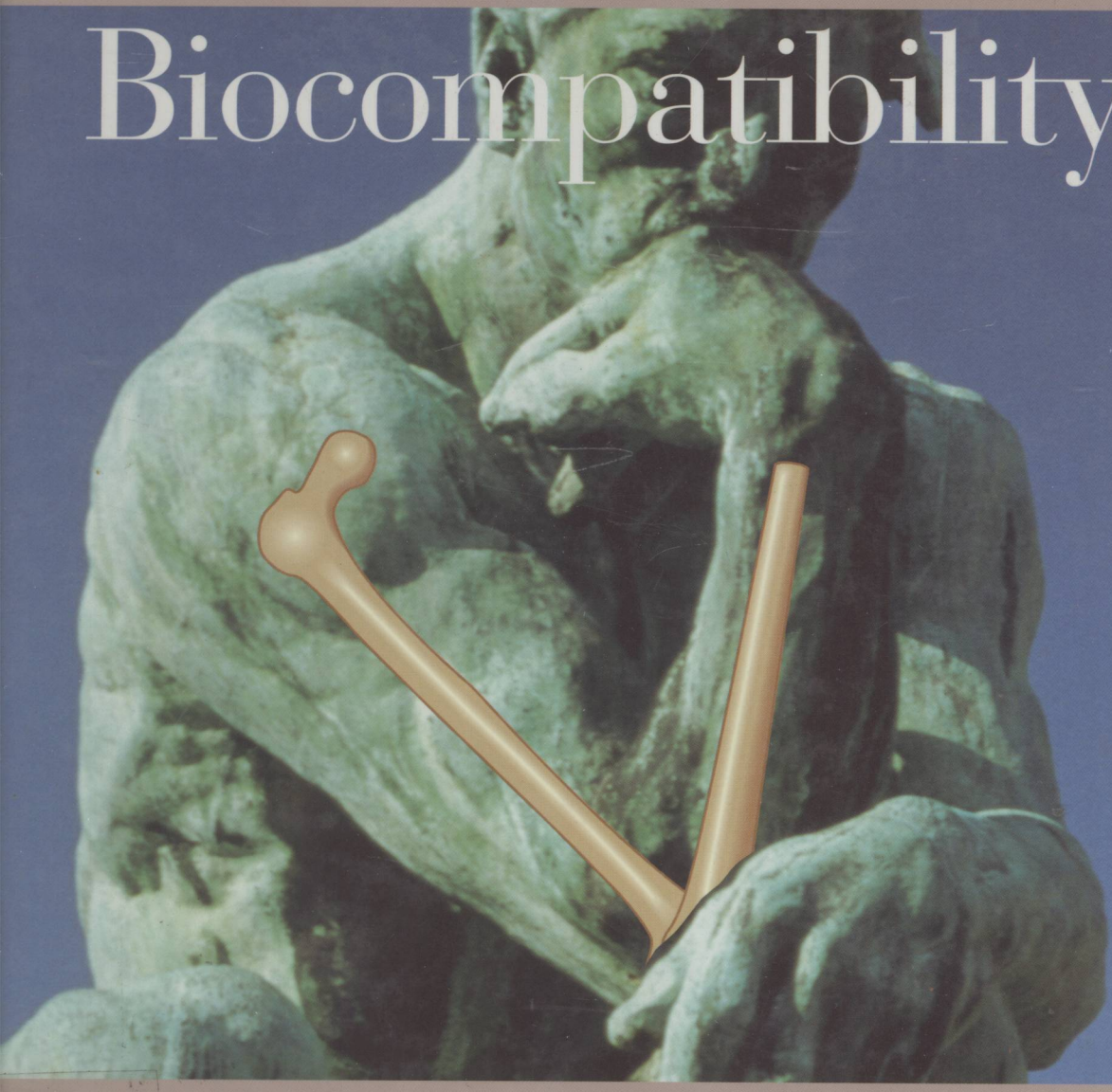
Biomaterials Science and Biocompatibility



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Preface

Although many advances have been made in the 1990s concerning the biocompatibility of implants, we still are only beginning to understand how foreign materials affect biological systems. The purpose of this book is to introduce the study of biocompatibility of implants by integrating background material, including information on the structure and properties of individual biological macromolecules, macromolecular packing, histology of tissues and organs, immunology, wound healing, and pathobiology. Although each of these topics is extensive enough to warrant its own course, we attempt to provide enough information and continuity among these topics so that the graduate student or biomaterials scientist can get a solid overview of the relationships among these topics without having to read more than one text. The information contained in this text was developed from course notes covering graduate courses in the Joint

Biomedical Engineering Program between Rutgers University and the University of Medicine and Dentistry of New Jersey entitled "Biopolymers" and "Pathobiology" during the past 15 years.

It is our hope that this book will provide the reader with all the information necessary to understand the complexity of the biological reactions that are set into motion by implantation of a material or a device. We hope that this book will provide a framework for thinking about implant interactions with biological systems. Although the field of studying pathobiological responses to implants is still in its infancy, we are now more aware of acute and chronic conditions that generate inflammatory responses as a result of wear debris, activation of complement, and acute hypersensitivity. As we learn more concerning these responses, it is hoped that our ability to design implants will also improve. We encourage readers to send to us any suggestions of additional topics that they would like to see covered in our book.

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Introduction to Biomaterials Science and Biocompatibility

Scope of Text

The field of biomaterials science dates back centuries to the ancient Greeks and Chinese, who used natural materials to ameliorate the effects of diseases. However, not until late in the twentieth century did the design and use of medical devices using synthetic and natural materials advance rapidly. The largely empirical problem-solving strategies, such as trial-and-error materials selection procedures, have evolved into a multidisciplinary field that requires in-depth knowledge of biochemistry, anatomy, structural biology, immunology, histology, pathobiology, engineering, and materials science.

The modern era in biomaterials science led to progress in the treatment of cardiovascular disease, thus extending the lives of patients with coronary artery disease, dissection or aneurysm of a major vessel, abnormal electrical con-

duction of the heart, or a weak heart. The first vascular prosthetics were introduced in the 1950s when parts of the aorta were replaced with vessels made of synthetic fabrics. At about the same time, the first pacemakers were introduced to prevent defibrillation. These advances resulted in decreased mortality from cardiovascular diseases and increased collaboration among scientists in the fields of materials sciences, engineering, and medicine.

It was also about 1950 when researchers discovered that soft and hard tissues are composed of collagen, a rodlike molecule, which, together with hydroxyapatite, is responsible for maintaining tissue shape and providing rigidity to the skeleton. Since that time, our knowledge of vertebrate and human tissue structure has exploded, yielding an information base that can require a lifetime to master. In this information base is contained the product of millions of years of evolutionary design. Studying materials such as collagen in the skin of prehistoric woolly mammoths, cuticles of worms, and the skins of fish and other invertebrates helps us understand collagens found in human tissue. This wealth of information in biological structure and architecture serves as nature's guide to artificial implant design.

In this book, we will attempt to understand biomaterials and their interaction with tissues by studying normal pathobiological processes. This approach relies on defining fundamental principles that relate the structure of natural tissues and their interaction with foreign materials. To do this, it is necessary to first define what is foreign and how it is recognized as foreign by the host. In addition, we will explain what goes wrong when the host treats its own tissues as foreign.

Perhaps the most exciting part of biomaterials science is the complexity of macromolecular structures that have been designed by nature to perform specific functions. The molecular structures are rich in interesting features, such as the ability of large molecules to change their sizes and shapes as a result of applied loads or chemical signals. These structures have evolved ordered packing patterns that not only have short-range order but form repeated patterns that continue for distances as long as meters. The tendons in the hand that control the movement of the fingers are controlled by insertions into the biceps muscle in the arm. The tendons are composed of collagen fibrils and bundles of fibrils that are composed of molecules only 0.00003 m long. The packing of millions of these molecules into a regular array allows for the precise movement of the fingers. It is this precise movement and the macromolecular packing patterns that have evolved in nature that are of interest to us in this book. As engineers, we are interested in how much force this precise array of molecules can generate

without failing. This knowledge can then be applied to the design of synthetic materials to replace those designed by nature.

This is an exciting area of study. We take structures apart, analyze their components, and crash test them—we pull and pound on these structures to see how strong they are. Much of what we learn in biomaterials science is a direct result of our inquisitiveness. It is essential to *think* and *feel* biological structures to get a better idea of what specific physical parameters mean and how they might function in biological settings. A good example of applying these physical principles is the question of how large macromolecular chains deform. Like a twisted rubber band, macromolecules extend by untwisting when a tensile force is applied to the ends. You can perform this experiment at home by twisting a rubber band and pulling on the ends; a twisted rubber band uncoils when a tensile force is applied at the ends. What happens when a tensile load is applied to a macromolecule is a little more complex; however, the response observed is still dictated by the physical principle that deformation occurs at the least rigid element. This will be discussed later when we address the mechanical properties of tissues.

Structures of Soft and Hard Tissues

The biomaterials scientist is responsible for developing replacement for tissues and organs and must be familiar with the structure and function of tissues and organs to be replaced. From a simple, engineering point of view, mammalian tissues are classified as either soft or nonmineralized and hard or mineralized; the mechanical properties of soft and hard tissues are widely divergent. More accurately we can classify body tissues as (1) surface and internal lining tissues, (2) conduit or fluid transport tissues, (3) parenchymal or organ-supporting structures, and (4) skeletal structures.

Surface and internal lining structures are similar; they are composed of an epithelial layer in contact with the external environment or a mesothelial layer in contact with internal organs that are supported by connective tissue containing collagen, proteoglycans, elastin, glycoproteins, cells, and water. These structures are found at external or internal interfaces and are composed of layers of cells and extracellular matrix and typically, with the exception of the cornea, contain blood vessels for nutrition. Examples of these structures are given in Table 1.1 and include external linings such as found in cornea, skin, oral mucosa, vagina, and uterus that provide mechanical, chemical, and microbiological barriers. These linings keep external substances out of the body, and internal

Table 1.1 Surface and internal lining structures

Structure	Composition of lining	Function
Alveoli	Squamous epithelium	Allows oxygen transport
Cornea	Stratified squamous epithelium	Protects eye from injury
Mouth	Stratified squamous epithelium	Protects oral tissues
Peritoneum	Mesothelial cells	Protects stomach organs
Pleura	Mesothelial cells	Protects chest organs
Skin	Stratified squamous epithelium	Protects body surface
Uterus	Columnar epithelium	Protects internal surfaces
Vagina	Stratified squamous epithelium	Protects internal surfaces

Table 1.2 Conduit and holding structures

Structure	Composition	Function
Bladder	Mucosa, muscularis, serosa	Holds urine
Blood vessels	Intima, media, adventitia	Transports blood
Bronchiole	Mucosa, smooth muscle, adventitia	Distributes air
Bronchus	Mucosa, submucosa, adventitia	Distributes air
Esophagus	Mucosa, submucosa, muscularis, fibrosa	Collect air
Large intestine (colon)	Mucosa, submucosa, muscularis externa, serosa	Transports food
Rectum	Mucosa, submucosa, muscularis externa, serosa	Transports waste
Stomach	Mucosa, submucosa, muscularis serosa	Hydrolyzes food
Small intestine (duodenum)	Mucosa, submucosa, muscularis externa, serosa	Adsorbs food
Trachea	Mucosa, submucosa, fibrocartilage, fibrosa	Distributes air
Ureter	Mucosa, muscularis, fibrosa	Transports liquid waste

Table 1.3 Dental and skeletal structures

Structure	Composition	Function
Articular cartilage	Superficial, intermediate, deep zones	Absorbs shock
Compact bone	Circumferential, concentric lamellar bone	Prevents bending of long bone
Cruciate ligaments	Collagen, proteoglycans	Stabilizes knee
Intervertebral disc	Nuclear pulposis, annular fibrosa	Supports spine
Muscular tissue	Smooth muscle	Constricts tubular walls
	Skeletal muscle	Allows for locomotion
Periodontal ligament	Collagen, proteoglycans	Connects tooth to bone
Spongy bone	Circumferential, concentric lamellar bone with cavities	Stores blood cell precursors

linings such as the pleural and peritoneal membranes protect organs in the thoracic and abdominal cavities from injury. A second classification of tissues includes conduit and holding structures (Table 1.2), which are tubes and containers that are characteristically composed of three layers. For example, blood vessels contain an intimal or cell layer in contact with flowing blood, a muscular or medial layer, and an adventitia that blends into the surrounding tissues. Other tubular structures are similar in that they consist of an internal cellular layer (mucosa), surrounded by a muscular layer (muscularis), and an external connective-tissue-containing layer (serosa).

The final classification of tissues is dental and skeletal tissues (Table 1.3). These tissues include oral tissues and joint and spine structures. Organ-supporting structures in the parenchyma of different tissues, such as the nephron in the kidney, are not discussed in detail in this book; however, their physiological function is described in the next section.

Structure of Surface and Internal Lining Tissues

Epithelial cells line the surface of external and internal tissues in mammals. They are derived from two of the primary layers in the embryo, the *ectoderm* and the *endoderm* (Figure 1.1). The epidermis of the skin and the epithelia of the cornea that together cover the external surfaces of the body develop from the ectoderm. The glandular appendages of the skin, including the sebaceous glands, which

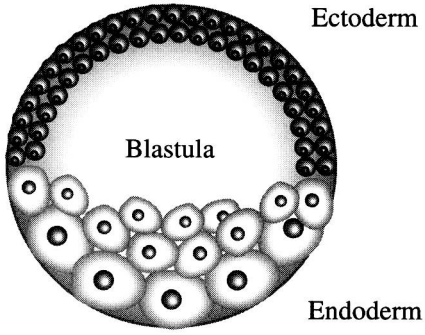

Figure 1.1 Embryonic development. Diagram showing the derivation of epithelial cells from the ectoderm and the endoderm in the embryo. The epidermis of the skin and the epithelia of the cornea develop from the ectoderm. Epithelium of the digestive system derives from the endoderm.

secrete an oily substance, and the mammary glands, are formed by folding and proliferation of the outer epithelia. The digestive system is lined by epithelia that derive from the endoderm, and its associated glands, including liver, pancreas, stomach, and intestines, arise by folding and outgrowth of primitive gut tissue. In addition to the epithelial structures that develop from the ectoderm and endoderm are several internal lining layers that are composed of epithelium derived from mesoderm. Examples include the epithelia of the kidney and the male and female reproductive tracts.

The linings of the blood and lymph vessels are all derivatives of the mesenchyme. The epithelial cell linings of blood and lymph vessels are usually referred to as *endothelium*, and the linings of the body cavities (peritoneum and pleura) are referred to as *mesothelium*. However, all these cells are considered epithelia.

All epithelia sit on connective tissue that contains collagen, the major structural protein; proteoglycans, sugar polymers that maintain tissue hydration; and glycoproteins, which act as connecting elements between epithelia and other cells and the extracellular matrix.

Types of Epithelia

Epithelia are classified according to the number of cell layers and the cell shape. A surface or lining with one cell layer is *simple* and one with two or more layers is *stratified*. The outermost or superficial layer of cells can be described as squa-