1.1.1 Introduction to Biomaterials Science: An Evolving, Multidisciplinary Endeavor

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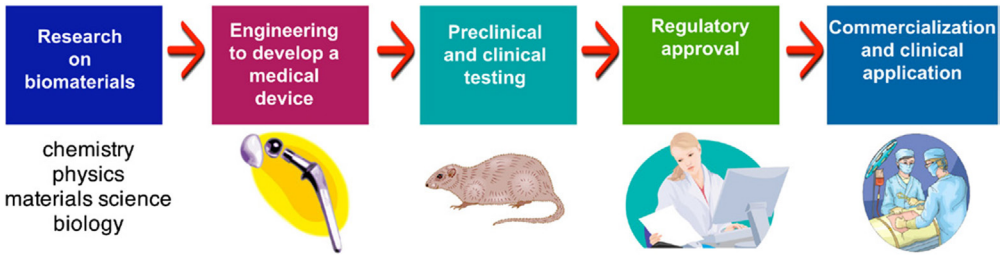
Biomaterials and Biomaterials Science

Biomaterials Science: *An Introduction to Materials in Medicine*, fourth edition, addresses the design, fabrication, testing, applications, and performance as well as nontechnical considerations integral to the translation of synthetic and natural materials that are used in a wide variety of implants, devices, and process equipment that contact biological systems. These materials are referred to as biomaterials.

> The compelling, human side to biomaterials is that millions of lives are saved, and the quality of life is improved for millions more.

The field of biomaterials is some 70–80 years old at the time of publication of this fourth edition. It significantly impacts human health, the economy, and many scientific fields. Biomaterials and the medical devices comprised of them are now commonly used as *prostheses* in cardiovascular, orthopedic, dental, ophthalmological, and reconstructive surgery, and in other interventions such as surgical sutures, bioadhesives, and controlled drug release devices. The compelling, human side to biomaterials is that millions of lives have been saved, and the quality of life improved for millions more, based on devices fabricated from biomaterials. The biomaterials field has seen accelerating growth since the



• **Figure 1.1.1.1** The path from the basic science of biomaterials, to a medical device, to clinical application.

first medical devices that were based on accepted medical and scientific principles made their way into human usage in the late 1940s and early 1950s. And the growth of the field is ensured, with the aging population, the increasing standard of living in developing countries, and the growing ability to address previously untreatable medical conditions.

Biomaterials science addresses both therapeutics and diagnostics. It encompasses basic sciences (biology, chemistry, physics) and engineering and medicine. The translation of biomaterials science to clinically important medical devices is dependent on: (1) sound engineering design; (2) testing in vitro, in animals and in humans; (3) clinical realities; and (4) the involvement of industry permitting product development and commercialization. Fig. 1.1.1.1 schematically illustrates the path from scientific development to the clinic.

Biomaterials science, in its modern incarnation, is an example of the emerging *convergence* paradigm that pushes multidisciplinary collaboration among experts and multidisciplinary integration of concepts and practice (Sharp and Langer, 2011). Not only biomaterials, but also bioinformatics, synthetic biology, computational biology, nanobiology, systems biology, molecular biology, and other forefront fields depend on convergence for their continued progress. This textbook aims to introduce these diverse multidisciplinary elements, particularly focusing on interrelationships rather than disciplinary boundaries, to systematize the biomaterials subject into a cohesive curriculum—a true convergence.

The title of this textbook, *Biomaterials Science*: *An Introduction to Materials in Medicine*, is accurate and descriptive. The intent of this work is: (1) to focus on the scientific and engineering fundamentals behind biomaterials and their applications; (2) to provide sufficient background knowledge to guide the reader to a clear understanding and appreciation of the clinical context where biomaterials are applied; and (3) to highlight the opportunities and challenges in the field. Every chapter in this text can serve as a portal to an extensive contemporary literature that expands on the basic ideas presented here. The magnitude of the biomaterials endeavor, its broadly integrated multidisciplinary scope, and examples of biomaterials applications will be revealed in this introductory chapter and throughout the book.

The common thread in biomaterials is the physical and chemical interactions between complex biological systems and synthetic or modified natural materials.

Although biomaterials are primarily used for medical applications (the focus of this text), they are also used to grow cells in culture, to assay for blood proteins in the clinical laboratory, in processing equipment for biotechnological applications, for implants to regulate fertility in cattle, in diagnostic gene arrays, in the aquaculture of oysters, and for investigational cell–silicon "neuronal computers." How do we reconcile these diverse uses of materials into one field? The common thread is the physical and chemical interactions between complex biological systems and synthetic materials or modified natural materials.

In medical applications, biomaterials are rarely used as isolated materials, but are more commonly integrated into devices or implants, and complex devices may use multiple biomaterials, often selected from several classes (e.g., metal and polymer). Chemically pure titanium can be called a biomaterial, but shaped (machined) titanium in conjunction with ultrahigh molecular weight polyethylene becomes the device, a hip prosthesis. Although this is a text on biomaterials, it will quickly become apparent that the subject cannot be explored without also considering biomedical devices and the biological response to them. Indeed, both the material and the device impact the recipient (patient) and, as we will see, the patient's host tissue impacts the device. These interactions can lead to device success or, where there is inappropriate choice of biomaterials or poor device design, device failure. Moreover, specific patient characteristics may influence the propensity to failure (e.g., obesity increasing the likelihood of fracture or excessive wear of a hip joint prosthesis, or clotting of a mechanical heart valve in a patient with a genetic mutation that causes hyper-coagulability).

Furthermore, a biomaterial must always be considered in the context of its final fabricated, sterilized form. For example, when a polyurethane elastomer is cast from a solvent onto a mold to form the pump bladder of a heart assist device, it can elicit different blood reactions compared to when injection molding is used to form the same device. A hemodialysis system serving as an artificial kidney requires materials that must function in contact with a patient's blood, and also exhibit appropriate membrane permeability and mass transport characteristics. Much fabrication technology is applied to convert the biomaterials of the hemodialysis system (polysulfone, silicone rubber, polyethylene) into the complex apparatus that is used for blood purification.

Due to space limitations and the materials focus of this work, many aspects of medical device design are not addressed in this book. Consider the example of the hemodialysis system. This textbook will overview membrane materials and

their biocompatibility; there will be little coverage of mass transport through membranes, the burst strength of membranes, dialysate water purification, pumps, flow systems, and monitoring electronics. Other books and articles cover these topics in detail, and chapter authors provide references useful to learn more about topics not explicitly covered.

Key Definitions

The words "biomaterial" and "biocompatibility" have already been used in this introduction without formal definition. A few definitions and descriptions are in order, and will be expanded upon in this and subsequent chapters.

A definition of "biomaterial" endorsed by a consensus of experts in the field is:

> *A biomaterial is a nonviable material used in a medical device, intended to interact with biological systems.*
>
> **WILLIAMS (1987).**

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Although biomaterials are most often applied to meet a therapeutic or diagnostic medical need, if the word "medical" is removed, this definition becomes broader and can encompass the wide range of applications already suggested. If the word "nonviable" is removed, the definition becomes even more general, and can address many new tissue-engineering and hybrid artificial organ applications where living cells are used.

"Biomaterials science" is the study (from the physical and/or biological perspective) of materials with special reference to their interaction with the biological environment. Traditionally, emphasis in the biomaterials field has been on synthesis, characterization, and the host–material interactions biology. Yet, most biomaterials (which meet the special criteria of biocompatibility—see Chapters 2.3.2 and 2.3.4) induce a nonspecific biological reaction that we refer to as the foreign-body reaction (Chapter 2.2.2). This leads us to consider a widely used definition of biocompatibility:

> *"Biocompatibility" is the ability of a material to perform with an appropriate host response in a specific application.*
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Examples of "appropriate host responses" include resistance to blood clotting, resistance to bacterial colonization, and normal, uncomplicated healing. Examples of "specific applications" include a hemodialysis membrane, a urinary catheter, or a hip joint replacement prosthesis. Note that the hemodialysis membrane might be in contact with the patient's blood for 5 h (and outside the body), the catheter may be inserted for a week (inside the body, and designed to be easily removed), and the hip joint may be in place for the life of the patient (deeply implanted and meant to be long-term). This general concept of biocompatibility has been extended to tissue engineering, in which in vitro and in vivo processes are harnessed by careful selection of cells, materials, and metabolic and biomechanical conditions to regenerate functional tissues. Ideas central to biocompatibility are elaborated upon in Ratner (2011) and Chapter 2.3.2.

In the discussion of these definitions, we are introduced to considerations that set biomaterials apart from most materials explored in materials science. Table 1.1.1.1 lists a few applications for biomaterials in the body. It includes many classes of materials used as biomaterials. Note that metals, ceramics, polymers, glasses, carbons, and natural and composite materials are listed. Such materials are used as molded or machined parts, coatings, fibers, films, membranes, foams, fabrics, and particulates. Table 1.1.1.1 also gives estimates of the specific device global market size and, where available, an estimate of the number of medical devices utilized annually. The human impact, and the size of the commercial market for biomaterials and the broad array of medical devices, is impressive (Tables 1.1.1.1 and 1.1.1.2).

TABLE 1.1.1.1 Key Applications of Synthetic Materials and Modified Natural Materials in Medicine

Application	Biomaterials Used	Number/Year—Global (or Global Market in US$)
Skeletal System		
Joint replacements (hip, knee, and shoulder)	Titanium, CoCr, polyethylene, alumina, zirconia	4,000,000 ($16B)
Trauma fixation devices (plates, screws, pins, and rods)	Titanium, stainless steel, CoCr, polyether ether ketone, poly(lactic acid) (PLA)	1,500,000 ($5.5B)
Spine disks and fusion hardware	Nitinol, titanium, polyether ether ketone, stainless steel	1,100,000 ($8.5B)
Bone defect repair	Calcium phosphates, human bone products	($4.5B)
Bone cement (fixation)	Polymethyl methacrylate (PMMA), glass polyalkenoate (ionomer), calcium phosphate cements	($1.1B)
Cartilage, tendon, or ligament repair and replacement	Decellularized porcine tissue, poly(lactide) and metallic fixation devices, collagen, hyaluronic acid lubricants	($8.6B)
Dental implant-tooth fixation	Titanium, zirconium	10,000,000 ($4B)

(Continued)

TABLE 1.1.1.1 Key Applications of Synthetic Materials and Modified Natural Materials in Medicine—cont'd

Application	Biomaterials Used	Number/Year—Global (or Global Market in US$)
Cardiovascular System		
Vascular grafts, patches, and endovascular devices (stent grafts)	Dacron, expanded poly(tetrafluoroethylene), Nitinol, CoCr, stainless steel, fixed tissue	($2.5B)
Heart valves: mechanical and bioprosthetic (transcatheter and traditional)	Dacron, carbon, CoCr, fixed bovine and porcine tissue, stainless steel, Nitinol	600,000 ($5.5B)
Pacemakers	Titanium, polyurethane	1,000,000 ($6.5B)
Implantable defibrillators	Titanium, polyurethane	300,000 ($9.0B)
Stents: coronary, peripheral vasculature, and nonvascular	Stainless steel, Nitinol, CoCr, Pt, tantalum, Mg alloys, poly(styrene-*b*-isobutylene-*b*-styrene), poly(*n*-butyl methacrylate), polyethylene-*co*-vinyl acetate, phosphoryl choline containing block copolymers, poly(lactic-*co*-glycolic acid), PLA	5,000,000 ($10.6B)
Catheters: cardiovascular, urologic, and others	Polytetrafluoroethylene (PTFE), poly(vinyl chloride), silicone, polyurethane	($28B)
Organs		
Cardiac assist devices (acute and chronic)	Titanium alloy, polycarbonate, PTFE, poly(ethylene terephthalate), stainless steel	($1.7B)
Hemodialysis	Polysulfone, modified cellulose, polyacrylonitrile, polycarbonate, silicone, polyvinylchloride	2,000,000 patients ($12B)
Blood oxygenator	Polymethylpentene, polypropylene, polysiloxane, poly(vinyl chloride), polycarbonate	($300M)
Skin substitute (chronic wounds, burns)	Collagen, cadaver skin, alginate, polyurethane, carboxymethylcellulose, nylon, silicone	($1.3B)
Ophthalmologic		
Contact lens	PMMA, polyhydroxyethylmethacrylate (PHEMA), polyvinyl alcohol, polyvinyl pyrrolidone, silicone (polydimethyl siloxane [PDMS])	($7.5B)
Intraocular lens	PMMA, PDMS, polyacrylate-PMMA, PHEMA	25,000,000 ($4.5B)
Glaucoma drains	Silicone, polypropylene, cross-linked collagen, stainless steel	($500M)
Other		
Cochlear prostheses	Platinum, platinum–iridium, PDMS, titanium, aluminum oxide	45,000 ($2.7B)
Breast implants	PDMS	3,600,000 ($1.2B)
Hernia and body wall repair meshes	Polypropylene, polyester, expanded PTFE, decellularized porcine/bovine tissue	($4.2B)
Sutures	Silk, nylon, poly(glycolic acid), PLA, polydioxanone, polyester copolymers, polypropylene, PTFE, processed bovine tissue	($3.9B)
Blood bags	Poly(vinyl chloride)	($170M)
Ear tubes (tympanostomy)	Silicone, PTFE	1,500,000 ($70M)
Intrauterine device	Polyethylene, copper, stainless steel, PDMS	168,000,000 ($2.9B)

Data compiled from multiple sources—these numbers should be considered rough estimates that are changing with growing markets and new technologies. Where only US numbers were available, world usage was estimated at approximately 2.5× US. *B*, Billion; *M*, million.

TABLE 1.1.1.2 The Medical Device Global Market by Segment With Projected Compound Annual Growth Rate (CAGR) ($ Millions)

Segments	2016	2017	2022	CAGR 2017–2022 (%)
Drug delivery devices	200,072	207,814	243,367	3.2
Urology and renal	75,378	82,668	109,003	5.7
In vitro diagnostics	66,143	72,816	99,357	6.4
Orthopedics and spine	65,756	72,086	99,559	6.7
Imaging devices	41,194	45,816	64,282	7.0
Cardiovascular devices	25,384	29,658	45,260	8.8
Endoscopy	9,573	10,372	13,693	5.7
Total	483,500	521,230	674,521	5.3

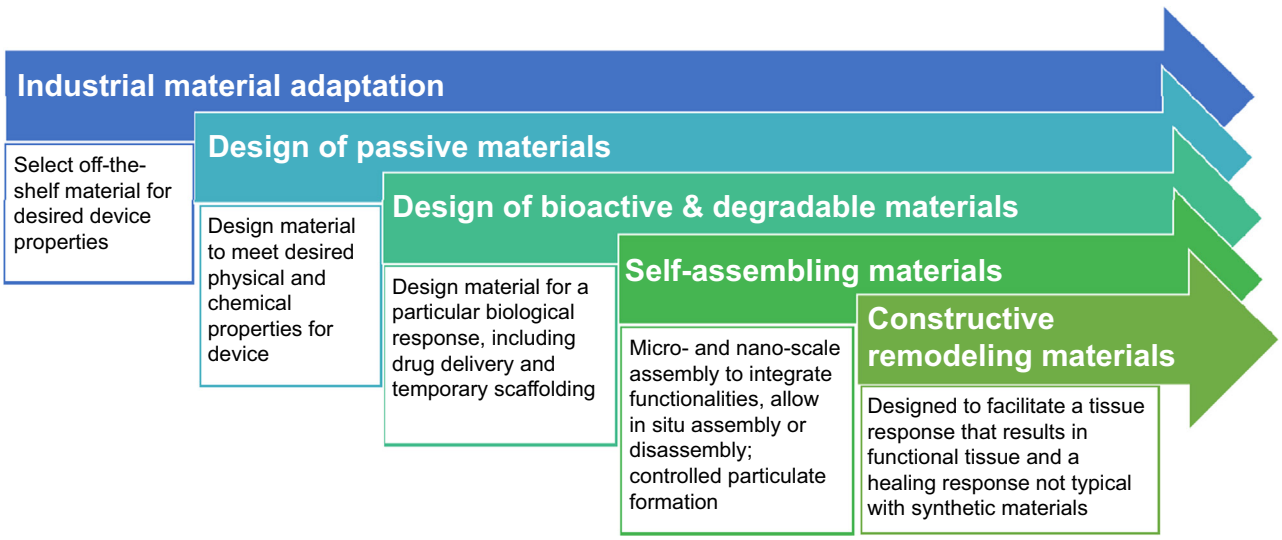
Source: BCC Research.

The Expansion of the Biomaterials Field

Biomaterials research and development have been stimulated and guided by advances in cell and molecular biology, pathology, clinical medicine and dentistry, chemistry, materials science, and engineering. The biomaterials community has been the major contributor to the understanding of the interactions of materials with the physiological environment (often referred to as the biointerface). The development of biomaterials for medical and dental applications has evolved with time, as new concepts and understandings are applied to offer a broadening repertoire of choices to meet device design objectives (Fig. 1.1.1.2).

Early applications of biomaterials sought to achieve a suitable combination of functional properties to adequately meet the design needs for the medical device under development. Generally, this would involve the layering of biocompatibility concerns from host–material interactions on top of those more readily understood physical and chemical requirements. For instance, for a mechanical cardiac valve, materials could be selected and integrated to provide the functional response in an altering pressure flow field, resistance to cyclic mechanical wear, and suturability. In these early applications, industrial materials were typically taken off the shelf, i.e. "medical grade" biomaterials were not yet available. Nevertheless from the array of industrially available materials that might meet these requirements, considerations of blood and tissue compatibility would be included.

Pioneers in the device field effectively applied empirical approaches to arrive at materials that could meet both the traditional (nonbiological) design requirements and



• **Figure 1.1.1.2** The growing palette of biomaterials. Generally moving with time from the 1940s adaptation of industrially available materials for early medical devices to the present, the breadth of described biomaterials continues to grow. In device development a biomaterial may be selected to leverage recent progress. However, it is important to note that major advances in the medical device field continue to be made with materials that could be considered first generation. The growing palette provides the design engineer with more tools to optimize device functionality in concert with other concerns such as manufacturability, regulatory burden, and economic considerations.

exhibit adequate levels of biocompatibility. Materials would generally be selected because they were tolerable (i.e., they elicited minimal response from the host tissues), and this would be consistent with *biocompatibility* for many applications (see Chapter 2.3.2). While the understanding of biomaterials science has evolved substantially from these early days, it is important to recognize that industrially repurposed materials continue to be utilized in many widely used medical devices today, including poly(tetrafluoroethylene) and poly(ethylene terephthalate), from which virtually all synthetic vascular grafts are made, stainless steel, cobalt–chromium alloys and titanium alloys, from which many orthopedic devices are constructed, and the polyurethanes and polysiloxanes that are utilized in a broad array of catheters and medical tubing. Furthermore, industrially adapted materials continue to be the biomaterials of choice for many revolutionary *new* devices introduced in recent years such as many of the components related to neurostimulatory devices and structural heart repair.

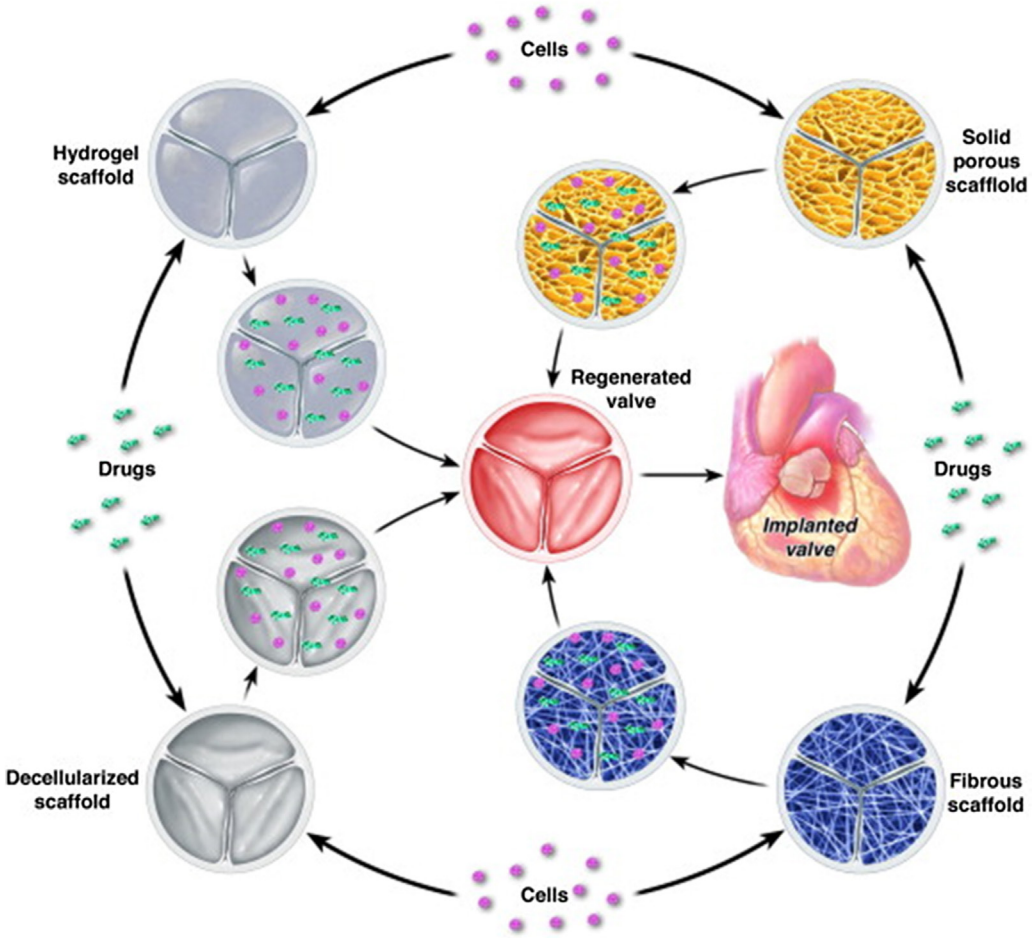
In this early period it would also occasionally be noted where an off-the-shelf material or class of materials might not fully achieve the target device design objectives and novel materials would be designed or refined specifically for a biomedical purpose. As highlighted in Chapter 1.1.2, biomaterials scientists would, for instance, create polyurethanes with segments selected for the purpose of improving blood biocompatibility. Hydrogels would be synthesized for soft tissue applications. Pyrolytic carbon, originally developed in the 1960s as a coating material for nuclear fuel particles, was studied and tuned for what is now in wide use in modified compositions to coat components of mechanical cardiac valves. These designed materials broadened the biomaterials palette, but the materials were still designed to be passive in achieving biocompatibility. As with early adapted industrial materials, these types of biomaterials continue to play an important part in device design and active research continues to seek to develop materials that are better suited for specific device applications while still targeting a passive, bioinert posture. For instance, efforts to find more degradation-resistant polymers for challenging device applications are ongoing (Chapter 2.4.2).

As knowledge of biological interactions with materials evolved, new types of biomaterials were developed with the intention of eliciting a controlled reaction with the tissues they contacted to induce a desired therapeutic effect. In the 1980s, these *bioactive* materials were in clinical use in orthopedic and dental surgeries as various compositions of bioactive glasses and ceramics (Hench and Pollak, 2002, Chapter 1.3.4), in controlled localized drug release applications such as the Norplant hormone-loaded contraceptive formulation (Meckstroth and Darney, 2001), and in the attachment of the anticoagulant heparin to the surfaces of membrane oxygenators with various modification strategies (Chapter 1.4.3B). Vascular stents have also been profoundly impacted by the implementation of a bioactive approach, with the application of polymer coatings that release antiproliferative agents and markedly reduce a major failure mechanism of tissue overgrowth and vessel occlusion (Chapter 2.5.2B).

Bioactive biomaterial development has also included the synthesis of resorbable polymeric biomaterials, with rates of degradation that could be tailored to the requirements of a desired application (Chapter 1.3.2F). Thus the discrete interface between the implant site and the host tissue could be eliminated in the long term, because the foreign material would ultimately be degraded to soluble, nontoxic products by the host. Many groups continue to develop new biodegradable polymers designed with defined objectives in strength, flexibility, a chemical composition conducive to tissue development, and a degradation rate consistent with the specific application. Degradable materials have been integral to the tissue-engineering paradigm where a scaffold, alone or in combination with cells and drugs, may provide for the generation of functional tissue. This paradigm as applied to the engineering of a cardiac valve is presented in Fig. 1.1.1.3 and is covered in the chapters of Section 2.6. Tissue-engineering approaches often leverage degradable biomaterials scaffolds, drug-releasing biomaterials, and in some cases utilize specific cell receptor–ligand interactions or enzymatic degradability to build bioactivity into the biomaterials scaffold (Chapters 1.4.4 and 1.4.5).

A characteristic of bioactive biomaterials development over the past several decades has been the leverage of fundamental knowledge from molecular biology. As this knowledge base has grown, biomaterials scientists and engineers have translated the understanding of biomolecular interactions to engineer biological interactions with designed materials. An early example of this was the application of knowledge of the adhesion peptide sequences from proteins such as fibronectin (e.g., Arg-Glu-Asp-Val) to engineer peptide-modified surfaces that would support specific types of cell adhesion (Hubbell et al., 1991). Polymeric materials with other novel properties such as shape-memory and programmable and interactive surfaces that control the cellular microenvironment are areas of development (Chapter 1.3.2G). In addition to having implications for medical applications, such engineered smart biomaterials systems have been used to advance our understanding of molecular biology principles, for instance, in elucidating the roles of substrate stiffness, ligand density, and three-dimensional culture in mammalian cell behavior.

The need for maximally effective pharmacologic dosing regimens and minimization of systemic toxicities has stimulated development of innovative particulate systems for targeted drug delivery and gene therapy (Chapter 1.3.8). Such systems may also provide the basis for targeted imaging or the combination of targeted imaging and therapeutic delivery, representing the growing field of theranostics. This focus area is experiencing a great deal of research attention at present by the biomaterials community and many of the approaches involve the production of nano- and microscale particulates using the principles of self-assembling materials. Several factors are driving this effort to design better biomaterials-based approaches: advances in protein and nucleic acid-based drugs (which cannot be taken in classical pill form, have high cost, and are labile); a better understanding of transport mechanisms systemically, within

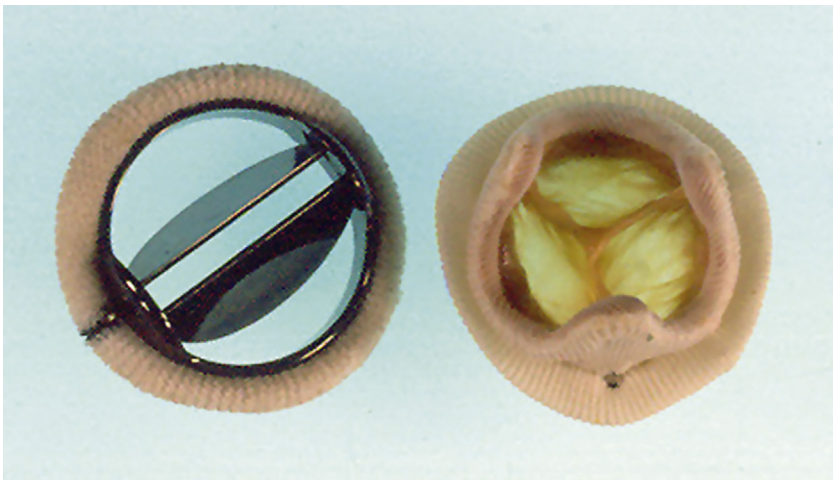


• **Figure 1.1.1.3** An example of various tissue-engineering paradigms applied to a cardiac valve. Current approaches for many tissues, including heart valves, may involve scaffolds, cells, and drugs. These components may be used alone or in combination. For each component, different material types, drugs, or cells may be used. Again, alone or in combination, bioreactors may be employed to allow some level of tissue construct maturation, or the body may serve as the bioreactor. (From Jana, S., Tefft, B.J., Spoon, D.B., Simari, R.D., 2014. Scaffolds for tissue engineering of cardiac valves. Acta Biomater. 10, 2877–2893.)

specific tissues or tumors, and intracellularly; and an increasing ability to create precise structures at macromolecular scales through controlled polymerization techniques and specific orthogonal reaction schemes.

Self-assembled biomaterials have allowed design at the nanoscale to protect drug payloads that are released with an appropriate signal (e.g., pH, radiation, intracellular environmental cues) upon delivery at the desired site through the surface presentation of targeting moieties and molecules that reduce fouling and improve pharmacokinetics. Self-assembled biomaterials have also found broad interest as injectable networks for the creation of scaffolds and depots in regenerative medicine, drug delivery, and immunoengineering (Sahoo et al., 2018). Here, by switching out functional groups on larger self-assembling molecules, the specific bioactivity and mechanical properties of an assembled network may be designed. Interest is also growing in the structural and functional tailoring of self-assembled two-dimensional organic biomaterials to open new opportunities by controlling biomaterials at the nanoscale for highly specific, spatially orchestrated biological interactions (Zhang et al., 2019).

A final category in the growing repertoire of biomaterials is what could be termed constructive remodeling materials. Such materials have been designed or processed to facilitate a healing response that does not follow the classic foreign-body response found with most synthetic tissues, but is characterized by remodeling of the tissue with minimal scarring. This response has been observed and well documented in biomaterials derived from animal-based tissues that have been decellularized to reduce immunogenicity, but which have not been chemically cross-linked. Chemical cross-linking is a critical part of maintaining structural viability for many biomaterials (e.g., bioprosthetic cardiac valves from bovine or porcine source tissues), but in this approach a tissue, such as porcine bladder or dermis, is meant to be degraded and remodeled at the implantation site, and in this remodeling process, be replaced with host tissue that is functional as opposed to fibrotic. These types of materials are described in Chapter 1.3.6, and the role of the immune response with these types of natural materials versus most synthetic materials or cross-linked natural materials is addressed in Chapter 2.2.2. As the biomaterials community better understands the mechanisms



• **Figure 1.1.1.4** Prosthetic heart valves. *Left*: A bileaflet tilting disk mechanical heart valve (St. Jude Medical Inc., St. Paul, MN). *Right*: A bioprosthetic (xenograft) tissue heart valve (Hancock valve, Medtronic Inc., MN).

by which constructive remodeling can be achieved, this knowledge is being applied in materials designed to orchestrate specific interactions with the immune system to moderate the host response. More broadly, biomaterials are being developed in the area of immunoengineering (Chapter 2.5.10) to impact the immune system in applications related to immunization, cancer, infection, and autoimmune diseases.

Examples of Today's Biomaterials Applications

Five examples of biomaterials applications now follow to illustrate important ideas. The specific devices discussed were chosen because they are widely used in humans with good success. However, key limitations with these biomaterial devices are also highlighted. Each of these examples is also discussed in detail in later chapters in this textbook.

Heart Valve Prostheses

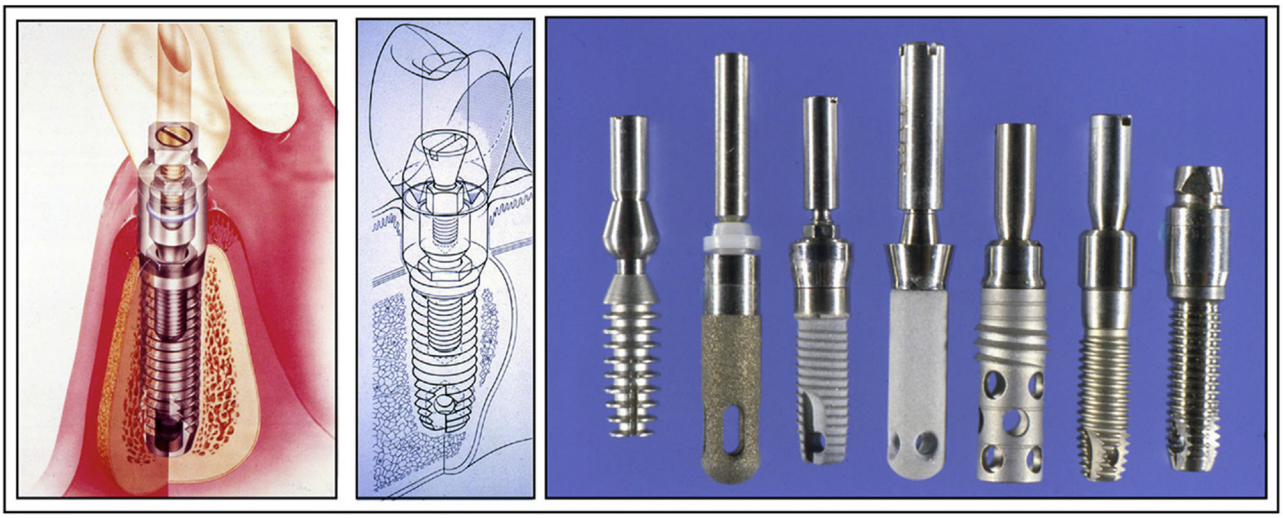
Diseases and degeneration of the heart valves often make surgical repair or replacement necessary. The natural heart valve opens and closes over 40 million times per year, and can require replacement due to disease or wear. Approximately 4,500,000 replacement valves are implanted each year worldwide, because of acquired damage to the natural valve and congenital heart anomalies. There are many types of heart valve prostheses, and they are fabricated from carbons, metals, elastomers, plastics, fabrics, and animal or human tissues chemically pretreated to reduce their immunologic reactivity, and to enhance durability. Fig. 1.1.1.4 shows a bileaflet tilting disk mechanical heart valve and a bioprosthetic (porcine xenograft) tissue heart valve, two of the most widely used designs. Generally, as soon as the valve is implanted, cardiac function is restored to near normal levels, and the patient shows rapid improvement. In spite of the overall success seen with replacement heart valves, there are problems, many of them specific to a certain type of valve; they include

• **Figure 1.1.1.5** A hip prosthesis. Microplasty titanium alloy femoral stem, Biolox alumina–zirconia ceramic femoral head, and ultrahigh molecular weight polyethylene acetabular cup infused with vitamin E antioxidant. (Image courtesy of Biomet, Inc.)

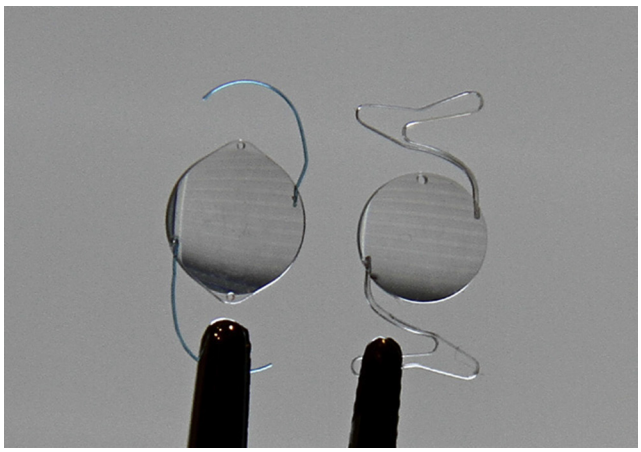
induction of blood clots, predominantly with mechanical valves (sometimes shed into the bloodstream as emboli and creating an ongoing risk for stroke, thus necessitating long-term therapy with potentially dangerous anticoagulant drugs), degeneration of valve tissue leaflets, mechanical failure, and infection. This biomaterial application continues to be an active area of innovation, most recently with growing clinical use of valve designs implanted through a catheter and in the advancement of tissue-engineering approaches for valve replacement (Zhang et al., 2019). Heart valve substitutes are discussed in Chapter 2.5.3A.

Total Hip Replacement Prostheses

The human hip joint is subjected to high levels of mechanical stress and receives considerable abuse in the course of normal and extraordinary activity. It is not surprising that after 50 or more years of cyclic mechanical stress or because of degenerative or rheumatoid disease, the natural joint wears out, leading to loss of mobility and sometimes confinement to a wheelchair. Hip joint prostheses are fabricated from a variety of materials, including titanium, stainless steel, special high-strength alloys, ceramics, composites, and ultrahigh molecular weight polyethylene. Replacement hip joints (Fig. 1.1.1.5) are implanted



• **Figure 1.1.1.6** Schematic images of early dental root form implants and a photograph of several designs used in clinical practice.



• **Figure 1.1.1.7** Two styles of multipiece intraocular lenses.

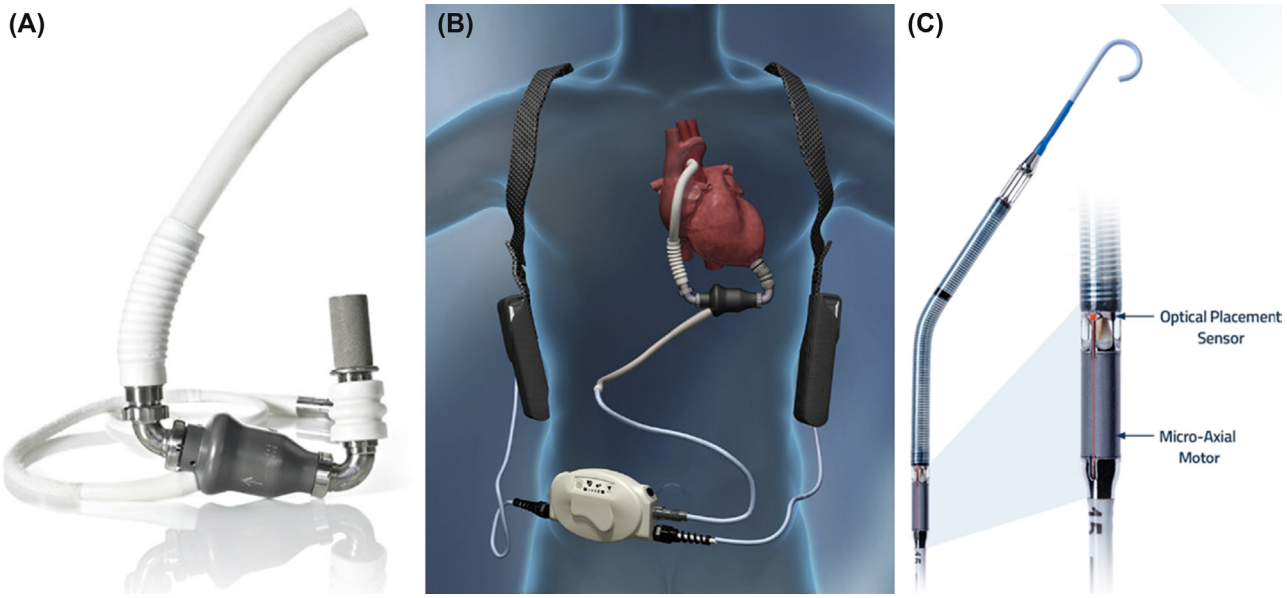
in more than 300,000 humans each year in the United States alone. With some types of replacement hip joints and surgical procedures that use a polymeric cement, ambulatory function is restored within days after surgery. For other types, a healing-in period is required for integration between bone and the implant before the joint can bear the full weight of the body. In most cases, good function is restored. Even athletic activities are possible, although those activities that subject the repaired joint to high stress are generally not advisable. After 10–15 years, many of these implants fail by loosening, which usually necessitates another operation (a revision procedure). Metal-on-metal implants also experience problems of corrosion and adverse responses to released metal ions. Artificial hip joint prostheses are discussed in Chapter 2.5.4.

Dental Implants

The development of root form designs of titanium implants (Fig. 1.1.1.6) by Per-Ingvar Brånemark revolutionized dental implantology (Carlsson et al., 1986). These devices form an implanted artificial tooth anchor upon which a crown is affixed and are implanted in 5,000,000 people each year in the United States alone, according to the American Dental Association. A special requirement of a material in this application is the ability to form a tight seal against bacterial invasion where the implant traverses the gingiva (gum). Other issues are associated with the rapidly growing junctional epithelium inhibiting regrowth of the slower growing bone. Also, in normal physiology, the tooth is connected to the jaw by the periodontal ligament and is not directly attached to the jawbone. One of the primary advantages originally cited for the titanium implant was its osseous integration with the bone of the jaw. In recent years, however, this attachment has been more accurately described as a tight apposition or mechanical fit, and not true bonding. Loss of tissue support leading to loosening remains an occasional problem, along with infection and issues associated with the mechanical properties of unalloyed titanium that is subjected to long-term cyclic loading. Dental implants are discussed in Chapter 2.5.5.

Intraocular Lenses

Implants to replace lenses in the eye that have clouded due to cataracts are called intraocular lenses (IOLs). They have been fabricated from a variety of transparent materials, including poly(methyl methacrylate), silicone elastomer, soft acrylic polymers, and hydrogels (Fig. 1.1.1.7). By the age of 75, more than 50% of the population suffers from cataracts severe enough to warrant IOL implantation. This now translates to an estimated 25 million implants worldwide as cataract treatment is expanding rapidly in healthcare systems with growing economies and aging populations. Good vision is generally restored almost immediately after the lens is inserted, and the success rate with this device is high. IOL surgical procedures are well developed, and implantation is most often performed on an outpatient



• **Figure 1.1.1.8** A commonly utilized chronic ventricular assist device (VAD). (A) Continuous flow pump with associated inflow/outflow grafts and electrical drive line (Heartmate II device). (B) Schematic of VAD implanted as a left ventricular assist device with associated external power source. (C) A catheter-based rotary blood pump from Impella for acute cardiac support. The tip of the device is placed in the ventricle where openings allow blood flow into the lumen of the device. Blood is pumped with a microaxial rotary motor and expelled through catheter openings in the region of the device that rests in the aorta. (Images A and B obtained with permission from Thoratec Corporation. Image C obtained from https://mms.businesswire.com/media/20190831005001/en/740858/5/SmartAssist_Press_release_image.jpg?download=1.)

basis. Observations of implanted lenses through the cornea using a microscope to directly study the implants show that inflammatory cells such as macrophages migrate to the surface of the lenses after implantation. Thus the conventional healing pathway is seen with these devices, similar to that observed with materials implanted in other sites in the body. Outgrowth of cells onto the IOL from the posterior lens capsule, stimulated by the presence of the IOL, can cloud vision, and this is a significant complication. IOLs are discussed in Chapter 2.5.6.

Ventricular Assist Devices

Nearly 5,000,000 Americans are living with seriously failing hearts (congestive heart failure), and 300,000 individuals will die each year from this disease. According to the American Heart Association, 50,000–100,000 of these individuals might benefit from cardiac transplantation or mechanical circulatory support. Since the available pool of donor hearts for transplantation is only ~3500 per year (United States), effective and safe mechanical cardiac assist or replacement seems like a desirable option. Ventricular assist devices (VADs) have evolved from a daring experimental concept, the mechanical total heart, to a life-prolonging tool (see Chapter 2.5.2A). A number of devices have received regulatory approval and designs have evolved from bulky pulsatile pumps with chambers and opposing valves (mimicking the human heart) to much smaller rotary devices compatible with a broader array of patients. VADs are now used in multiple ways: to maintain ("bridge") a patient with a failing heart while awaiting a donor organ, as a permanent source of support for patients not destined for a heart transplant, and as temporary support where cardiac function is at risk due to a procedure, or when a weakened heart is expected to recover in the short term and device support can be withdrawn. A commonly utilized rotary VAD for extended cardiac support and a catheter-based device used for temporary support are illustrated in Fig. 1.1.1.8. Recipients of VADs designed for chronic support can have considerable mobility and freedom, with most being discharged from the hospital setting. Despite patients being supported in some cases for several years, there remains an elevated risk for device-related infection (particularly in the region where the control and power line crosses the skin) and stroke related to the embolization of clots formed within the device. Furthermore, although VAD therapy that sends a patient home with a device may be economically more efficient and provide better outcomes than an extended period in an intensive care unit, the therapy remains expensive and is not feasible for broad application in the health systems of many countries. Can so expensive an innovation be made available to the wide patient base that could benefit from them? Wider adoption and increased entries into the market are reducing costs, but the fact of profound global disparities in medical device adoption remains for VADs and other complex and new device technologies. Developing approaches for best practices in medical device management are an area of interest and study within the World Health Organization and the reader is referred to an ongoing series of publications and forums from this source that consider how to best translate medical device advances across disparate healthcare economies.

These five cases, only a small fraction of the important medical devices that could have been used as examples,

spotlight central ideas and themes relevant to most medical devices interfacing with the human biology. A few generalizations are:

- Implantation in hundreds of thousands of patients with good success is noted.
- A broad range of synthetic materials of varying properties are used.
- Most anatomical sites can be interfaced with a device.
- The normal response by which the body responds to foreign bodies is observed.
- Problems, concerns, unexplained observations, or unintended consequences may be noted for each device.
- Most device complications are related to biomaterials–tissue interactions.
- Companies are manufacturing devices and bringing value to shareholders (and patients).
- Regulatory agencies are carefully assessing device performance, and making policy decisions to monitor the device industry, ensure quality, and protect the patient.
- Ethical and societal issues are associated with each device.

These ideas are relevant to nearly all medical devices. As you work through this text, consider how these ideas impact the specific topic you are studying.

Characteristics of Biomaterials Science

Now that we have defined key terms and reviewed specific examples highlighting successes and also complications, we can examine core characteristics of the field of biomaterials.

Multidisciplinary

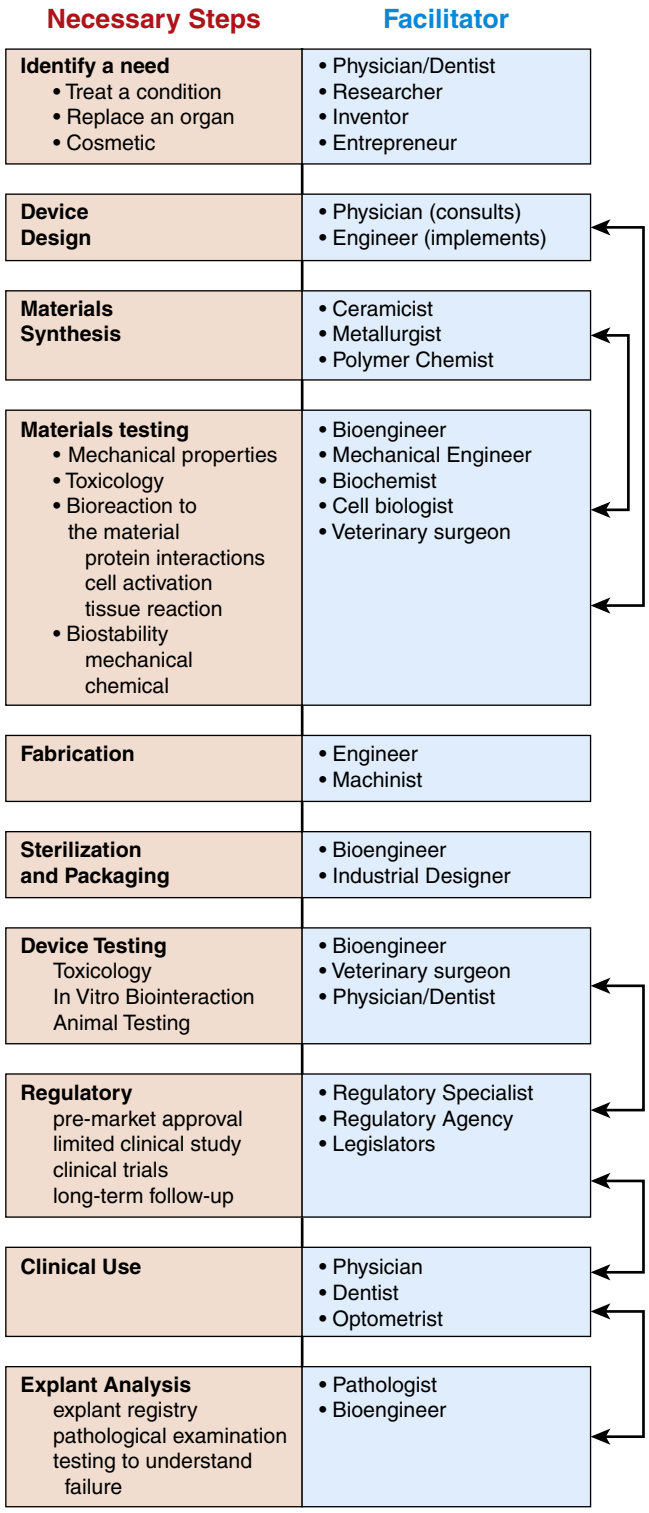
More than any other field of contemporary technology, biomaterials science brings together teams of researchers from diverse academic and industrial backgrounds, who characteristically speak different "languages" yet must clearly communicate and integrate complex concepts and data. Fig. 1.1.1.9 lists some of the disciplines and key steps that are encountered in the progression from identifying the need for a biomaterial or device to its testing, regulation, manufacture, sale, and implantation.

Diverse Materials Are Used

The biomaterials scientist must have an appreciation of materials science, including polymers, metals, ceramics, glasses, composites, and biological materials. This may range from an impressive command of the theory and practice of the field demonstrated by the professional materials scientist to a general understanding of the properties of materials that should be possessed by the physician or biologist investigator involved in biomaterials-related research.

A wide range of materials is routinely used in medical devices (Table 1.1.1.1), and no one researcher will be comfortable synthesizing, processing, characterizing, designing, and fabricating with all these materials. Thus specialization is common and appropriate. However, a broad appreciation of the properties and applications of these materials, the palette from which the biomaterials scientist "creates" medical devices, is a hallmark of professionals in the field.

There is a tendency to group biomaterials and researchers into the "hard tissue replacement" camp, typically represented by those involved in orthopedic and dental materials, and the "soft tissue replacement" camp, frequently associated with cardiovascular implants and general plastic surgery materials.



• **Figure 1.1.1.9** The path from an identified need to a clinical product, and some of the disciplines that facilitate this developmental process.

TABLE 1.1.1.3 Cardiovascular Device Market by Region and With Projected Compound Annual Growth Rate (CAGR) ($ Millions)

Region	2016	2017	2020	CAGR 2017–2022 (%)
North America	9,811	11,329	16,543	7.9
Europe	7,293	8,458	12,084	7.4
Asia	5,610	6,709	11,406	11.2
Rest of World	2,670	3,162	5,218	10.6
Total	25,384	29,658	45,260	8.8

Source: BCC Research.

Hard tissue biomaterials researchers are thought to focus on metals and ceramics, while soft tissue biomaterials researchers are considered polymer experts. In practice, this division is artificial: a heart valve may be fabricated from polymers, metals, and carbons (and processed tissue). A hip joint will also be composed of metals and polymers (and sometimes ceramics), and may be interfaced with the body via a polymeric bone cement. There is a need for a general understanding of all classes of materials and the common conceptual theme of their interaction with the biological milieu. This text provides a background to the important classes of materials, hard and soft, and their interactions with the biological environment.

Biomaterials to Devices to Markets and Medicine

Thomas Edison once said that he would only invent things that people would buy. In an interesting way, this idea is central to biomaterials device development. The process of biomaterials/medical device innovation is driven by clinical need: an informed engineer, patient, or physician defines a need and then initiates an invention. However, someone must test and manufacture the device, and shepherd it though the complex and expensive development process, which includes rigorous regulatory requirements. This "someone" is generally a company, and a company exists (by law) to return value to its shareholders. Fig. 1.1.1.9 illustrates multidisciplinary interactions in biomaterials, and shows the progression in the development of a biomaterial or device. It provides a perspective on how different disciplines work together, starting from the identification of a need for a biomaterial through development, manufacture, implantation, and (possibly) removal from the patient. Note that the development process for medical devices is very different from that for drugs. There are insightful reference works available to help understand this specialized device commercialization process (Yock et al., 2015) and this pathway is the general focus of Part 3 of this text.

Magnitude of the Field

The magnitude of the medical device field expresses both the magnitude of the need and a sizable and growing commercial market (Table 1.1.1.2). Of particular note is how various medical devices are seeing growth occurring in more recently expanding economies. This is exemplified by the cardiovascular device market (Table 1.1.1.3) and reflects economic growth, extending lifespans, and (unfortunately) increased cardiovascular disease burden in these regions.

Consider four commonly used biomaterial devices: a contact lens; a hip joint; a hydrocephalous drainage shunt; and a heart valve. Let us examine these devices in the contexts of human needs and commercial markets. The contact lens offers improved vision and, some will argue, a cosmetic enhancement. The hip joint offers mobility to the patient who would otherwise need a cane or crutch or be confined to a bed or wheelchair. The hydrocephalus shunt will allow an infant to survive without brain damage. The heart valve offers a longer life with improved quality of life. A disposable contact lens may sell for less than $0.50, and the hip joint, hydrocephalus shunt, and heart valve may sell for $1000–$5000 each. Each year there will be hundreds of millions of contact lenses purchased worldwide, 4,500,000 heart valves, 160,000 hydrocephalus shunts, and 1,400,000 total artificial hip prostheses. Here are the issues for consideration: (1) the large number of devices (an expression of both human needs and commercial markets); (2) medical significance (cosmetic to life saving); and (3) commercial potential (who will manufacture it and why, for example, what is the market for the hydrocephalus shunt?). Always, human needs and economic issues color this field we call "biomaterials science." Medical practice, market forces, and bioethics come into play almost every day.

Lysaght and O'Laughlin (2000) estimated the magnitude and economic scope of the contemporary organ replacement enterprise to be much larger than was generally recognized. In the year 2000, the lives of over 20 million patients were sustained, supported, or significantly improved by functional organ replacement. The impacted population grows at over 10% per year. Worldwide, first-year and follow-up costs of organ replacement and prostheses exceed US$300 billion per year and represent between 7% and 8% of total worldwide healthcare spending. In the United States, the costs of therapies enabled by organ replacement technology exceed 2% of the gross national product. The costs are also impressive when reduced to the

needs of the individual patient. For example, the cost of an implanted heart valve is roughly $5000. The surgery to implant the device entails a hospital bill and first-year follow-up costs upward of at least $40,000. Reoperation for replacing a failed valve will have these same costs. Reoperations for failed valves now exceed 10% of all valve operations. Global expenditures on medical devices by category are summarized in Table 1.1.1.2.

Success and Failure

Most biomaterials and medical devices perform satisfactorily, improving the quality of life for the recipient or saving lives. However, no artificial construct is perfect. All manufactured devices have a failure rate. Also, all humans are different, with differing ethnicities, ages, genetics, gender, body chemistries, living environments, and degrees of physical activity. Furthermore, physicians implant or use these devices with varying degrees of skill. The other side to the medical device success story is that there are problems, compromises, complications, and unintended consequences that often occur with medical devices. Central issues for the biomaterials scientist, manufacturer, patient, physician, and attorney are: (1) is the design competent and optimal; (2) who should be responsible when devices perform "with an inappropriate host response"; and (3) what are the risk/benefit or cost/benefit ratios for the implant or therapy?

Some examples may clarify these issues. Clearly, heart valve disease is a serious medical problem. Patients with diseased aortic heart valves have a 50% chance of dying within 3 years. Surgical replacement of the diseased valve leads to an expected survival of 10 years in 70% of the cases. However, of these patients whose longevity and quality of life have clearly been enhanced, approximately 60% will suffer a serious valve-related complication within 10 years after the operation. Another example involves VADs. A clinical trial called Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) led to the following important statistics (Rose et al., 2001). Patients with an implanted Heartmate VAD had a 52% chance of surviving for 1 year, compared with a 25% survival rate for patients who took medication. Survival for 2 years in patients with the Heartmate was 23% versus 8% in the medication group. Also, the VAD enhanced the quality of life for the patients—they felt better, were less depressed, and were mobile. Importantly, patients participating in the REMATCH trial were not eligible for a heart transplant. In the cases of the heart valve and the VAD, clinical complications possibly associated with less than stellar biomaterials performance do not preclude widespread clinical acceptance.

Biomaterials science:
- multidisciplinary;
- multibiomaterial;
- clinical need driven;
- substantial world market; and
- risk/benefit issues.

Thus, these five characteristics of biomaterials science:
- multidisciplinary
- multibiomaterial
- clinical need driven
- substantial world market, and
- risk/benefit issues

color all aspects of the field.

In addition, there are certain unique subjects that are particularly prominent in our field and help delineate the biomaterials endeavor as a unique field of science and engineering. Let us review a few of these.

Subjects Integral to Biomaterials Science

Toxicology

A biomaterial should not be toxic, unless it is specifically engineered for such requirements (e.g., a "smart" drug delivery system that targets cancer cells with a toxic drug). Since the nontoxic requirement is the norm, toxicology for biomaterials has evolved into a sophisticated science. It deals with the substances that migrate out of biomaterials or result from their degradation. For example, for polymers, many low molecular weight "leachables" exhibit some level of physiologic activity and cell toxicity. It is reasonable to say that a biomaterial should not give off anything from its mass unless it is specifically designed to do so. Toxicology also deals with methods to evaluate how well this design criterion is met when a new biomaterial is under development. Chapter 2.2.5 provides an overview of methods in biomaterials toxicology. Implications of toxicity are addressed in Chapters 2.3.2–2.3.4.

Biocompatibility

The understanding and measurement of biocompatibility are unique to biomaterials science. Unfortunately, we do not have precise definitions or accurate measurements of biocompatibility. More often than not, biocompatibility is defined in terms of performance or success at a specific task. Thus for a patient who is doing well with an implanted large diameter Dacron fabric vascular prosthesis, few would argue that this prosthesis is not "biocompatible." However, the prosthesis probably did not recellularize, and may also generate a small amount of surface-bound clot that may embolize, usually with little clinical consequence. This operational definition of biocompatible ("the patient is alive and not experiencing complications, so it must be biocompatible") offers us little insight in designing new or improved vascular prostheses. It is probable that biocompatibility may have to be specifically defined for applications in soft tissue, hard tissue, and the cardiovascular system (blood compatibility, Chapters 2.2.6 and 2.3.5). In fact, biocompatibility may have to be uniquely defined for each application. The problems and meanings of biocompatibility will be explored and expanded upon throughout this textbook; in particular see Chapters 2.3.1 and 2.3.2.

Inflammation and Healing

Specialized biological mechanisms are triggered when a material or device interfaces with the body. Injury to tissue will

stimulate the well-defined inflammatory reaction sequence that ultimately leads to healing. Healing can be normal (physiological) or abnormal (pathological). Where a foreign body (e.g., an implant) is present in the wound site (the surgical incision), the reaction sequence is referred to as the "foreign-body reaction" (Chapters 2.2.2 and 2.3.4). The normal response of the body will be modulated because of the solid implant. Furthermore, this reaction will differ in intensity and duration, depending upon the anatomical site involved. An understanding of how a foreign object shifts the normal inflammatory reaction sequence is an important concern for the biomaterials scientist, and how some classes of materials may avoid this reaction is an area of growing interest, as already noted.

Functional Tissue Structure and Pathobiology

Biomaterials-based medical devices are implanted into almost all tissues and organs. Tissues and organs vary widely in cell composition, morphological organization, vascularization, and innervation. Implantation of a biomaterial into bone, liver, or heart will have special physiological consequences. Therefore key principles governing the structure of normal (and abnormal) cells, tissues, and organs are important to biomaterials researchers. Also, techniques by which the structure and function of normal and abnormal tissue are studied must be mastered. In addition, fundamental mechanisms leading to abnormal cell, tissue, and organ structures (i.e., diseases and other pathologies) are critical considerations to biomaterials researchers (see Chapters 2.1.4 and 2.1.5).

Dependence on Specific Anatomical Sites of Implantation

Consideration of the anatomical site of an implant is essential. An intraocular lens may be implanted into the lens capsule or the anterior chamber of the eye. A hip joint will be implanted in bone across an articulating joint space. A prosthetic heart valve will be sutured into cardiac muscle and will contact both soft tissue and blood. A catheter may be placed in an artery, a vein, or the urinary tract. Each of these sites challenges the biomedical device designer with special requirements for anatomy, physiology, geometry, size, mechanical properties, and bioresponses.

Mechanical Requirements and Physical Performance Requirements

Each biomaterial and device has mechanical and performance requirements originating from the need to perform a physiological function. These requirements can be divided into three categories: mechanical performance, mechanical durability, and physical properties.

First, consider mechanical performance. A hip prosthesis must be strong and rigid. A tendon material must be strong and flexible. A tissue heart valve leaflet must be flexible and tough. A dialysis membrane must be strong and flexible, but not elastomeric. An articular cartilage substitute must be soft and elastomeric. One significant example of a controlled micromechanical interface is the contact zone between a synthetic biomaterial (titanium, tantalum, alumina, zirconia, and hydroxyapatites) and oral bones. Microstrain magnitudes have been controlled through macro/micro/nanosurface topographies and construct designs to be within the microstrain limits of bone. The result has been decades of chemical stability, now called osseous integration.

Then, we must address mechanical durability. A catheter may only have to perform for 3 days. A bone plate may fulfill its function in 6 months or longer. A leaflet in a heart valve must flex 60 times per minute without tearing for the lifetime of the patient (realistically, at least for 10 or more years). A hip joint must not fail under heavy loads for 20 years or more.

Finally, the bulk physical properties impact other aspects of performance as they meet the physical and/or mechanical demands of the medical devices for which they are designed. In addition to mechanical durability, the dialysis membrane has a specified permeability, the acetabular cup of the hip joint must have high lubricity, and the intraocular lens has transparency and refraction requirements. To meet these requirements, design principles are borrowed from physics, chemistry, mechanical engineering, chemical engineering, and materials science.

Industrial Involvement

A significant basic research effort is now under way, primarily at universities, to understand how biomaterials function and how to optimize them. At the same time, companies are producing implants for use in humans and, appropriate to the mission of a company, earning profits on the sale of medical devices. Thus although we are now only learning about the fundamentals of biointeraction, we manufacture millions of devices for implantation in humans. How is this dichotomy explained? Basically, as a result of 50 or more years of experience we now have a set of materials that perform satisfactorily in the body. The medical practitioner can use them with reasonable confidence, and the performance in the patient is largely acceptable (generally considerably better than other alternatives). Though the devices and materials are far from perfect, the complications associated with the devices are fewer or of less impact than the complications of the original diseases.

Risk/Benefit and Corporate Realities

A risk/benefit analysis must be considered in developing new devices and improving existing devices. Central to biomaterials science is the desire to alleviate suffering and death, and also the desire to improve the quality of life for patients. These considerations are convoluted with the excitement of new scientific ideas, the corporate imperative to turn a profit, and the mandate of the regulatory agencies to protect the public. Indeed, although failure of biomaterials and medical devices is common, benefit to risk ratio in individual cases is often high, and despite a device complication, a patient may have had a markedly improved outcome (enhanced survival and/or quality of life) over the natural history of the disease.

The acceptable risk varies with different types of medical devices. Moreover, the acceptable risk of devices that sustain life (e.g., heart valve, defibrillator, cardiac assist device, hemodialysis device/access graft, hydrocephalus shunt) is greater than that of devices that alleviate pain/disability or enhance function (e.g., hip joint, drug delivery device, intraocular lens, intrauterine contraceptive device). Then consider the

acceptable risk for devices that have only cosmetic application (e.g., collagen injections, breast implants). Obviously, ethical concerns enter into the risk/benefit picture. Remember that companies have large investments in the development, manufacture, quality control, clinical testing, regulatory clearance, and distribution of medical devices. How much of an advantage (for the company and the patient) will be realized in introducing an improved device? The improved device may indeed work better for the patient. However, the company will incur a large expense (development and regulatory costs) that will be perceived by the stockholders as reduced profits. The development of a new or improved device, as well as offering benefits, entails risks that months or years after introduction some unforeseen complication will compromise the device. Product liability issues are a major concern to manufacturers. Consider questions about the ethics of withholding improved devices from people who could benefit from them because of development costs and regulatory hurdles, the market share advantages of having a better product, and the gargantuan costs (possibly nonrecoverable) of introducing a new product into the medical marketplace. If companies did not have the profit incentive, would there be any medical devices, let alone improved ones, available for clinical application?

From the biomaterials industry we see specialized, essential contributions to our field. Industry deals well with technologies such as packaging, sterilization, storage, distribution, quality control, and analysis. These subjects are grounded in specialized technologies, often ignored in academic communities, but having the potential to generate stimulating research questions. Also, many companies support in-house basic research laboratories, and contribute in important ways to the fundamental study of biomaterials science.

Ethics

A wide range of ethical considerations impact biomaterials science. Some key ethical questions in biomaterials science are summarized in Table 1.1.1.4. Typical of ethical questions, an absolute answer may be difficult to come by. Some articles have addressed ethical questions in biomaterials and debated the important points (Saha and Saha, 1987; Schiedermayer and Shapiro, 1989; Merryman, 2008). Chapter 3.1.11 introduces moral and ethical issues related to biomaterials and medical devices.

Regulation

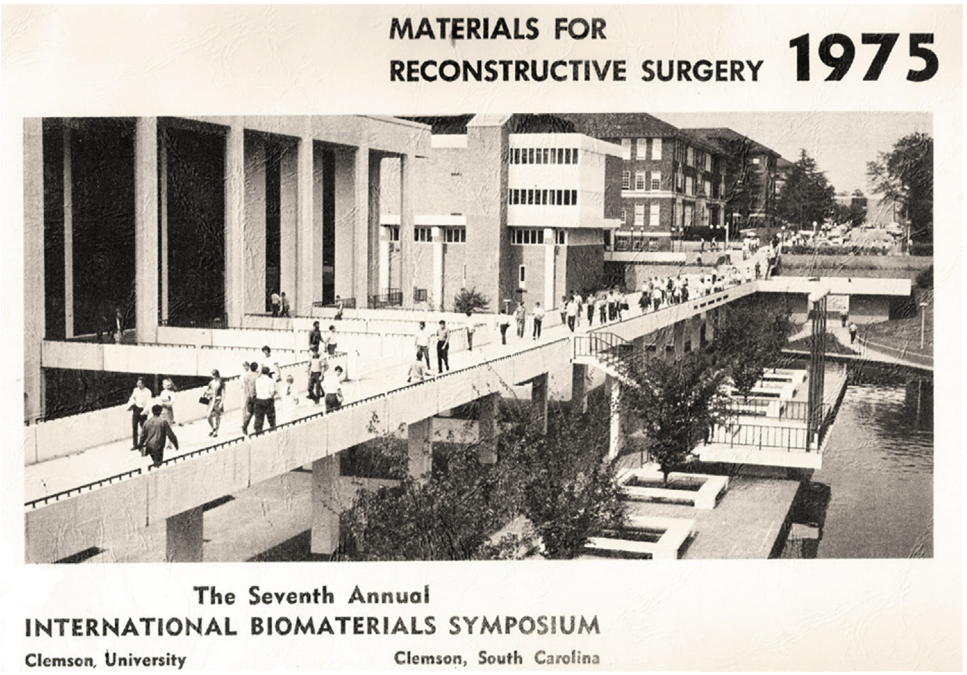
The consumer (the patient) and the physician demand safe medical devices. To prevent inadequately tested devices and materials from coming on the market, and to screen out those clearly unqualified to produce biomaterials, the US government has evolved a complex regulatory system administered by the US Food and Drug Administration. In the United States, medical device regulatory requirements were introduced less than 50 years ago (with the 1976 Medical Device Amendments legislation). Most nations of the world have similar medical device regulatory bodies. The International Standards Organization has introduced international standards for the world community. Obviously, a substantial base of biomaterials knowledge went into establishing these standards. The costs to comply with the standards and to implement materials, biological, and clinical testing are enormous. Introducing a new biomedical device to the market requires a regulatory investment of tens of millions of dollars. Are the regulations and standards truly addressing the safety issues? Is the cost of regulation inflating the cost of healthcare and preventing improved devices from reaching those who need them? Under this regulation topic, we see the intersection of all the players in the biomaterials community: government, industry, scientists, physicians, and patients. The answers are not simple, but the problems must be addressed every day. Part 3 of this text contains several chapters that expand on standards and regulatory concerns to provide a whole-spectrum view, including issues related to device life cycle, safety and risk, sterilization and disinfection, verification and validation, commercialization, and legal concepts.

TABLE 1.1.1.4 Ethical Concerns Relevant to Biomaterials Science

Animals	Is the animal model relevant to human physiology? Specifically, is the experiment well designed and the outcome sufficiently important so that the data obtained will justify the suffering and sacrifice of the life of a living creature?
Human Subjects	How should human subject research be conducted to minimize negative outcomes to the patient and offer a reasonable risk/benefit ratio? How can we best ensure informed consent?
Industrial Involvement	Companies fund much biomaterials research and also own proprietary biomaterials. How can the needs of the patient be best balanced with the financial goals of a company? Consider that someone must manufacture devices—these would not be available if a company did not choose to manufacture them.
Researchers	Since researchers often stand to benefit financially from a successful biomedical device, and sometimes even have devices named after them, how can investigator bias be minimized in biomaterials research?
Patients	For life-sustaining devices, what is the trade-off between sustaining life and the quality of life with the device for the patient? Should the patient be permitted to "pull the plug" if the quality of life is not satisfactory?
Regulatory Agencies	With so many unanswered questions about the basic science of biomaterials, do government regulatory agencies have sufficient information to define adequate tests for materials and devices and to properly regulate biomaterials?

Biomaterials Literature

Over the past 70 years, the field of biomaterials has evolved from individual physicians innovating to save the lives of their patients to the science-grounded multidisciplinary endeavor we see today. In 1950, there were no biomaterials or medical device journals, and few books. Concurrent with the evolution



• **Figure 1.1.1.10** The cover of the program book for the 1975 International Biomaterials Symposium, Clemson, South Carolina.

of the discipline, a literature has also developed addressing basic science, applied science, engineering, medicine, and commercial issues. A bibliography is provided in Appendix D to highlight some of the key reference works and technical journals in the biomaterials field. As might be expected, these journals stem from many disciplines and technical societies.

Biomaterials Societies

The biomaterials field evolved from individual researchers and clinicians who intellectually associated their efforts with established disciplines such as medicine, chemistry, chemical engineering, materials science, or mechanical engineering, to a modern field called "biomaterials." This evolution was paralleled by a growing sense of professionalism and the formation of biomaterials societies as homes for the profession to develop in. Probably the first biomaterials-related society was the American Society for Artificial Internal Organs. Founded in 1954, this group of visionaries established a platform to consider the development of devices such as the artificial kidney and the artificial heart. A Division of Interdisciplinary Studies, the administrative home of a nascent biomaterials effort, was established at Clemson University, Clemson, South Carolina, in 1969. Clemson began organizing annual International Biomaterials Symposia (IBS) in 1969. The first of these symposia was titled "Use of Ceramics in Surgical Implants." About 100 scientists and physicians attended, and 17 papers were presented. Between 1969 and 1975, seven IBS were held at Clemson. The cover of the 1975 International Biomaterials Symposium program is shown in Fig. 1.1.1.10.

The Society for Biomaterials (SFB) was chartered in San Antonio, Texas, in 1974 with 205 charter members from across the United States and nine other countries—a truly international society. One unique feature of the SFB founding members was that they included clinicians, engineers, chemists, and biologists. Their common interest, biomaterials, was the engaging focus for the multidisciplinary participants. Because of the founding of the SFB in 1974, the seventh IBS in 1975 was also known as the world's inaugural meeting of the SFB. Table 1.1.1.5 lists the timeline of events leading to the start of the SFB annual meetings and the quadrennial World Biomaterials Congress (WBC), as well as the establishment of Clemson Awards and the honorary status of "Fellow, Biomaterials Science and Engineering." The Canadian Biomaterials Society/Société Canadienne des Biomatériaux was established in 1973, a year earlier than the SFB. The European Society for Biomaterials was founded in 1975, and the Japanese Society for Biomaterials was formed in 1978. To promote international communication and cooperation, these four societies decided to establish an International Liaison Committee of Societies for Biomaterials (ILC) in 1980 to organize a WBC every 4 years and the first WBC was held in Baden, Vienna, Austria, that year. Six more international societies for biomaterials were established afterward: the Society for Biomaterials & Artificial Organs (India) in 1986, the Australasian Society for Biomaterials and Tissue Engineering in 1989, the Korean Society for Biomaterials in 1996, the Chinese Taipei Society for Biomaterials and Controlled Release in 1997, the Latin American Society for Biomaterials and Artificial Organs in 1998, and the Chinese Society for Biomaterials in 2011. In 1997, the constituent societies renamed the ILC to the International Union of Societies for Biomaterials Science and Engineering. Aside from these societies, there are other groups. For example, the Controlled Release Society is a group strongly rooted in biomaterials for drug delivery, and the Tissue Engineering and Regenerative Medicine International Society is also very active in biomaterials-related research.

TABLE 1.1.1.5 Timeline for Development of the Society for Biomaterials and Other International Biomaterials Organizations

1969	1st **IBS** Clemson, SC
1970	2nd **IBS** Clemson, SC
1971	3rd **IBS** Clemson, SC
1972	4th **IBS** Clemson, SC
1973	5th **IBS** Clemson, SC **Clemson Awards** **Canadian Society**
1974	6th **SFB** Clemson, SC **Society For Biomaterials**
1975	7th **IBS** / 1st **SFB Meeting** Clemson, SC **European Society**
1978	**Japanese Society**
1980	1st **WBC Meeting** Baden, Vienna, Austria **ILC**
1986	**India Society**
1989	**Australasian Society**
1992	4th **WBC Meeting** Berlin, Germany **FBSE**
1996	**Korean Society**
1997	**Chinese Taipei Society** **ILC → IUSBSE**
1998	**Latin American Society**
2011	**Chinese Society**
2020	11th **WBC Meeting** Glasgow, UK

FBSE, Fellow, Biomaterials Science and Engineering; *IBS*, International Biomaterials Symposia; *ILC*, International Liaison Committee of Societies for Biomaterials; *IUSBSE*, International Union of Societies for Biomaterials Science and Engineering; *SC*, South Carolina; *SFB*, Society for Biomaterials; *WBC*, World Biomaterials Congress.

The development of biomaterials professionalism and a sense of identity for the biomaterials field can be attributed to these societies and the researchers who organized and led them.

Summary

This chapter provides a broad overview of the biomaterials field. It offers a vantage point from which the reader can gain a perspective to see how the subthemes fit into the larger whole.

Biomaterials science may be the most multidisciplinary of all the sciences. Consequently, biomaterials scientists must master certain key material from many fields of science, technology, engineering, and medicine to be competent and conversant in this profession. The reward for mastering this volume of material is immersion in an intellectually stimulating endeavor that advances a new basic science of biointeraction and contributes to reducing human suffering.

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