Preface

THE SCIENTIFIC FIELD OF TISSUE ENGINEERING and regenerative medicine is about 30 years old but it has its roots in science dating to the ancient Greeks. To understand its history, its goals, and its approaches, an acquaintance with the scientific tradition that contributed to its conceptualization is useful. A discussion of the human need it seeks to address is also important. Once contextualized, we can look at the development of the field over the last one-third of a century. This book's purpose is then to use several specific examples of progress in areas that not only are important but also serve as models for advancing the field into new areas.

The history of modern *Homo sapiens* has been recently summarized by Yuval Noah Harari in his 2015 book, *Sapiens: A Brief History of Humankind*. The relevant question is, "When did humans first start caring for others who were injured or infirmed?" The evidence indicates that as long as there have been humans other humans have tried to help individuals in need. Traditional twentieth century work demonstrates trephination of the human skull as early as the Mesolithic Period between 10,000 and 5000 BC. The purposes of this surgical procedure remain largely unknown as causes of mental and physical ailments were obscured by ignorance, belief in magic, and mysticism. But even more remarkable is more recent evidence summarized by Harari (2015):

> Archeologists have discovered the bones of Neanderthals who lived for many years with severe physical handicaps, evidence that they were cared for by their relatives.

Since we now know that *Homo sapiens* carries DNA from Neanderthals, our early caring dates to an era when they shared the planet with other human species. All of modern medicine and surgery has progressed through the ages based on this fundamental human trait. Progress and improvements in care, recovery, and cure are coincident with advances in our knowledge of nature and biologic systems, technologic development in multiple areas of human endeavor based on empiric trial and error, as well as scientific discovery.

When an individual suffers loss of living tissue from trauma, disease, or congenital malformation, loss of function as well as cosmetic deformity can result. In severe instances, death follows. The first historically documented attempts at reconstruction include reconstruction of the nose. Punishment for crimes in ancient India was amputation of the nose. Although there are claims to nose reconstruction in India as early as 1000 BC, sometime after 100 AD, a surgical technique employing a forehead skin flap is described in the *Sushruta Samhita*. This was translated into Arabic ∼800 AD. In Europe, a forearm flap for nasal reconstruction was described in 1597 AD by Tagliacozzi of the University of Bologna, and it was in use through World War I (Rutkow 1993). These early forms of reconstruction involve the use of living tissue, taken from one position and moved to another location for a different purpose. The most radical application of this approach was the development of organ transplantation in the mid-twentieth century. Taking a living organ from one individual and transporting and successfully implanting it into another individual was a triumph of biology, surgery, and ingenuity.

Perhaps even older is another approach to replacement, which is the use of artificial materials to create artificial replacement structures, again, in an attempt to recreate form and function. Excellent examples of limb-replacement structures survive from the European Renaissance Period. A metal artificial hand with a mechanism for grasping from the 15th century is displayed at Museum of the History of Science (University of Oxford). Another metal upper limb prosthetic device from a

German feudal knight (1480–1562) is in the Science Museum of London. It has an articulated elbow, an articulated wrist, and movable articulated fingers, controlled from a cord operated from the shoulder. This approach to replacement has been improved and modernized to the present day, making use of remarkable materials, digital technologies, and modern science and engineering to improve and save lives.

Thus, with our ancient human trait of caring for others, two strategies evolved for replacing lost structure and function, namely, the use of living materials or the use of inanimate, nonliving materials. Tissue engineering and regenerative medicine have been conceptualized in the latter third of the 20th century to fill the void where the two old and enduring approaches fall short of their intended therapeutic goals. Tissue engineering seeks to fabricate living structures on demand to replace, repair, or regenerate organs and tissues that are damaged by trauma, disease, or congenital deformity. Organ transplantation is the best example because its very success has led to its most difficult barrier, the donor organ shortage. Multiple millions of people globally have a need for organs, but the supply is only in the thousands. In a sense, the idea is an inevitable outcome of history, but the road to success is dependent on biologic discovery and the application of engineering to biology, materials science, and design.

Although the science in these areas is complex and not directly the subject of this preface, we can look to a few historical observations in nature and mathematics, which have had a fundamental and profound effect on the development of this new approach to human therapy.

> The body of anything whatsoever that receives nourishment continually dies and is continually renewed. Unless therefore you supply nourishment equivalent to that which has departed the life fails in its vigors; and if you deprive it of this nourishment, the life is completely destroyed. (Leonardo da Vinci, Anat. Ms. B, fol. 28r)

This fundamental fact of all biological systems, both plant and animal, has never been more elegantly observed or stated since Leonardo da Vinci. It is a fundamental biophysical constraint for the design of all living systems for the field of tissue engineering. Its mathematical formulation was articulated by Folkman and Hochberg in 1973 when discussing the necessity of new blood vessel formation in the growth of tumors. To provide nourishment to the interior of a mass of living cells, new blood vessels need to form to deal with the problem that all nourishment to a sphere of living cells occurs at the surface of the cells (Folkman and Hochberg 1973). Mathematically, as the mass of cells grows, the surface increases only as the square of the radius, but the mass or volume of the cells needing nourishment increases as the cube of the radius. This mismatch of surface area to volume was solved by nature over the long experiment of evolution by breaking the surface into more and more subunits through branching algorithms that produce the vascular system in the case of mammals such as ourselves. This simple architectural solution continually matches surface area to volume to keep enlarging masses of cells alive, healthy, and functioning.

As an interesting historical footnote: the mathematics necessary to understand and solve this problem for our field were solved over 1700 years before da Vinci by the greatest scientist and mathematician of antiquity, the Greek Archimedes of Syracuse in Sicily (287 BC–212 BC). In the two books on the sphere and the cylinder found in the *Archimedes Palimpsest* (Netz 2011), he develops the mathematical treatment of spheres and cylinders, which leads to the relationship of surface area to volume. This finding was so important to Archimedes that legend has it that Archimedes requested that his grave marker be engraved with a sphere within a cylinder, as Cicero has claimed to have found. So important is this ratio in biology, that D'Arcy Wentworth Thompson begins the second chapter of his groundbreaking work *On Growth and Form* with a discussion of it and refers to Archimedes as its source. His brilliant book, first published in 1917, links biology with the fields of mathematics and physics (Thompson 1942).

This large body of knowledge led to the observation of branching architecture in seaweed that informed the design of scaffolding systems for tissue engineering (Vacanti 1988). Between 1986 and 1998, it was the principal design approach for model systems in many structures, including liver, intestine, cartilage, bone, tendon, blood vessels, and heart valves (Vacanti 1988). The discovery of stem cells beyond those in the bone marrow led to the next major advance in tissue engineering and regenerative medicine.

This book examines many of the current tools available to scientists and engineers in the field and shows how their creative application can lead to therapeutically relevant living devices in many of the tissues and organs of the human body. The first chapter characterizes biologically active scaffolds that induce the regenerative response in healing. In contrast, the second chapter examines scaffold-free approaches using cells capable of self-assembly. The third chapter examines a powerful new technology for the creation of complex three-dimensional scaffolds and the very recent addition of 3D bioprinting strategies, which print cells along with matrix. The fourth chapter summarizes optimization of conditions needed to generate new bone and cartilage, while the fifth chapter focuses on the methods and possibilities of craniofacial tissue engineering. The sixth and seventh chapters focus on engineering of the heart and blood vessels, and the eighth chapter examines the role of stem cells and progenitor cells in the creation of new intestinal tissue. The final chapter covers tissue engineering and its place in art and design.

This amalgamation of many approaches, tools, and targets of tissue engineering and regenerative medicine speaks to its potential to be very broad and paradigm changing. This volume is not intended to be comprehensive nor detailed in its science. Rather it is intended to be a brief overview to entice the reader to be aware of what may be coming and perhaps even to participate in the discovery and invention required fulfill its promise of helping to alleviate human suffering. Archimedes, da Vinci, and Thompson likely had no idea that their creative thoughts might be applicable to better approaches to improve the human condition, but by systematic and rigorous study they wrote what they learned for future generations to read and apply to new ideas. Now we understand that our bodies are complex electro-chemical-mechanical-analog machines that are carbon based, optimized by 3.5 billion years of evolutionary trial and error, with self-awareness and an enormous capacity to care for other individuals and communities. We can understand these systems and we can repair and replace defective parts with new living parts indistinguishable from normal counterparts developed in utero. It is such an exciting and challenging time.

The book is the 25th in the series *Cold Spring Harbor Perspectives in Medicine*, the latest incarnation of a monograph series that started almost 50 years ago. In covering the emerging science and technology of tissue engineering and regenerative medicine, it is important to note that there are many examples of applications in clinical use with the promise of many more to come. The authors of the nine book chapters are all experts in the field and pioneers in the creation of the field. The breadth of the topics discussed foretell how widely applicable this field may become over the next decade and beyond. I thank all of the authors for their generosity of time and effort. I also thank the publishers for their invaluable efforts in bringing this book to fruition, especially our project manager Barbara Acosta. Finally, I thank my administrative assistant Jacquelyn Ferraro-Pipes for her tireless efforts in coordinating the project.

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