INTRODUCTION

Biomaterials Science: A Multidisciplinary Endeavor

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BIOMATERIALS AND BIOMATERIALS SCIENCE

Biomaterials Science: An Introduction to Materials in Medicine addresses the properties and applications of materials (synthetic and natural) that are used in contact with biological systems. These materials are commonly called biomaterials. Biomaterials, an exciting field with steady, strong growth over its approximately half century of existence, encompasses aspects of medicine, biology, chemistry, and materials science. It sits on a foundation of engineering principles. There is also a compelling human side to the therapeutic and diagnostic application of biomaterials. This textbook aims to (1) introduce these diverse elements, particularly focusing on their interrelationships rather than differences and (2) systematize the subject into a cohesive curriculum.

We title this textbook *Biomaterials Science: An Introduction to Materials in Medicine* to reflect, first, that the book highlights the scientific and engineering fundamentals behind biomaterials and their applications, and second, that this volume contains sufficient background material to guide the reader to a fair appreciation of the field of biomaterials. Furthermore, every chapter in this textbook can serve as a portal to an extensive contemporary literature. The magnitude of the biomaterials endeavor, its interdisciplinary scope, and examples of biomaterials applications will be revealed in this introductory chapter and throughout the book.

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 equipment for processing biomolecules for biotechnological applications, for implants to regulate fertility in cattle, in diagnostic gene arrays, in the aquaculture of oysters, and for investigational cell-silicon "biochips." How do we reconcile these diverse uses of materials into one field? The common thread is the interaction between biological systems and synthetic or modified natural materials.

In medical applications, biomaterials are rarely used as isolated materials but are more commonly integrated into devices or implants. Although this is a text on materials, 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 effect of the materials/device on the recipient and that of the host tissues on the device can lead to device failure. 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 than 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. It also must employ mechanical and electronic systems to pump blood and control flow rates.

Because of space limitations and the materials focus of this work, many aspects of device design are not addressed in this book. Consider the example of the hemodialysis system. The focus here is on membrane materials and their biocompatibility; there is little coverage of mass transport through membranes, the burst strength of membranes, flow systems, and monitoring electronics. Other books and articles cover these topics in detail.

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).

If the word "medical" is removed, this definition becomes broader and can encompass the wide range of applications suggested above.

If the word "nonviable" is removed, the definition becomes even more general and can address many new

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tissue-engineering and hybrid artificial organ applications where living cells are used.

"Biomaterials science" is the physical and biological study of materials and their interaction with the biological environment. Traditionally, the most intense development and investigation have been directed toward biomaterials synthesis, optimization, characterization, testing, and the biology of host–material interactions. Most biomaterials introduce a non–specific, stereotyped biological reaction. Considerable current effort is directed toward the development of engineered surfaces that could elicit rapid and highly precise reactions with cells and proteins, tailored to a specific application.

Indeed, a complementary definition essential for understanding the goal (i.e., specific end applications) of biomaterials science is that of "biocompatibility."

> Biocompatibility is the ability of a material to perform with an appropriate host response in a specific application (Williams, 1987).

Examples of "appropriate host responses" include the 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 3 hours, the catheter may be inserted for a week, and the hip joint may be in place for the life of the patient.

This general concept of biocompatilility has been extended recently in the broad approach called "tissue engineering" in which *in-vitro* and *in-vivo* pathophysiological processes are harnessed by careful selection of cells, materials, and metabolic and biomechanical conditions to regenerate functional tissues.

Thus, in these definitions and discussion, we are introduced to considerations that set biomaterials apart from most materials explored in materials science. Table 1 lists a few applications for synthetic materials in the body. It includes many materials that are often classified as "biomaterials." Note that metals, ceramics, polymers, glasses, carbons, and composite materials are listed. Such materials are used as molded or machined parts, coatings, fibers, films, foams and fabrics. Table 2 presents estimates of the numbers of medical devices containing biomaterials that are implanted in humans each year and the size of the commercial market for biomaterials and medical devices.

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

TABLE 1 Some Applications of Synthetic Materials and Modified Natural Materials in Medicine

Application	Types of materials
Skeletal system	
Joint replacements (hip, knee)	Titanium, Ti–Al–V alloy, stainless steel, polyethylene
Bone plate for fracture fixation	Stainless steel, cobalt–chromium alloy
Bone cement	Poly(methyl methacrylate)
Bony defect repair	Hydroxylapatite
Artificial tendon and ligament	Teflon, Dacron
Dental implant for tooth fixation	Titanium, Ti–Al–V alloy, stainless steel, polyethylene Titanium, alumina, calcium phosphate
Cardiovascular system	
Blood vessel prosthesis	Dacron, Teflon, polyurethane
Heart valve	Reprocessed tissue, stainless steel, carbon
Catheter	Silicone rubber, Teflon, polyurethane
Organs	
Artificial heart	Polyurethane
Skin repair template	Silicone–collagen composite
Artificial kidney (hemodialyzer)	Cellulose, polyacrylonitrile
Heart–lung machine	Silicone rubber
Senses	
Cochlear replacement	Platinum electrodes
Intraocular lens	Poly(methyl methacrylate), silicone rubber, hydrogel
Contact lens	Silicone-acrylate, hydrogel
Corneal bandage	Collagen, hydrogel

EXAMPLES OF BIOMATERIALS APPLICATIONS

Heart Valve Prostheses

Diseases of the heart valves often make surgical repair or replacement necessary. Heart valves open and close over 40 million times a year and they can accumulate damage sufficient to require replacement in many individuals. More than 80,000 replacement valves are implanted each year in the United States 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. Figure 1 shows a bileaflet tilting-disk mechanical heart valve, one of the most widely used designs. Other types of heart valves are made of chemically treated pig valve or cow pericardial tissue. Generally, almost 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 that may differ with different types of valves; they include induction of blood clots, degeneration of tissue, mechanical failure, and infection. Heart valve substitutes are discussed in Chapter 7.3.

Artificial Hip Joints

The human hip joint is subjected to high levels of mechanical stress and receives considerable abuse in the course of

TABLE 2 The Biomaterials and Healthcare Market—Facts and Figures (per year) (U.S. numbers—Global numbers are typically 2–3 times the U.S. number)

Total U.S. health care expenditures (2000)	$1,400,000,000,000
Total U.S. health research and development (2001)	$82,000,000,000
Number of employees in the medical device industry (2003)	300,000
Registered U.S. medical device manufacturers (2003)	13,000
Total U.S. medical device market (2002)	$77,000,000,000
U.S. market for disposable medical supplies (2003)	$48,600,000,000
U.S. market for biomaterials (2000)	$9,000,000,000
Individual medical device sales:	
Diabetes management products (1999)	$4,000,000,000
Cardiovascular Devices (2002)	$6,000,000,000
Orthopedic-Musculoskeletal Surgery U.S. market (1998)	$4,700,000,000
Wound care U.S. market (1998)	$3,700,000,000
In Vitro diagnostics (1998)	$10,000,000,000
Numbers of devices (U.S.):	
Intraocular lenses (2003)	2,500,000
Contact lenses (2000)	30,000,000
Vascular grafts	300,000
Heart valves	100,000
Pacemakers	400,000
Blood bags	40,000,000
Breast prostheses	250,000
Catheters	200,000,000
Heart-Lung (Oxygenators)	300,000
Coronary stents	1,500,000
Renal dialysis (number of patients, 2001)	320,000
Hip prostheses (2002)	250,000
Knee prostheses (2002)	250,000
Dental implants (2000)	910,000

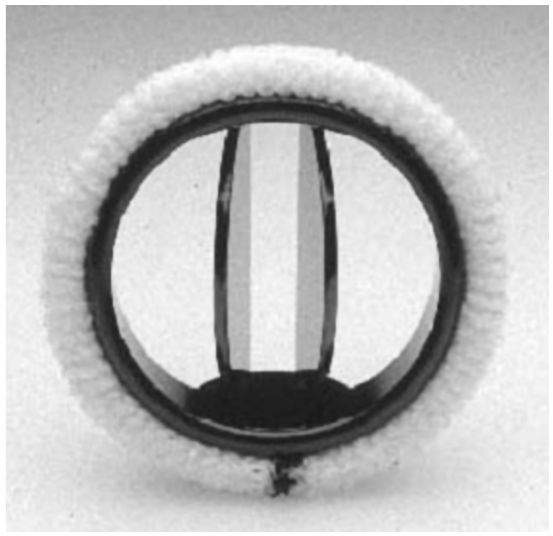

FIG. 1. A replacement heart valve.

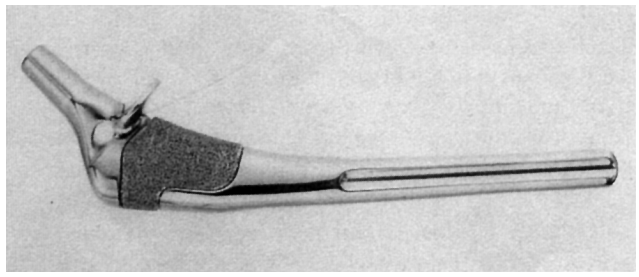

FIG. 2. A metalic hip joint. (Photograph courtesy of Zimmer, Inc.)

normal activity. It is not surprising that after 50 or more years of cyclic mechanical stress, or because of degenerative or rheumatological disease, the natural joint wears out, leading to considerable loss of mobility and often confinement to a wheelchair. Hip-joint prostheses are fabricated from titanium, stainless steel, special high-strength alloys, ceramics, composites, and ultrahigh-molecular-weight polyethylene. Replacement hip joints (Fig. 2) are implanted in more than 200,000 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 they are generally not advised. After 10–15 years, the implant may loosen, necessitating another operation. Artificial hip joints are discussed in Chapter 7.7.

Dental Implants

The widespread introduction of titanium implants (Fig. 3) has revolutionized dental implantology. These devices form an implanted artificial tooth anchor upon which a crown is affixed and are implanted in approximately 300,000 people each year, with some individuals receiving more than 12 implants. 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). 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 7.8.

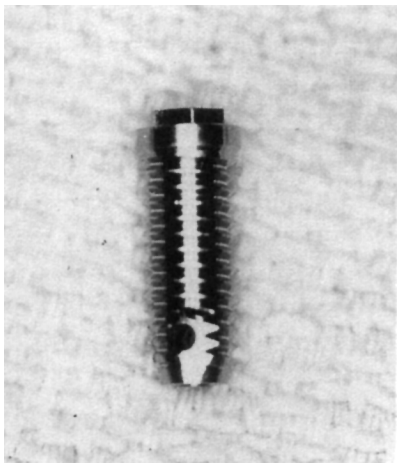

FIG. 3. A titanium dental implant. (Photograph courtesy of Dr. A. Norman Cranin, Brookdale Hospital Medical Center, Brooklyn, NY.)

Intraocular Lenses

A variety of intraocular lenses (IOLs) have been fabricated of poly(methyl methacrylate), silicone elastomer, soft acrylic polymers, or hydrogels and are used to replace a natural lens when it becomes cloudy due to cataract formation (Fig. 4). By the age of 75, more than 50% of the population suffers from cataracts severe enough to warrant IOL implantation. This translates to almost 4 million implantations in the United States alone each year, and double that number worldwide. 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 often performed on an outpatient basis. Recent observations of implanted lenses using a microscope to directly observe the implanted lens through the cornea show that inflammatory cells 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 from the posterior lens capsule stimulated by the IOL can cloud the vision, and this is a significant complication. IOLs are discussed in Chapter 7.11.

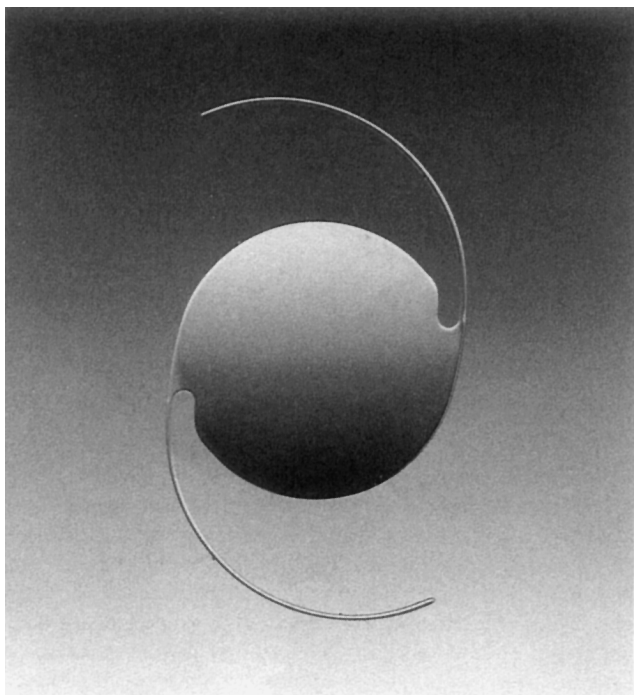

FIG. 4. An intraocular lens. (Photograph courtesy of Alcon Laboratories, Inc.)

Left Ventricular Assist Device

With a large population of individuals with seriously failing hearts (estimated at as many as 50,000 per year) who need cardiac assist or replacement and an available pool of donor hearts for transplantation of approximately 3000 per year, effective and safe mechanical cardiac assist or replacement has been an attractive goal. Left ventricular assist devices (LVADs), that can be considered as one half of a total artificial heart, have evolved from a daring experimental concept to a life-prolonging tool. They are now used to maintain a patient with a failing heart while the patient awaits the availability of a transplant heart and some patients receive these LVADs as a permanent ("destination") therapy. An LVAD in an active adult is illustrated in Fig. 5. He is not confined to the hospital bed, although this pump system is totally supporting his circulatory needs. Patients have lived on LVAD support for more than 4 years. However, a patient with an LVAD is always at risk for infection and serious blood clots initiated within the device. These could break off (embolize) and possibly obstruct blood flow to a vital organ. LVADs are elaborated upon in Chapter 7.4.

These five cases, only a small fraction of the many important medical devices that could have been described here, spotlight a number of themes. Widespread application with good success is generally noted. A broad range of synthetic materials varying in chemical, physical, and mechanical properties are used in the body. Many anatomical sites are involved. The mechanisms by which the body responds to foreign bodies and heals wounds are observed in each case. Problems, concerns, or unexplained observations are noted for each device. Companies are manufacturing each of the devices and making a profit. Regulatory agencies are carefully looking at device performance and making policy intended to control the industry and protect the patient. Are there ethical or social issues that should be addressed? To set the stage for the formal introduction of biomaterials science, we will return to the five examples just discussed to examine the issues implicit to each case.

CHARACTERISTICS OF BIOMATERIALS SCIENCE

Now that we've defined some terms and reviewed a few specific examples, we can discern characteristics central to the

FIG. 5. A left ventricular assist device worn by a patient. (Photograph courtesy of Novacor.)

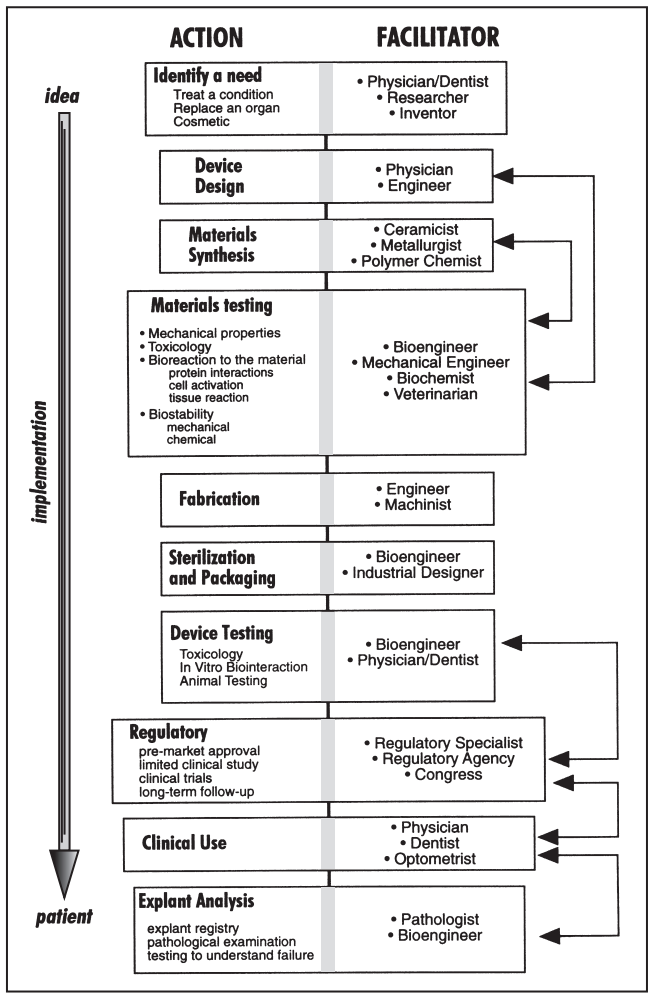

FIG. 6. Disciplines involved in biomaterials science and the path from a need to a manufactured medical device.

field of biomaterials. Here are a few considerations that are so central that it is hard to imagine biomaterials without them.

Multidisciplinary

More than any other field of contemporary technology, biomaterials science brings together researchers from diverse backgrounds who must communicate clearly. Figure 6 lists some of the disciplines that are encountered in the progression from identifying the need for a biomaterial or device to its manufacture, sale, and implantation.

Many Diverse Materials

The biomaterials scientist will have an appreciation of materials science. 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 might be demonstrated by the physician or biologist investigator involved in biomaterials-related research.

A wide range of materials is routinely used (Table 1), and no one researcher will be comfortable synthesizing, characterizing, and designing 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, 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. 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. A hip joint will be composed of metals and polymers (and sometimes ceramics) and will be interfaced to 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 book provides a background to the important classes of materials, hard and soft.

Development of Biomaterials Devices

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 biomaterial/medical device innovation is driven by clinical need: a patient or a physician defines a need and then initiates an invention. Figure 6 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 removal from the patient.

Magnitude of the Field

The magnitude of the medical device field expresses both a magnitude of need and a sizeable commercial market (Table 2). A conflict of interest can arise with pressures from both the commercial quarter and from patient needs. Consider four commonly used biomaterial devices: a contact lens, a hip joint, a hydrocephalus drainage shunt, and a heart valve. All fill medical needs. 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. The contact lens may sell for $100, and the hip joint, hydrocephalus shunt, and heart valve may sell for $1000–4000 each. Each year there will be 75 million contact lenses purchased worldwide, 275,000 heart valves, 5000 hydrocephalus shunts, and 500,000 total artificial hip and knee prostheses. Here are the issues for consideration: (1) the 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 most every day.

Lysaght and O'Laughlin (2000) have estimated that the magnitude and economic scope of the contemporary organ replacement enterprise are much larger than is generally recognized. In the year 2000, the lives of more than 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 exceeds $300 billion U.S. dollars per year and represents between 7% and 8% of total worldwide health-care spending. In the United States, the costs of therapies enabled by organ-replacement technology exceed 1% of the gross national product. The costs are also impressive when reduced to the needs of the individual patient. For example, the cost of a substitute heart valve is roughly $4000. The surgery to implant the device entails a hospital bill and first-year follow-up costs of approximately $60,000. Reoperation for replacing a failed valve will have these same costs. Reoperations for failed valves now exceed 10% of all valve replacements.

Success and Failure

Most biomaterials and medical devices perform satisfactorily, improving the quality of life for the recipient or saving lives. However, no manmade construct is perfect. All manufactured devices have a failure rate. Also, all humans are different with differing genetics, gender, body chemistries, living environment, 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, and complications that occur with medical devices. Central issues for the biomaterials scientist, manufacturer, patient, physician, and attorney are, (1) what represents good design, (2) who should be responsible when devices perform "with an *in*appropriate host response," and (3) what are the cost/risk 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 LVADs. 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 LVAD (Thoratec Laboratories) 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 LVAD 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 LVAD, long-term clinical complications associated with imperfect performance of biomaterials do not preclude clinical success overall.

These five characteristics of biomaterials science: multidisciplinary, multimaterial, need-driven, substantial market, and risk–benefit, flavor all aspects the field. In addition, there are certain subjects that are particularly prominent in our field and help delineate biomaterials science as a unique endeavor. 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 a requirement (e.g., a "smart" drug delivery system that targets cancer cells and destroys them). 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. 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 5.2 provides an overview of methods in biomaterials toxicology. Implications of toxicity are addressed in Chapters 4.2, 4.3 and 4.5.

Biocompatibility

The understanding and measurement of biocompatibility is 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 Dacron fabric vascular prosthesis, few would argue that this prosthesis is not "biocompatible." However, the prosthesis probably did not recellularize (though it was designed to do so) and also is embolic, though the emboli in this case usually have little clinical consequence. This operational definition of biocompatible ("the patient is alive 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). 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 4 and 5.

Functional Tissue Structure and Pathobiology

Biomaterials incorporated into medical devices are implanted into tissues and organs. Therefore, the key principles governing the structure of normal and abnormal cells, tissues, and organs, the techniques by which the structure and function of normal and abnormal tissue are studied, and the fundamental mechanisms of disease processes are critical considerations to workers in the field.

Healing

Special processes are invoked when a material or device heals in the body. Injury to tissue will stimulate the well-defined inflammatory reaction sequence that leads to healing. Where a foreign body (e.g., an implant) is present in the wound site (surgical incision), the reaction sequence is referred to as the "foreign-body reaction" (Chapter 4.2). 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 alters the normal inflammatory reaction sequence is an important concern for the biomaterials scientist.

Dependence on Specific Anatomical Sites of Implantation

Consideration of the anatomical site of an implant is essential. An intraocular lens may go 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 substitute 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 geometry, size, mechanical properties, and bioresponses. Chapter 3.4 introduces these ideas about special requirements to consider for specific anatomical sites.

Mechanical and Performance Requirements

Each biomaterial and device has mechanical and performance requirements that originate from the need to perform a physiological function consistent with the physical (bulk) properties of the material. 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. 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 more than 10 years. The bulk physical properties will also address other aspects of performance. The dialysis membrane has a specified permeability, the articular cup of the hip joint must have high lubricity, and the intraocular lens has clarity 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 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 and implant millions of devices in humans. How is this dichotomy explained? Basically, as a result of considerable experience we now have a set of materials that

performs satisfactorily in the body. The medical practitioner can use them with reasonable confidence, and the performance in the patient is largely acceptable. Though the devices and materials are far from perfect, the complications associated with the devices are less than the complications of the original diseases.

The complex balance between the desire to alleviate suffering and death, the excitement of new scientific ideas, the corporate imperative to turn a profit, the risk/benefit relationship, and the mandate of the regulatory agencies to protect the public forces us to consider the needs of many constituencies. Obviously, ethical concerns enter into the picture. Also, 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 that will be perceived by the stockholders as reduced profits. Moreover, product liability issues are a major concern of manufacturers. The industrial side of the biomaterials field raises questions about the ethics of withholding improved devices from people who need them, 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?

When the industrial segment of the biomaterials field is examined, we see other essential contributions to our field. Industry deals well with technologies such as packaging, sterilization, storage, distribution, and quality control and analysis. These subjects are grounded in specialized technologies, often ignored in academic communities, but have 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 3. Like most 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). Chapter 10.4 introduces ethics in biomaterials.

Regulation

The consumer (the patient) demands safe medical devices. To prevent inadequately tested devices and materials from coming on the market, and to screen out individuals clearly unqualified to produce biomaterials, the United States

TABLE 3 Ethical Concerns Relevant to Biomaterials Science

Is the use of animals justified? Specifically, is the experiment well designed and important so that the data obtained will justify the suffering and sacrifice of the life of a living creature?
How should research using humans be conducted to minimize risk to the patient and offer a reasonable risk-to-benefit ratio? How can we best ensure informed consent?
Companies fund much biomaterials research and 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.
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?
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?
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?
Should the government or other "third-party payors" of medical costs pay for the health care of patients receiving devices that have not yet been formally approved for general use by the FDA and other regulatory bodies?
Should the CEO of a successful multimillion dollar company that is the sole manufacturer a polymer material (that is a minor but crucial component of the sewing ring of nearly all heart valves) yield to the stockholders' demands that he/she terminate the sale of this material because of litigation concerning one model of heart valve with a large cohort of failures? The company sells 32 pounds of this material annually, yielding revenue of approximately $40,000?
Should an orthopedic appliance company manufacture two models of hip joint prostheses: one with an expected "lifetime" of 20 years (for young, active recipients) and another that costs one-fourth as much with an expected lifetime of 7 years (for elderly individuals), with the goal of saving resources so that more individuals can receive the appropriate care?

government has evolved a complex regulatory system administered by the U.S. Food and Drug Administration (FDA). Most nations of the world have similar medical device regulatory bodies. The International Standards Organization (ISO) 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 health care 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, ethics, and basic science. The answers are not simple, but the problems must be addressed every day. Chapters 10.2 and 10.3 expand on standards and regulatory concerns.

BIOMATERIALS LITERATURE

Over the past 50 years, the field of biomaterials has evolved from individual medical researchers innovating to save the lives of their patients into the sophisticated, regulatory/ethics-driven multidisciplinary endeavor we see today. Concurrent with the evolution of the discipline, a literature has also developed addressing basic science, applied science, engineering, and commercial issues. A bibliography is provided in Appendix D "The Biomaterials Literature" to highlight key reference works and technical journals in the biomaterials field.

BIOMATERIALS SOCIETIES

The evolution of the biomaterials field, from its roots with individual researchers and clinicians who intellectually associated their efforts with established disciplines such as medicine, chemistry, chemical engineering, or mechanical engineering, to a modern field called "biomaterials," parallels the formation of biomaterials societies. Probably the first biomaterials-related society was the American Society for Artificial Internal Organs (ASAIO). 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 Department of Bioengineering was established at Clemson University, Clemson, South Carolina, in 1963. In 1969, Clemson began organizing annual International Biomaterials Symposia. In 1974–1975, these symposia evolved into the Society For Biomaterials, the world's first biomaterials society. Founding members, those who joined in 1975 and 1976, numbered about 50 and included clinicians, engineers, chemists, and biologists. Their common interest, biomaterials, was the engaging focus for the multidisciplinary participants. The European Society for Biomaterials was founded in 1975. Shortly after that, the Canadian Society For Biomaterials and the Japanese Society of Biomaterials were formed. The Controlled Release Society, a group strongly rooted in biomaterials for drug delivery, was founded in 1978. At this time there are many national biomaterials societies and related societies. The development of biomaterials professionalism and a sense of identity for the field called biomaterials 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 provides 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 in order 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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A History of Biomaterials

BUDDY D. RATNER

At the dawn of the 21st century, biomaterials are widely used throughout medicine, dentistry and biotechnology. Just 50 years ago biomaterials as we think of them today did not exist. The word "biomaterial" was not used. There were no medical device manufacturers (except for external prosthetics such as limbs, fracture fixation devices, glass eyes, and dental devices), no formalized regulatory approval processes, no understanding of biocompatibility, and certainly no academic courses on biomaterials. Yet, crude biomaterials have been used, generally with poor to mixed results, throughout history. This chapter will broadly trace from the earliest days of human civilization to the dawn of the 21st century the history of biomaterials. It is convenient to organize the history of biomaterials into four eras: prehistory, the era of the surgeon hero, designed biomaterials/engineered devices, and the contemporary era leading into a new millennium. However, the emphasis of this chapter will be on the experiments and studies that set the foundation for the field we call biomaterials, largely between 1920 and 1980.

BIOMATERIALS BEFORE WORLD WAR II

Before Civilization

The introduction of nonbiological materials into the human body was noted far back in prehistory. The remains of a human found near Kennewick, Washington, USA (often referred to as the "Kennewick Man") was dated (with some controversy) to be 9000 years old. This individual, described by archeologists as a tall, healthy, active person, wandered through the region now know as southern Washington with a spear point embedded in his hip. It had apparently healed in and did not significantly impede his activity. This unintended implant illustrates the body's capacity to deal with implanted foreign materials. The spear point has little resemblance to modern biomaterials, but it was a "tolerated" foreign material implant, just the same.

Dental Implants in Early Civilizations

Unlike the spear point described above, dental implants were devised as implants and used early in history. The Mayan people fashioned nacre teeth from sea shells in roughly 600 A.D. and apparently achieved what we now refer to as bone integration (see Chapter 7.8), basically a seamless integration into the bone (Bobbio, 1972). Similarly, an iron dental implant in a corpse dated 200 A.D. was found in Europe (Crubezy *et al.,* 1998). This implant, too, was described as properly bone integrated. There were no materials science, biological understanding, or medicine behind these procedures. Still, their success (and longevity) is impressive and highlights two points: the forgiving nature of the human body and the pressing drive, even in prehistoric times, to address the loss of physiologic/anatomic function with an implant.

Sutures for 32,000 Years

There is evidence that sutures may have been used as long as 32,000 years ago (NATNEWS, 1983, **20**(5): 15–7). Large wounds were closed early in history by one of two methods—cautery or sutures. Linen sutures were used by the early Egyptians. Catgut was used in the Middle Ages in Europe.

Metallic sutures are first mentioned in early Greek literature. Galen of Pergamon (circa 130–200 A.D.) described ligatures of gold wire. In 1816, Philip Physick, University of Pennsylvania Professor of Surgery, suggested the use of lead wire sutures noting little reaction. In 1849, J. Marion Sims, of Alabama, had a jeweler fabricate sutures of silver wire and performed many successful operations with this metal.

Consider the problems that must have been experienced with sutures in eras with no knowledge of sterilization, toxicology, immunological reaction to extraneous biological materials, inflammation, and biodegradation. Yet sutures were a relatively common fabricated or manufactured biomaterial for thousands of years.

Artificial Hearts and Organ Perfusion

In the 4th century B.C., Aristotle called the heart the most important organ in the body. Galen proposed that veins connected the liver to the heart to circulate "vital spirits throughout the body via the arteries." English physician William Harvey in 1628 espoused a relatively modern view of heart function when he wrote, "The heart's one role is the transmission of the blood and its propulsion, by means of the arteries, to the extremities everywhere." With the appreciation of the heart as a pump, it was a logical idea to think of replacing the heart with an artificial pump. In 1812, the French physiologist Le Gallois expressed his idea that organs could be kept alive by pumping blood through them. A number of experiments on organ perfusion with pumps were performed from 1828–1868. In 1881, Étienne-Jules Marey, a brilliant scientist and thinker who published and invented in photography theory, motion

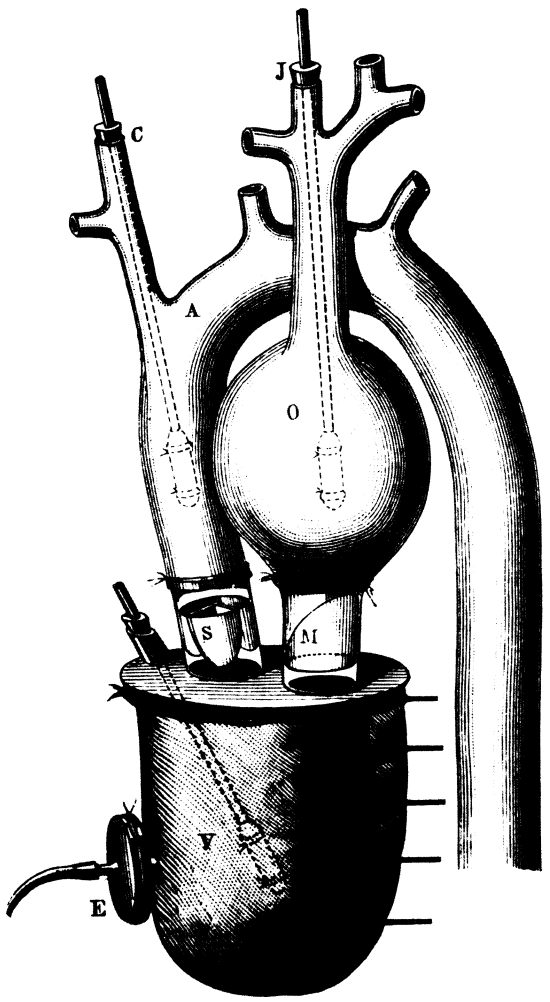

FIG. 1. An artificial heart by Étienne-Jules Marey, Paris, 1881.

studies and physiology, described an artificial heart device (Fig. 1), but probably never constructed such an apparatus.

In 1938, aviator (and engineer) Charles Lindbergh and surgeon (and Nobel prize winner) Alexis Carrel wrote a visionary book, *The Culture of Organs*. They addressed issues of pump design (referred to as the Lindbergh pump), sterility, blood damage, the nutritional needs of perfused organs and mechanics. This book must be considered a seminal document in the history of artificial organs. In the mid-1950s, Dr. Paul Winchell, better known as a ventriloquist, patented an artificial heart. In 1957, Dr. Willem Kolff and a team of scientists tested the artificial heart in animals. (The modern history of the artificial heart will be presented later in Chapter 7.4).

Contact Lenses

Leonardo DaVinci, in the year 1508, developed the contact lens concept. Rene Descartes is credited with the idea of the corneal contact lens (1632) and Sir John F. W. Herschel (1827) suggested that a glass lens could protect the eye. Adolf Fick, best known for his laws of diffusion, was an optometrist by profession. One of his inventions (roughly 1860) was a glass contact lens, possibly the first contact lens offering real success. He experimented on both animals and humans with contact lenses. In a period from 1936 to 1948, plastic contact lenses were developed, primarily poly(methyl methacrylate).

Basic Concepts of Biocompatibility

Most implants prior to 1950 had a low probability of success because of a poor understanding of biocompatibility and sterilization. As will be elaborated upon throughout the textbook, factors that contribute to biocompatibility include the chemistry of the implant, leachables, shape, mechanics, and design. Early studies, especially with metals, explored primarily chemistry ideas to explain the observed bioreaction.

Possibly the first study assessing the *in vivo* bioreactivity of implant materials was performed by H. S. Levert (1829). Gold, silver, lead, and platinum specimens were studied in dogs and platinum, in particular, was found to be well tolerated. In 1886, bone fixation plates of nickel-plated sheet steel with nickel-plated screws were studied. In 1924, A. Zierold published a study on tissue reaction to various materials in dogs. Iron and steel were found to corrode rapidly leading to resorption of adjacent bone. Copper, magnesium, aluminum alloy, zinc, and nickel discolored the surrounding tissue while gold, silver, lead, and aluminum were tolerated but inadequate mechanically. Stellite, a Co–Cr–Mo alloy, was well tolerated and strong. In 1926, M. Large noted inertness displayed by 18-8 stainless steel containing molybdenum. By 1929 Vitallium alloy (65% Co–30% Cr–5% Mo) was developed and used with success in dentistry. In 1947, J. Cotton of the UK discussed the possible use for titanium and alloys for medical implants.

The history of plastics as implantation materials is not nearly as old as metals, simply because there were few plastics prior to the 1940s. What is possibly the first paper on the implantation of a modern synthetic polymer, nylon as a suture, appeared in 1941. Papers on the implantation of cellophane, a polymer made from plant sources, were published as early as 1939, where it was used as a wrapping for blood vessels. The response to this implant was described as a "marked fibrotic reaction." In the early 1940s papers appeared discussing the reaction to implanted poly(methyl methacrylate) and nylon. The first paper on polyethylene as a synthetic implant material was published in 1947 (Ingraham *et al.*). The paper pointed out that polyethylene production using a new high-pressure polymerization technique began in 1936. This process enabled the production of polyethylene free of initiator fragments and other additives. Ingraham *et al.* demonstrated good results on implantation (i.e., a mild foreign body reaction) and attributed these results to the high purity of the polymer they used. A 1949 paper commented on the fact that additives to many plastics had a tendency to "sweat out" and this may be responsible for the strong biological reaction to those plastics (LeVeen and Barberio, 1949). They found a vigorous foreign body reaction to cellophane, Lucite, and nylon but extremely mild reaction to "a new plastic," Teflon. The authors incisively concluded, "Whether the tissue reaction is due to the dissolution of traces of the unpolymerized chemical used in plastics manufacture or

actually to the solution of an infinitesimal amount of the plastic itself cannot be determined." The possibility that cellulose might trigger the severe reaction by activating the complement system could not have been imagined because the complement system was not yet discovered.

POST WORLD WAR II—THE SURGEON/ PHYSICIAN HERO

At the end of World War II, high-performance metal, ceramic, and especially polymeric materials transitioned from wartime restricted to peacetime available. The possibilities for using these durable, novel, inert materials immediately intrigued surgeons with needs to replace diseased or damaged body parts. Materials originally manufactured for airplanes and automobiles were taken "off the shelf" by surgeons and applied to medical problems. These early biomaterials include silicones, polyurethanes, Teflon, nylon, methacrylates, titanium, and stainless steel.

A historical context helps us appreciate the contribution made primarily by medical and dental practitioners. After World War II, there was little precedent for surgeons to collaborate with scientists and engineers. Medical and dental practitioners of this era felt it was appropriate to invent (improvise) on their own where the life or functionality of their patient was at stake. Also, there was minimal government regulatory activity and minimal human subjects protections. The physician was implicitly entrusted with the life and health of the patient and had much more freedom than is seen today to take heroic action where other options were exhausted.[1] These medical practitioners had read about the post–World War II marvels of materials science. Looking at a patient open on the operating table, they could imagine replacements, bridges, conduits, and even organ systems based on such materials. Many materials were tried on the spur of the moment. Some fortuitously succeeded. These were high-risk trials, but usually they took place where other options were not available. The term "surgeon hero" seems justified since the surgeon often had a life (or a quality of life) at stake and was willing to take a huge technological and professional leap to repair the individual. This laissez faire biomaterials era quickly led to a new order characterized by scientific/engineering input, government quality controls, and a sharing of decisions prior to attempting high-risk, novel procedures. Still, a foundation of ideas and materials for the biomaterials field was built by courageous, fiercely committed, creative individuals and it is important to look at this foundation to understand many of the attitudes, trends, and materials common today.

[1]The regulatory climate in the Uinted States in the 1950s was strikingly different from now. This can be appreciated in this recollection from Willem Kolff about a pump oxygenator he made and brought with him from Holland to the Cleveland Clinic (Kolff, 1998): "Before allowing Dr. Effler and Dr. Groves to apply the pump oxygenator clinically to human babies, I insisted they do 10 consecutive, successful operations in baby dogs. The chests were opened, the dogs were connected to a heart-lung machine to maintain the circulation, the right ventricles were opened, a cut was made in the interventricular septa, the septa holes were closed, the right ventricles were closed, the tubes were removed and the chests were closed. (I have a beautiful movie that shows these 10 puppies trying to crawl out of a basket)."

Intraocular Lenses

Sir Harold Ridley, M.D. (1906–2001) (Fig. 2), inventor of the plastic intraocular lens (IOL), made early, accurate observations of biological reaction to implants consistent with currently accepted ideas of biocompatibility. After World War II, he had the opportunity to examine aviators who were unintentionally implanted in their eyes with shards of plastic from shattered canopies in Spitfire and Hurricane fighter planes. Most of these flyers had plastic fragments in their eyes for years. The conventional wisdom at that time was that the human body would not tolerate implanted foreign objects, especially in the eye—the body's reaction to a splinter or a bullet was cited as examples of the difficulty of implanting materials in the body. The eye is an interesting implant site because you can look in through a transparent window to see what happened. When Ridley did so, he noted that the shards had healed in place with no further reaction. They were, by his standard, tolerated by the eye. Today, we would describe this type of stable healing without significant ongoing inflammation or irritation as "biocompatible." This is an early observation of "biocompatible" in humans, perhaps the first, using criteria similar to those accepted today. Based on this observation, Ridley traced down the source of the plastic domes, ICI Perspex poly(methyl methacrylate), and ordered sheets of the material. He used this material to fabricate implant lenses (intraocular lenses) that were found, after some experimentation, to function reasonably in humans as replacements for surgically removed natural lenses that had been clouded by cataracts. The first implantation in a human was November 29, 1949. For many years, Ridley was the center of fierce controversy because he challenged the dogma that spoke against implanting foreign materials in eyes—it hard to believe in the 21st century that the implantation of a biomaterial would provoke such an outcry. Because of this controversy, this industry did not spontaneously arise—it has to await the early 1980s before IOLs became a major force in the biomedical device market. Ridley's insightful observation, creativity, persistence, and surgical talent in the late 1940s evolved to an industry that presently puts more than 7,000,000 of these lenses annually in humans. Through all of human history, cataracts meant blindness, or a surgical procedure that left the recipient needing thick, unaesthetic eye glasses that poorly corrected the vision. Ridley's concept, using a plastic material found to be "biocompatible," changed the course of history and substantially improved the quality of life for millions of individuals with cataracts. Harold Ridley's story is elaborated upon in an obituary (Apple and Trivedi, 2002).

Hip and Knee Prostheses

The first hip replacement was probably performed in 1891 by a German surgeon, Theodore Gluck, using a cemented ivory ball. This procedure was not successful. Numerous attempts were made between 1920 and 1950 to develop a hip replacement prosthesis. Surgeon M. N. Smith-Petersen, in 1925, explored a glass hemisphere to fit over the ball of the hip joint. This failed because of poor durability. Chrome-based alloys

FIG. 2. Sir Harold Ridley, inventor of the intraocular lens.

and stainless steel offered improvements in mechanical properties and many variants of these were explored. In 1938, the Judet Brothers of Paris, Robert and Jean, explored an acrylic surface for hip procedures, but it had a tendency to wear and loosen. The idea of using fast-setting dental acrylics to anchor prosthetics to bone was developed by Dr. Edward J. Haboush in 1953. In 1956, McKee and Watson-Farrar developed a "total" hip with an acetabular cup of metal that was cemented in place. Metal-on-metal wear products probably led to high complication rates. It was John Charnley (1911–1982) (Fig. 3), working at an isolated tuberculosis sanatorium in Wrightington, Manchester, England, who invented the first really successful hip joint prosthesis. The femoral stem, ball head, and plastic acetabular cup proved to be a reasonable solution to the problem of damaged joint replacement. In 1958, Dr. Charnley used a Teflon acetabular cup with poor outcomes due to wear debris. By 1961 he was using a high-molecular-weight polyethylene cup and was achieving much higher success rates. Interestingly, Charnley learned of high-molecular-weight polyethylene from a salesman selling novel plastic gears to one of his technicians. Dr. Dennis Smith contributed in an important way to the development of the hip prosthesis by introducing Dr. Charnley to poly(methyl methacrylate) cements, developed in the dental community, and optimizing those cements for hip replacement use. Total knee replacements borrowed elements of the hip prosthesis technology and successful results were obtained in the period 1968–1972 with surgeons Frank Gunston and John Insall leading the way.

FIG. 3. Sir John Charnley.

Dental Implants

Some of the "prehistory" of dental implants was described earlier. In 1809, Maggiolo implanted a gold post anchor into fresh extraction sockets. After allowing this to heal, he fastened to it a tooth. This has remarkable similarity to modern dental implant procedures. In 1887, this procedure was used with a platinum post. Gold and platinum gave poor long-term results and so this procedure was never widely adopted. In 1937, Venable used surgical Vitallium and Co–Cr–Mo alloy for such implants. Also around 1937, Strock at Harvard used a screw-type implant of Vitallium and this may be the first successful dental implant. A number of developments in surgical procedure and implant design (for example, the endosteal blade implant) then took place. In 1952, a fortuitous discovery was made. Per Ingvar Branemark, an orthopedic surgeon at the University of Lund, Sweden, was implanting an experimental cage device in rabbit bone for observing healing reactions. The cage was a titanium cylinder that screwed into the bone. After completing the experiment that lasted several months, he tried to remove the titanium device and found it tightly integrated in the bone (Branemark *et al.,* 1964). Dr. Branemark named the phenomenon osseointegration and explored the application of titanium implants to surgical and dental procedures. He also developed low-impact surgical protocols for tooth implantation that reduced tissue necrosis and enhanced the probability of good outcomes. Most dental implants and many other orthopedic implants are now made of titanium and its alloys.

The Artificial Kidney

Kidney failure, through most of history, was a sentence to unpleasant death lasting over a period of about a month. In 1910, at Johns Hopkins University, the first attempts to

remove toxins from blood were made by John Jacob Abel. The experiments were with rabbit blood and it was not possible to perform this procedure on humans. In 1943, in Nazi-occupied Holland, Willem Kolff (Fig. 4), a physician just beginning his career at that time, built a drum dialyzer system from a 100-liter tank, wood slats, and sausage-casing (cellulose) as the dialysis membrane. Some successes were seen in saving lives where prior to this there was only one unpleasant outcome to kidney failure. Kolff took his ideas to the United States and in 1960, at the Cleveland Clinic, developed a "washing machine artificial kidney" (Fig. 5). Major advances in kidney dialysis were made by Dr. Belding Scribner (1921–2003) at the University of Washington. Scribner devised a method to routinely access the bloodstream for dialysis treatments. Prior to this, after just a few treatments, access sites to the blood were used up and further dialysis was not possible. After seeing the potential of dialysis to help patients, but only acutely, Scribner tells the story of waking up in the middle of the night with an idea to gain easy access to the blood—a shunt implanted between an artery and vein that emerged through the skin as a "U." Through the exposed portion of the shunt, blood access could be readily achieved. When Dr. Scribner heard about this new plastic, Teflon, he envisioned how to get the blood out of and into the blood vessels. His device used Teflon tubes to access the vessels, a Dacron sewing cuff through the skin, and a silicone rubber tube for blood flow. The Scribner shunt made chronic dialysis possible and is said to be responsible for more than a million patients being alive today. Additional important contributions to the artificial kidney were made by Professor Les Babb of the University of Washington who, working with Scribner, improved dialysis performance and invented a proportioning mixer for the dialysate fluid.

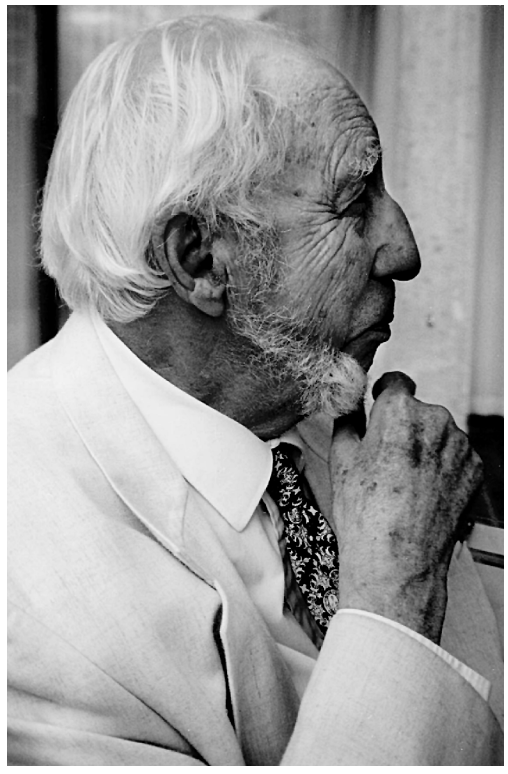

FIG. 4. Dr. Willem Kolff at age 92. (Photo by B. Ratner.)

The Artificial Heart

Willem Kolff was also a pioneer in the development of the artificial heart. He implanted the first artificial heart in the Western hemisphere in a dog in 1957 (a Russian artificial heart was implanted in a dog in the late 1930s). The Kolff artificial heart was made of a thermosetting poly(vinyl chloride) cast inside hollow molds to prevent seams. In 1953, the heart–lung machine was invented by John Gibbon, but this was useful only for acute treatment as during open heart surgery. After the National Heart and Lung Institute of the NIH in 1964 set a goal of a total artificial heart by 1970, Dr. Michael DeBakey implanted a left ventricular assist device in a human in 1966 and Dr. Denton Cooley implanted a polyurethane total artificial heart in 1969. In the period 1982–1985, Dr. William DeVries implanted a number of Jarvik hearts with patients living up to 620 days on the devices.

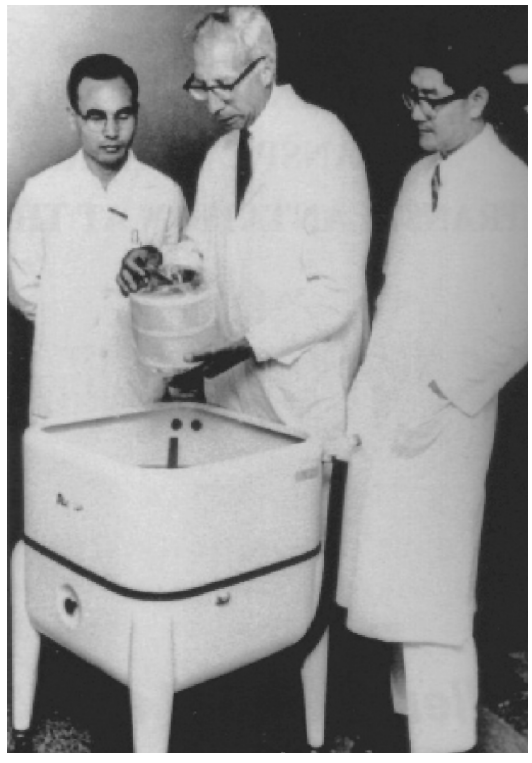

FIG. 5. Willem Kolff (center) and the washing machine artificial kidney.

Breast Implants

The breast implant evolved to address the poor results achieved with direct injection of substances into the breast for augmentation. In fact, in the 1960s, California and Utah classified silicone injections as a criminal offense. In the 1950s,

poly(vinyl alcohol) sponges were implanted as breast prostheses, but results with these were also poor. University of Texas plastic surgeons Thomas Cronin and Frank Gerow invented the first silicone breast implant in the early 1960s, a silicone shell filled with silicone gel. Many variants of this device have been tried over the years, including cladding the device with polyurethane foam (the Natural Y implant). This variant of the breast implant was fraught with problems. However, the basic silicone rubber–silicone gel breast implant was generally acceptable in performance (Bondurant *et al.,* 1999).

Vascular Grafts

Surgeons have long needed methods and materials to repair damaged and diseased blood vessels. Early in the century, Dr. Alexis Carrel developed methods to anastomose (suture) blood vessels, an achievement for which he won the Nobel Prize in medicine in 1912. In 1942, Blackmore used Vitallium metal tubes to bridge arterial defects in war-wounded soldiers. Columbia University surgical intern Arthur Voorhees (1922–1992), in 1947, noticed during a post-mortem that tissue had grown around a silk suture left inside a lab animal. This observation stimulated the idea that a cloth tube might also heal by being populated by the tissues of the body. Perhaps such a healing reaction in a tube could be used to replace an artery? His first experimental vascular grafts were sewn from a silk handkerchief and then parachute fabric (Vinyon N), using his wife's sewing machine. The first human implant of a prosthetic vascular graft was in 1952. The patient lived many years after this procedure, inspiring many surgeons to copy the procedure. By 1954, another paper was published establishing the clear benefit of a porous (fabric) tube over a solid polyethylene tube (Egdahl *et al.*, 1954). In 1958, the following technique was described in a textbook on vascular surgery (Rob, 1958): "The Terylene, Orlon or nylon cloth is bought from a draper's shop and cut with pinking shears to the required shape. It is then sewn with thread of similar material into a tube and sterilized by autoclaving before use."

Stents

Partially occluded coronary arteries lead to angina, diminished heart functionality, and eventually, when the artery occludes (i.e., myocardial infarction), death of a section of the heart muscle. Bypass operations take a section of vein from another part of the body and replace the occluded coronary artery with a clean conduit—this is major surgery, hard on the patient and expensive. Synthetic vascular grafts in the 3-mm diameter appropriate to the human coronary artery anatomy will thrombose and thus cannot be used. Another option is percutaneous transluminal coronary angioplasty (PTCA). In this procedure, a balloon is threaded on a catheter into the coronary artery and then inflated to open the lumen of the occluding vessel. However, in many cases the coronary artery can spasm and close from the trauma of the procedure. The invention of the coronary artery stent, an expandable metal mesh that holds the lumen open after PTCA, was a major revolution in the treatment of coronary occlusive disease. In his own words, Dr. Julio Palmaz (Fig. 6) describes the origins and history of the cardiovascular stent.

> I was at a meeting of the Society of Cardiovascular and Interventional Radiology in February 1978, New Orleans when a visiting lecturer, Doctor Andreas Gruntzig from Switzerland, was presenting his preliminary experience with coronary balloon angioplasty. As you know, in 1978 the mainstay therapy of coronary heart disease was surgical bypass. Doctor Gruntzig showed his promising new technique to open up coronary atherosclerotic blockages without the need for open chest surgery, using his own plastic balloon catheters. During his presentation, he made it clear that in a third of the cases, the treated vessel closed back after initial opening with the angioplasty balloon because of elastic recoil or delamination of the vessel wall layers. This required standby surgery facilities and personnel, in case of acute closure after balloon angioplasty prompted emergency coronary bypass. Gruntzig's description of the problem of vessel reclosure elicited in my mind the idea of using some sort of support, such as used in mine tunnels or in oil well drilling. Since the coronary balloon goes in small (folded like an umbrella) and is inflated to about 3–4 times its initial diameter, my idealistic support device needed to go in small and expand at the site of blockage with the balloon. I thought one way to solve this was a malleable tubular criss-cross mesh. I went back home in the Bay Area and started making crude prototypes with copper wire and lead solder, which I first tested in rubber tubes mimicking arteries. I called the device a BEIS or balloon-expandable intravascular graft. However, the reviewers of my first submitted paper wanted to call it a stent. When I looked the word up, I found out that it derives from Charles Stent, a British dentist who died at turn of the century. Stent invented a wax material to make dental molds for dentures. This material was later used by plastic surgeons to keep tissues in place, while healing after surgery. The word "stent" was then generically used for any device intended to keep tissues in place while healing.
>
> I made the early experimental device of stainless steel wire soldered with silver. These were materials I thought would be appropriate for initial laboratory animal testing. To carry on with my project I moved to the University of Texas Health Science Center in San Antonio (UTHSCSA) were I had a research laboratory and time for further development. From 1983–86 I performed mainly bench and animal testing. Dozens of ensuing projects showed the promise of the technique and the potential applications it had in many areas of vascular surgery and cardiology. With a UTHSCSA pathologist, Doctor Fermin Tio, we observed our first microscopic specimen of implanted stents in awe. After weeks to months after implantation by catheterization under X-ray guidance, the stent had remained open, carrying blood flow. The metal mesh was covered with translucent, glistening tissue similar to the lining of a normal vessel. The question remained whether the same would happen in atherosclerotic vessels. We tested this question in the atherosclerotic rabbit model and to our surprise, the new tissue free of atherosclerotic plaque encapsulated the stent wires, despite the fact that the animals were still on a high cholesterol diet. Eventually, a large sponsor (Johnson and Johnson) adopted the project and clinical trials were instituted under the scrutiny of the Food and Drug Administration, to compare stents to balloon angioplasty.

Coronary artery stenting is now performed in well over 1.5 million procedures per year.

FIG. 6. Dr. Julio Palmaz, inventor of the coronary artery stent.

FIG. 7. The Albert Hyman Model II portable pacemaker, circa 1932–1933. (With permission of NASPE Heart Rhythm Society.)

Pacemakers

In London, in 1788, Charles Kite wrote "An Essay Upon the Recovery of the Apparently Dead" where he discussed electrical discharges to the chest for heart resuscitation. In the period 1820–1880, it was already known that electric shocks could modulate the heartbeat (and, of course, consider the Frankenstein story from that era). The invention of the portable pacemaker, hardly portable by modern standards, may have taken place almost simultaneously in two groups in 1930–31—Dr. Albert S. Hyman (USA) (Fig. 7) and Dr. Mark C. Lidwill (working in Australia with physicist Major Edgar Booth).

Canadian electrical engineer John Hopps, while conducting research on hypothermia in 1949, invented an early cardiac pacemaker. Hopps' discovery was that if a cooled heart stopped beating, it could be electrically restarted. This led to Hopps' invention of a vacuum tube cardiac pacemaker in 1950. Paul M. Zoll developed a pacemaker in conjunction with the Electrodyne Company in 1952. The device was about the size of a large table radio, was powered with external current, and stimulated the heart using electrodes placed on the chest—this therapy caused pain and burns, though it could pace the heart.

In the period 1957–58, Earl E. Bakken, founder of Medtronic, Inc., developed the first wearable transistorized (external) pacemaker at the request of heart surgeon, Dr. C. Walton Lillehei. Bakken quickly produced a prototype that Lillehei used on children with postsurgery heart block. Medtronic commercially produced this wearable, transistorized unit as the 5800 pacemaker.

In 1959, the first fully implantable pacemaker was developed by engineer Wilson Greatbatch and cardiologist W. M. Chardack. He used two Texas Instruments transitors, a technical innovation that permitted small size and low power drain. The pacemaker was encased in epoxy to inhibit body fluids from inactivating it.

Heart Valves

The development of the prosthetic heart valve paralleled developments in cardiac surgery. Until the heart could be stopped and blood flow diverted, the replacement of a valve would be challenging. Charles Hufnagel, in 1952, implanted a valve consisting of a poly(methyl methacrylate) tube and nylon ball in a beating heart. This was a heroic operation and basically unsuccessful, but an operation that inspired cardiac surgeons to consider that valve prostheses might be possible. The 1953 development of the heart–lung machine by Gibbon allowed the next stage in the evolution of the prosthetic heart valve to take place. In 1960, a mitral valve replacement was performed in a human by surgeon Albert Starr using a valve design consisting of a silicone ball and poly(methyl methacrylate) cage (later replaced by a stainless steel cage). The valve was invented by engineer Lowell Edwards. The heart valve was based on a design for a bottle stopper invented in 1858. Starr was quoted as saying, "Let's make a valve that works and not worry about its looks," referring to its design that was radically different from the leaflet valve that nature evolved in mammals. Prior to the Starr–Edwards valve, no human had lived with a prosthetic heart valve longer than 3 months. The Starr–Edwards valve was

found to permit good patient survival. The major issues in valve development in that era were thrombosis and durability. Warren Hancock started the development of the first leaflet tissue heart valve in 1969 and his company and valve were acquired by Johnson & Johnson in 1979.

DESIGNED BIOMATERIALS

In contrast to the biomaterials of the surgeon-hero era, largely off-the-shelf materials used to fabricate medical devices, the 1960s on saw the development of materials designed specifically for biomaterials applications. Here are some key classes of materials and their evolution from commodity materials to engineered/synthesized biomaterials.

Silicones

Though the class of polymers known as silicones has been explored for many years, it was not until the early 1940s that Eugene Rochow of GE pioneered the scale-up and manufacture of commercial silicones via the reaction of methyl chloride with silicon in the presence of catalysts. In Rochow's 1946 book, *The Chemistry of Silicones* (John Wiley & Sons, Publishers), he comments anecdotally on the low toxicity of silicones but did not propose medical applications. The potential for medical uses of these materials was realized shortly after this. In a 1954 book on silicones, McGregor has a whole chapter titled "Physiological Response to Silicones." Toxicological studies were cited suggesting to McGregor that the quantities of silicones that humans might take into their bodies should be "entirely harmless." He mentions, without citation, the application of silicone rubber in artificial kidneys. Silicone-coated rubber grids were also used to support a dialysis membrane (Skeggs and Leonards, 1948). Many other early applications of silicones in medicine are cited in Chapter 2.3.

Polyurethanes

Polyurethanes, reaction products of diisocyanates and diamines, were invented by Otto Bayer and colleagues in Germany in 1937. The chemistry of polyurethanes intrinsically offered a wide range of synthetic options leading to hard plastics, flexible films, or elastomers (Chapter 2.2). Interestingly, this was the first class of polymers to exhibit rubber elasticity without covalent cross-linking. As early as 1959, polyurethanes were explored for biomedical applications, specifically heart valves (Akutsu *et al.,* 1959). In the mid-1960s a class of segmented polyurethanes was developed that showed both good biocompatibility and outstanding flex life in biological solutions at 37°C (Boretos and Pierce, 1967). Sold under the name Biomer, these segmented polyurethanes comprised the pump diaphragms of the Jarvik 7 hearts that were implanted in seven humans.

Teflon

DuPont chemist Roy Plunkett discovered a remarkably inert polymer, Teflon (polytetrafluoroethylene), in 1938. William L. Gore and his wife Vieve started a company in 1958 to apply Teflon for wire insulation. In 1969, their son Bob found that Teflon, if heated and stretched, forms a porous membrane with attractive physical and chemical properties. Bill Gore tells the story that, on a chairlift at a ski resort, he pulled from his parka pocket a piece of porous Teflon tubing to show to his fellow ski lift passenger. The skier was a physician and asked for a specimen to try as a vascular prosthesis. Now, Goretex porous Teflon is the leading synthetic vascular graft and has numerous applications in surgery and biotechnology.

Hydrogels

Hydrogels have been found in nature since life on earth evolved. Bacterial biofilms, hydrated living tissues, extracellular matrix components, and plant structures are ubiquitous, hydrated, swollen motifs in nature. Gelatin and agar were also explored early in human history. But, the modern history of hydrogels as a class of materials designed for medical applications can be accurately traced.

In 1936, DuPont scientists published a paper on recently synthesized methacrylic polymers. In this paper, poly(2-hydroxyethyl methacrylate) (polyHEMA) was mentioned. It was briefly described as a hard, brittle, glassy polymer and clearly not considered of importance. After that paper, this polymer was essentially forgotten until 1960. Wichterle and Lim published a paper in *Nature* describing the polymerization of HEMA monomer and a cross-linking agent in the presence of water and other solvents (Wichterle and Lim, 1960). Instead of a brittle polymer, they obtained a soft, water-swollen, elastic, clear gel. This innovation led to the soft contact lens industry and to the modern field of biomedical hydrogels as we know them today.

Interest and applications for hydrogels have steadily grown over the years and these are described in detail in Chapter 2.5. Important early applications included acrylamide gels for electrophoresis, poly(vinyl alcohol) porous sponges (Ivalon) as implants, many hydrogel formulations as soft contact lenses, and alginate gels for cell encapsulation.

Poly(ethylene glycol)

Poly(ethylene glycol) (PEG), also called poly(ethylene oxide) (PEO) in its high-molecular-weight form, can be categorized as a hydrogel, especially when the chains are cross-linked. However, PEG has many other applications and implementations. It is so widely used today that it is best discussed in its own section.

The low reactivity of PEG with living organisms has been known since at least 1944 where it was examined as a possible vehicle for intravenously administering fat-soluble hormones (Friedman, 1944). In the mid-1970s, Abuchowski and colleagues (Abuchowski *et al.,* 1977) discovered that if PEG chains were attached to enzymes and proteins, they would a have a much longer functional residence time *in vivo* than

biomolecules that were not PEGylated. Professor Edward Merrill of MIT, based upon what he called "various bits of evidence" from the literature, concluded that surface-immobilized PEG would resist protein and cell pickup. The experimental results from his research group in the early 1980s bore this conclusion out (Merrill, 1992). The application of PEGs to wide range of biomedical problems has been significantly accelerated by the synthetic chemistry developments of Dr. Milton Harris while at the University of Alabama, Huntsville.

Poly(lactic–glycolic acid)

Though originally discovered in 1833, the anionic polymerization from the cyclic lactide monomer in the early 1960s made materials with mechanical properties comparable to Dacron possible. The first publication on the application of poly(lactic acid) in medicine may have been by Kulkarni *et al.* (1966). This group demonstrated that the polymer degraded slowly after implantation in guinea pigs or rats and was well tolerated by the organisms. Cutright *et al.* (1971) was the first to apply this polymer for orthopedic fixation. Poly(glycolic acid) and copolymers of lactic and glycolic acid were subsequently developed. Early clinical applications of polymers in this family were for sutures. The glycolic acid/lactic acid polymers have also been widely applied for controlled release of drugs and proteins. Professor Robert Langer's group was the leader in developing these polymers in the form of porous scaffolds for tissue engineering (Langer and Vacanti, 1993).

Hydroxyapatite

Hydroxyapatite is one of the most widely studied materials for healing in bone. It is both a natural component of bone (i.e., a material of ancient history) and a synthetic material with a modern history. Hydroxyapatite can be easily made as a powder. One of the first papers to apply this material for biomedical application was by Levitt *et al.* (1969), in which they hot-pressed the hydroxyapatite power into useful shapes for biological experimentation. From this early appreciation of the materials science aspect of a natural biomineral, a literature of thousands of papers has evolved. In fact, the nacre implant described in the prehistory section may owe its effectiveness to hydroxyapatite—recent data have shown that the calcium carbonate of nacre can transform in phosphate solutions to hydroxapatite (Ni and Ratner, 2003).

Titanium

In 1791, William Gregor, a Cornish amateur chemist, used a magnet to extract the ore that we now know as ilmenite from a local river. He then extracted the iron from this black powder with hydrochloric acid and was left with a residue that was the impure oxide of titanium. After 1932, a process developed by William Kroll permitted the commercial extraction of titanium from mineral sources. At the end of World War II, titanium metallurgy methods and titanium materials made their way from military application to peacetime uses. By 1940, satisfactory results had already been achieved with titanium implants (Bothe *et al.,* 1940). The major breakthrough in the use of titanium for bony tissue implants was the Branemark discovery of osseointegration, described earlier in the section on dental implants.

Bioglass

Bioglass is important to biomaterials as one of the first completely synthetic materials that seamlessly bonds to bone. It was developed by Professor Larry Hench and colleagues. In 1967 Hench was an assistant professor at the University of Florida. At that time his work focused on glass materials and their interaction with nuclear radiation. In August of that year, he shared a bus ride to an Army Materials Conference in Sagamore, New York, with a U.S. Army Colonel who had just returned from Vietnam where he was in charge of supplies to 15 MASH units. He was not terribly interested in the radiation resistance of glass. Rather, he challenged Hench with the following: hundreds of limbs a week in Vietnam were being amputated because the body was found to reject the metals and polymer materials used to repair the body. "If you can make a material that will resist gamma rays, why not make a material the body won't resist?"

Hench returned from the conference and wrote a proposal to the U.S. Army Medical R and D Command. In October 1969 the project was funded to test the hypothesis that silicate-based glasses and glass-ceramics containing critical amounts of Ca and P ions would not be rejected by bone. In November 1969 Hench made small rectangles of what he called 45S5 glass (44.5 wt.% SiO_2) and Ted Greenlee, Assistant Professor of Orthopaedic Surgery at the University of Florida, implanted them in rat femurs at the VA Hospital in Gainesville. Six weeks later Greenlee called—"Larry, what are those samples you gave me? They will not come out of the bone. I have pulled on them, I have pushed on them, I have cracked the bone and they are still bonded in place." Bioglass was born, and with the first composition studied! Later studies by Hench using surface analysis equipment showed that the surface of the Bioglass, in biological fluids, transformed from a silicate-rich composition to a phosphate-rich structure, possibly with resemblance to hydroxyapatite (Clark *et al.,* 1976).

THE CONTEMPORARY ERA (MODERN BIOLOGY AND MODERN MATERIALS)

It is probable that the modern era in the history of biomaterials, biomaterials engineered to control specific biological reactions, was ushered in by rapid developments in modern biology. In the 1960s, when the field of biomaterials was laying down its foundation principles and ideas, concepts such as cell-surface receptors, growth factors, nuclear control of protein expression and phenotype, cell attachment proteins, and gene delivery were either controversial observations or undiscovered. Thus, pioneers in the field, even if so moved, could not have designed materials with these ideas in mind. It is to the credit of the biomaterials community that it has been quick

to embrace and exploit new ideas from biology. Similarly, new ideas from materials science such as phase separation, anodization, self-assembly, surface modification, and surface analysis were quickly assimilated into the biomaterial scientists' toolbox and vocabulary. A few of the important ideas in the biomaterials literature that set the stage for the biomaterials science we see today are useful to list:

Protein adsorption
Biospecific biomaterials
Nonfouling materials
Healing and the foreign-body reaction
Controlled release
Tissue engineering
Regenerative medicine

Since these topics are well elaborated upon in *Biomaterials Science: An Introduction to Materials in Medicine,* 2nd edition, they will not be expanded upon in this history section. Still, it is important to appreciate the intellectual leadership of many researchers that promoted these ideas that make up modern biomaterials.

CONCLUSIONS

Biomaterials have progressed from surgeon-heroes, sometimes working with engineers, to a field dominated by engineers and scientists, to our modern era with the biologist as a critical player. As *Biomaterials Science: An Introduction to Materials in Medicine*, 2nd edition, is being published, many individuals who were biomaterials pioneers in the formative days of the field are well into their ninth decade. A number of leaders of biomaterials, pioneers who spearheaded the field with vision, creativity, and integrity, have passed away. Biomaterials is a field with a history modern enough so the first-hand accounts of its roots are available. I encourage readers of the textbook to document their conversations with pioneers of the field (many of whom still attend biomaterials conferences), so that the exciting stories that led to the successful and intellectually alive field we see today are not lost.

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