on organ synthesis. Lack of a unifying text has frustrated both university students and practitioners in industry. For years, my graduate students have had to confront a motley array of lecture notes. This volume is partly based on the author's notes for undergraduate and graduate classes in biomaterials–tissue interactions, tissue engineering, and design of medical devices at Massachusetts Institute of Technology. This work should be of interest to three groups of investigators: biologists, experimental surgeons, and biomedical engineers. Biologists should be interested in the molecular biological basis of induced regeneration, a process that appears to reverse the developmental process that normally converts the wound-healing response of the fetus to that of the adult.

Experimental surgeons interested in organ regeneration should benefit from a fresh approach toward making their experimental protocols more quantitative and standardized. Biomedical engineers will gain a new look at the treatment of old ailments. In particular, it is hoped that the generic organ-blind methodology described in this volume should be useful to most students and practitioners of tissue engineering.

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## Outline

This volume is divided into four major sections. Loss of organ function, the basic medical problem treated in this volume, is defined in Chap. 1. The basic methodology of organ synthesis in vivo is described in Chaps 2–4. Application to adult skin and peripheral nerves is treated in detail in Chaps 5–7. Finally, detailed mechanistic hypotheses of induced tissue and organ regeneration are presented in Chaps 8–10, leading to generic methodology for organ regeneration.

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## Preface to Second Edition

Five developments have marked the field of tissue and organ regeneration since the First Edition was published in 2001.

The role of contractile cells in wound healing and their specific interactions with ligands on the surface of a regeneratively active collagen scaffold have been largely elucidated. Improved understanding of this interaction and its consequences has introduced the concept of surface biology, an exciting landscape in which cell phenotype changes from repair to regeneration via specific molecular interactions of cells with the active surface.

Decellularized matrices have been studied by a large number of investigators and led to regeneration of several organs, including the urethra, large defects in the abdominal wall, the bladder, Achilles tendon, the larynx, the lungs, and other organs. A possible mechanism of the regenerative activity of decellularized matrices, one which may improve functional outcomes from the use of these matrices, has been presented.

In the two organs, skin and peripheral nerves, where repair and regeneration have been studied most extensively by investigators, the differences in their respective healing processes have been shown to be much smaller than originally thought to be. This finding simplifies greatly the description of repair and regeneration and inspires its extension to other organs.

Scar formation has been the perennial explanation in the literature for lack of regeneration in adults. There is now evidence that scar is a derivative process to wound contraction. Future efforts to induce regeneration must apparently be directed primarily towards modification of wound contraction rather than scar formation.

Not least is the increasing clinical use of the regeneratively active collagen scaffold, dermis regeneration template, as a treatment for skin loss in massive burns, plastic surgery and closure of chronic skin wounds. The mechanism of activity of this clinical treatment appears to derive from surface biological interactions that have been described in a preliminary fashion in this volume.

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