BIOMATERIALS SCIENCE

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An Introduction to Materials in Medicine

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Society for Biomaterials

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Cover photographs: Background is detail of grains in cold-worked 316L stainless steel showing evidence of plastic deformation. (See Chapter 2.2, courtesy of Zimmer USA, Warsaw, IN.) Inset is cardiac pacemaker with polyurethane lead tine and connector. (See Chapter 6.2, courtesy of Medtronic, Inc.)

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CONTENTS

PART III
PRACTICAL ASPECTS OF BIOMATERIALS

CHAPTER 9 Implants and Devices

CHAPTER 10 New Products and Standards

CHAPTER 11 Perspectives and Possibilities in Biomaterials Science

APPENDIX Properties of Biological Fluids

Biomaterials Science: An Interdisciplinary Endeavor

BUDDY D. RATNER

A VERY SHORT HISTORY OF BIOMATERIALS

The modern field we call biomaterials is too new for a formal history to have been compiled. However, a few comments are appropriate to place both ancient history and rapidly moving contemporary history in perspective. The Romans, Chinese, and Aztec used gold in dentistry more than 2000 years ago. Through much of recorded history, glass eyes and wooden teeth have been in common use. At the turn of this century, synthetic plastics became available. Their ease of fabrication led to many implantation experiments, most of them, in light of our contemporary understanding of biomaterials toxicology, doomed to failure. Poly(methyl methacrylate) (PMMA) was introduced in dentistry in 1937. During World War II, shards of PMMA from shattered gunnery turrets, unintentionally implanted in the eyes of aviators, suggested that some materials might evoke only a mild foreign body reaction. Just after World War II, Voorhees experimented with parachute cloth (Vinyon N) as a vascular prosthesis. In 1958, in a cardiovascular surgery textbook by Rob, the suggestion was offered that surgeons might visit their local draper's shop and purchase Dacron fabric that could be cut with pinking shears to fabricate an arterial prosthesis. In the early 1960s Charnley used PMMA, ultrahigh-molecular-weight polyethylene, and stainless steel for total hip replacement. While these applications for synthetic materials in medicine spanned much of written history, the term "biomaterial" was not invoked.

It is difficult to pinpoint the precise origins of the term "biomaterial." However, it is probable that the field we recognize today was solidified through the early Clemson University biomaterials symposia in the late 1960s and early 1970s. The scientific success of these symposia led to the formation of the Society For Biomaterials in 1975. The individual physician-visionaries who implanted miscellaneous materials to find a solution to pressing, often life-threatening, medical problems were, with these Clemson symposia, no longer the dominant force. We had researchers and engineers designing materials to meet specific criteria, and scientists exploring the nature of biocompatibility. Around this term "biomaterial" a unique scientific discipline evolved. The evolution of this field and the Society For Biomaterials were intimately connected. From biomaterials ideas, many of which originated at society meetings, other fields evolved. Drug delivery, biosensors, and bioseparations owe much to biomaterials. Now we have academic departments of biomaterials, many biomaterials programs, and research institutes devoted to education and exploration in biomaterials science and engineering (Society For Biomaterials Educational Directory, 1992). Paralleling the research and educational effort, hundreds of companies that incorporate biomaterials into devices have developed. This textbook looks at a now well-established biomaterials field, circa the 1990s.

BIOMATERIALS SCIENCE

Although biomaterials are primarily used for medical applications, which will be the focus of this text, they are also used to grow cells in culture, in apparatus for handling proteins in the laboratory, in devices to regulate fertility in cattle, in the aquaculture of oysters, and possibly in the near future they will be used in a cell-silicon "biochip" that would be integrated into computers. 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 simple materials and are more commonly integrated into devices. Although this is a text on materials, it will quickly become apparent that the subject cannot be explored without

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also considering biomedical devices. In fact, 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 a heart assist device, it can elicit different blood–material interactions 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 exhibit appropriate membrane permeability and mass transport characteristics. It also must employ mechanical and electronic systems to pump blood and control flow rates.

Unfortunately, many aspects of the design of devices are beyond the scope of this book. Consider the example of the hemodialysis system. The focus here is on membrane materials and their biocompatibility; there is less information on mass transport through membranes, and little information on flow systems and monitoring electronics.

A few definitions and descriptions are in order and will be expanded upon in this and subsequent chapters.

Many definitions have been proposed for the term "biomaterial." One definition, 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.

A complementary definition essential for understanding the goal 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)

Thus, we are introduced to considerations that set a biomaterial 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. 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.

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

EXAMPLES OF BIOMATERIALS APPLICATIONS

Substitute Heart Valves

Degeneration and other diseases of heart valves often make surgical repair or replacement necessary. Heart valve prostheses are fabricated from carbons, metals, elastomers, fabrics, and natural (e.g., pig) valves and other tissues chemically pretreated to reduce their immunologic reactivity and to enhance durability. More than 45,000 replacement valves are implanted each year in the United States because of acquired damage to the natural valve and congenital heart anomalies. Figure 1 shows a bileaflet tilting disk heart valve, the most widely used design. 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 good overall success seen with replacement heart valves, there are problems with different types of valves; they include degeneration of tissue, mechanical failure, postoperative infection, and induction of blood clots.

Artificial Hip Joints

The human hip joint is subjected to high mechanical stresses and undergoes considerable abuse. It is not surprising that because of 50 years or more 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 joints are fabricated from titanium, specific high-strength alloys, ceramics, composites, and ultrahigh molecular weight polyethylene. Replacement hip joints (Fig. 2) are implanted in more than 90,000 humans each year in the United States alone. With some types of replacement hip joints and surgical procedures, ambulatory function is restored within days after surgery. For other types, a healing-in period is required for attachment between bone and the implant before the joint can bear the full weight of the body. In most cases, good function is restored, and even athletic activities are possible, although they are generally not advised. After 10–15 years, the implant may loosen, necessitating another operation.

Dental Implants

The widespread introduction of titanium implants (Fig. 3) has revolutionized dental implantology. These devices, which form an artificial tooth root on which a crown is affixed, are implanted in approximately 275,000 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 bonding 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. Wear, corrosion, and the mechanical properties of titanium have also been of concern.

Intraocular Lenses

Intraocular lenses (IOLs) made of poly(methyl methacrylate), silicone elastomer, or other materials are used to replace

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, 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

a natural lens when it becomes cloudy and cataractous (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 over 1.4 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 biomicroscope show that inflammatory cells migrate to the surface of the lenses after periods of implantation. Thus, the conventional healing pathway is seen with these devices, as is observed with materials implanted in other sites in the body.

Many themes are illustrated by these four vignettes. 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 four examples just discussed to examine the issues implicit to each case.

CHARACTERISTICS OF BIOMATERIALS SCIENCE

Interdisciplinary

More than any other field of contemporary technology, biomaterials science brings together researchers with diverse academic backgrounds who must communicate clearly. Figure 5 lists some of the disciplines that are encountered in the progression from identifying the need for a biomaterial or device to the manufacture, sale, and implantation of it.

Many 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 materials scientist, to a general understanding of the properties of materials that might be demonstrated by the physician biomaterials scientist.

A wide range of materials is routinely used (Table 1) and no one researcher will be comfortable synthesizing and designing with all these materials. Thus, specialization is the rule. However, a broad appreciation of the properties and applications of these materials, the palette from which the biomaterials scientist chooses, is a hallmark of professionals in the field.

There is a tendency to group the materials (and the researchers) into the "hard tissue replacement biomaterials" camp (e.g., metals, ceramics), typically repesented by those involved in orthopedic and dental materials, and the "soft tissue replace-

TABLE 2 The Biomaterials and Healthcare Market—Facts and Figures (per year)

Total U.S. health care expenditures (1990)	$666,200,000,000
Total U.S. health research and development (1990)	$22, 600,000,000
Number of employees in the medical device industry (1988)	194,250
Registered U.S. medical device manufacturers (1991)	19,300
Total medical device sales:	
Surgical appliances	$8,414,000,000
Surgical instruments	$6,444,000,000
Electromedical devices	$5,564,000,000
U.S. market for biomaterials (1992)	$402,000,000
Individual medical device sales:	
Catheters, U.S. market (1991)	$1,400,000,000
Angioplasty catheters (market by mid 1990s)	$1,000,000,000
Orthopedic, U.S. market (1990)	$2,200,000,000
Wound care products (1988 estimate)	$4,000,000,000
Biomedical sensor market (1991)	$365,000,000
Artificial pancreas (if one existed, and was used by 10% of the U.S. insulin-dependent diabetics; 1985 estimate)	$2,300,000,000
Numbers of devices:	
Intraocular lenses	1,400,000[a]
Contact lenses:	
Extended wear soft lens users	4,000,000[a]
Daily wear soft lens users	9,000,000[a]
Rigid gas-permeable users	2,600,000[a]
Vascular grafts	250,000[b]
Heart valves	45,000[a]
Pacemakers	460,000[a]
Blood bags	30,000,000[b]
Breast prostheses	544,000[a]
Catheters	200,000,000[b]
Oxygenators	500,000[b]
Renal dialyzers	16,000,000[b]
Orthopedic (knee, hip)	500,000[b]
Knee	816,000[a]
Hip	521,000[a]

[a]1990 estimate for United States.
[b]1981 estimate for western countries and Japan.

ment biomaterials" camp (e.g., polymers), which is often associated with cardiovascular and general plastic surgery materials. In practice, this division does not hold up well—a heart valve may be fabricated from polymers, metals, and carbons, while a hip joint will also be composed of metals and polymers 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 this book will provide this background.

Development of Biomaterials Devices

Figure 5 illustrates interdisciplinary interactions in biomaterials and shows the usual progression in the devleopment 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

Magnitude expresses both a *magnitude of need* and *magnitude of a commercial market*. Needless to say, a conflict of interest can arise with pressures from both the commercial quarter and from ethical considerations. Consider three commonly used biomaterial devices: a contact lens, a hip joint, and a heart valve. All fill a medical need. The contact lens offers improved vision and in some cases a cosmetic enhancement. The hip joint offers mobility to the patient who would otherwise be confined to a bed or wheelchair. The heart valve offers life. The contact lens may sell for $100, and the hip joint and heart valve may sell for up to $3000 each. There will be 20 million contact lenses purchased each year, but only perhaps 100,000 heart valves (worldwide) and 500,000 total artificial hip prostheses. Here are the issues for consideration: a large number of devices, differing magnitudes of need, and differing (but large) commercial potential. There is no simple

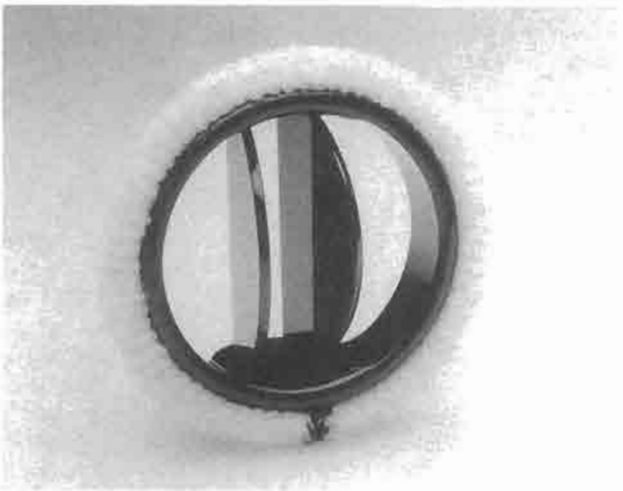

FIG. 1. A replacement heart valve. (Photograph courtesy of St. Jude Medical, Inc.)

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

answer to how these components are integrated in this field we call "biomaterials science." As you work your way through this volume, view each of the ideas and devices presented in the context of these considerations.

Along with these characteristics of biomaterials science—the interdisciplinary flavor, the magnitude of the need, and the sophisticated materials science—there are certain, often unique, subjects that occupy particularly prominent positions in our field. 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 bomb" drug release system that seeks out 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

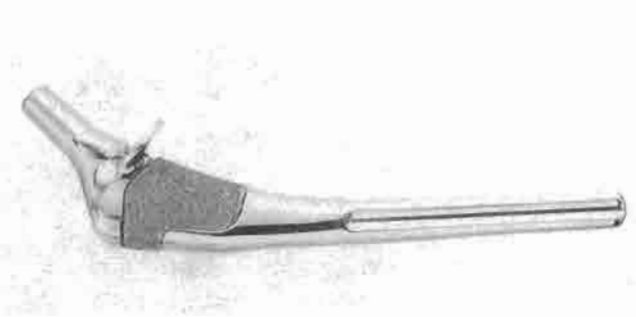

FIG. 2. A synthetic hip joint. (Photograph courtesy of Zimmer, Inc.)

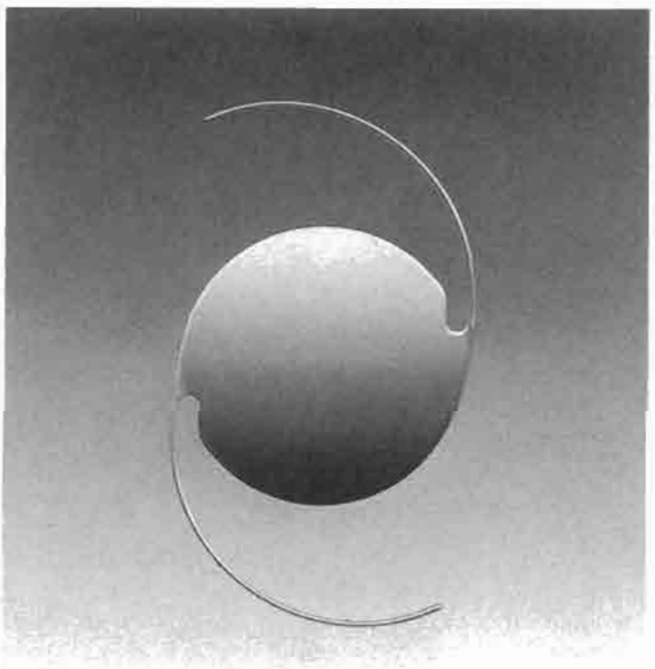

FIG. 4. An intraocular lens. (Photograph courtesy of Alcon Laboratories, Inc.)

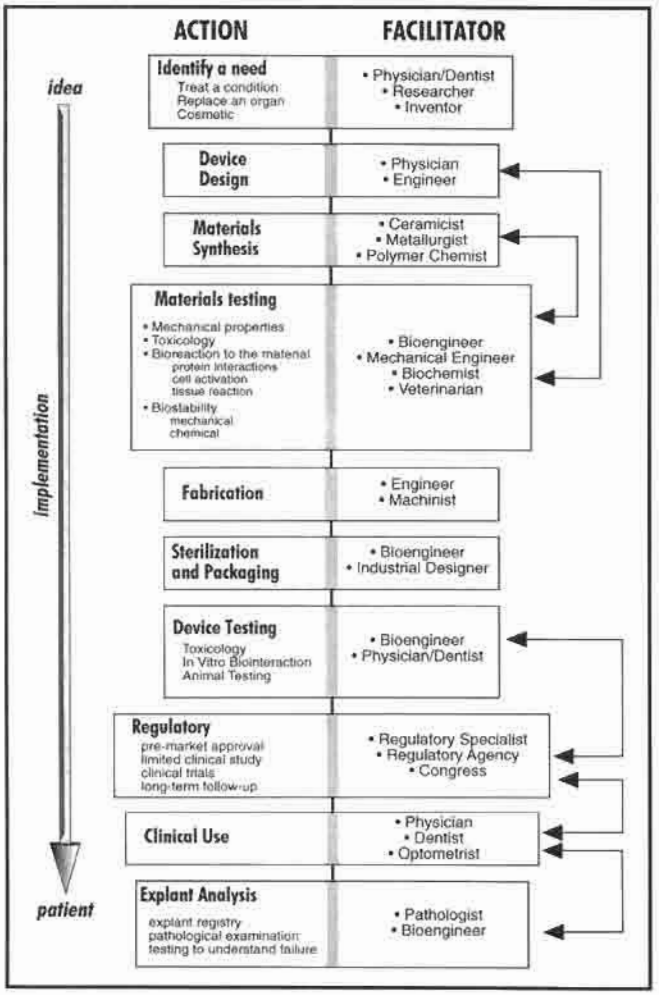

FIG. 5. Disciplines involved in biomaterials science and the path from a need to a manufactured medical device.

this design criterion is met when a new biomaterial is under development. Chapter 5.2 provides an overview of methods in biomaterials toxicology. The implications of toxicity are addressed in Chapters 4.2 and 4.4.

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, it is defined in terms of performance or success at a specific task. Thus, for a patient who is alive and doing well, with a vascular prosthesis that is unoccluded, few would argue that this prosthesis is, in this case, not "biocompatible." However, this operational definition offers us little to use 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.

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 involved, 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.

Unique Anatomical Sites

Consideration of the anatomical site of an implant is essential. An intraocular lens may go into the lens capsule or the anterior chamber. A hip joint will be implanted in bone across an articulating joint space. A heart valve will be sutured into cardiac muscle. A catheter may be placed in a vein. Each of these sites challenges the biomedical device designer with special requirements for geometry, size, mechanical properties, and bioreaction. Chapter 3.4 introduces these ideas.

Mechanical and Performance Requirements

Each biomaterial and device has imposed upon it mechanical and performance requirements that originate from 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 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 (it is hoped, for 10 or more years). A hip joint must not fail under heavy loads for more than 10 years. Finally, the bulk physical properties will address performance. The dialysis membrane has a specified permeability, the articular cup of the hip joint has a lubricity, and the intraocular lens has a clarity and refraction requirement. To meet these requirements, design principles are borrowed from mechanical engineering, chemical engineering, and materials science.

Industrial Involvement

At the same time as a significant basic research effort is under way to understand how biomaterials function and how

to optimize them, companies are producing millions of implants for use in humans and earning billions of dollars on the sale of medical devices. Thus, although we are now only learning about the fundamentals of biointeraction, we manufacture and implant materials and devices. How is this dichotomy explained? Basically, as a result of considerable experience, trial and error, inspired guesses, and just plain luck, 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. In essence, the complications of the devices are less than the complicatons of the original diseases. Companies make impressive profits on these devices. Yet, in some respects, the patient is trading one disease for another, and there is much evidence that better materials and devices can be made through basic science and engineering exploration. So, in the field of biomaterials, we always see two sides of the coin—a basic science and engineering effort, and a commercial sector.

The balance between the desire to alleviate loss of life and suffering, and the corporate imperative to turn a profit forces us to look further afield for guidance. Obviously, ethical concerns enter into the picture. Companies have large investments in the manufacture, quality control, clinical testing, regulatory clearance, and distribution of medical devices. How much of an advantage 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, in the short term, be perceived by the stockholders as a cut in the profits. Moreover, product liability issues are a major concern of manufacturers. When looking at the industrial side of the biomaterials field, questions are asked about the ethics of withholding an improved device from people who need it, 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 medical devices, let alone improved ones, available for clinical application?

When the industrial segment of the biomaterials field is examined, we see other contributions to our field. Industry deals well with technological developments such as packaging, sterilization, and quality control and analysis. These subjects require a strong technological base, and have generated 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

There are a wide range of other ethical considerations in 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).

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, a complex national regulatory system has been erected by the United States government through the Food and Drug Administration (FDA). Through the International Standards Organization (ISO), international regulatory standards have been developed for the world community. Obviously, a substantial base of biomaterials knowledge went into these standards. The costs to meet the standards and to demonstrate compliance with material, biological, and clinical testing are enormous. Introducing a new biomedical device to the market requires a regulatory investment of many 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 are addressed every day. Chapters 10.2 and 10.3 expand on standards and regulatory concerns.

TABLE 3 Some Ethical Concerns Relevant to Biomaterials Science

Is the use of animal models 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 tradeoff 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?

BIOMATERIALS LITERATURE

Over the past 40 years, the field of biomaterials has developed from individual medical researchers "trying things out," to the defined discipline we have today. Concurrent with the evolution of the discipline, a literature has also developed. A bibliography is provided at the end of this introduction to

highlight key reference works and technical journals in the biomaterials field.

SUMMARY

This chapter provides a broad overview of the biomaterials field. It is intended to provide a vantage point from which the reader can begin to place all the subthemes (chapters) within the perspective of the larger whole.

To reiterate a key point, biomaterials science may be the most interdisciplinary of all the sciences. Consequently, biomaterials scientists must master material from many fields of science, technology, engineering, and medicine in order to be competent in this profession. The reward for mastering this volume of material is involvement in an intellectually stimulating endeavor that advances our understanding of basic sciences and also contributes to reducing human suffering.

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CHAPTER

2

Classes of Materials Used in Medicine

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2.1 INTRODUCTION

Allan S. Hoffman

The wide diversity and sophistication of materials currently used in medicine and biotechnology is testimony to the significant technological advances which have occurred over the past 25 years. As little as 25 years ago, common, commercial polymers and metals were being used in implants and medical devices. There was relatively little stimulus or motivation for development of new materials. However, a relatively small group of "biomaterials scientists" with a strong interest in medicine, in collaboration with a like-minded group of physicians, evolved out of traditional fields such as chemistry, chemical engineering, metallurgy, materials science and engineering, physics and medicine. They recognized not only the need for new and improved materials, implants and devices, but also the challenges and opportunities involved. With the early support of the National Institutes of Health and a few enlightened companies, a wide range of new and exciting biomaterials began to emerge, and over the past 15–20 years, the field, its diversity, and the number of professionals working in the field have grown enormously. Materials and systems for biological use have been synthesized and fabricated in a wide variety of shapes and forms, including composites and coated systems. Some of the new materials and technologies have been developed especially for biological uses, while others have been borrowed from such unexpected areas as space technology. This section covers the background and most recent developments in the science and engineering of biomaterials.

2.2 METALS

John B. Brunski

Metallic implant materials have a significant economic and clinical impact on the biomaterials field. The total U.S. market for implants and instrumentation in orthopedics was about $2.098 million in 1991, according to recent estimates. This includes $1.379 million for joint prostheses made of metallic materials, plus a variety of trauma products ($340 million), instrumentation devices ($266 million), bone cement accessories ($66 million), and bone replacement materials ($29 million). Projections for 2002 indicate that the total global biomaterials market will be $6 billion. The clinical numbers are equally impressive. Of the 3.6 million orthopedic operations per year in the U.S., four of the ten most frequent involve metallic implants: open reduction of a fracture and internal fixation (first on the list), placement or removal of an internal fixation device without reduction of a fracture (sixth), arthroplasty of the knee or ankle (seventh), and total hip replacement or arthroplasty of the hip (eighth).

Besides orthopedics, there are other markets for metallic implants and devices, including oral and maxillofacial surgery (e.g., dental implants, craniofacial plates and screws) and cardiovascular surgery (e.g., parts of artificial hearts, pacemakers, balloon catheters, valve replacements, aneurysm clips). Interestingly, in 1988, about 11 million Americans (about 4.6% of the civilian population) had at least one implant (Moss *et al.*, 1990).

In view of this wide utilization of metallic implants, the objective of this chapter is to describe the composition, structure, and properties of current metallic implant alloys. A major emphasis is on the metallurgical principles underlying fabrication and structure-property relationships.

STEPS IN THE FABRICATION OF IMPLANTS

Understanding the structure and properties of metallic implant materials requires an appreciation of the metallurgical significance of the material's processing history (Fig. 1). Since each metallic device differs in the details of its manufacture, "generic" processing steps are presented in Fig. 1.

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substrate while maintaining adequate properties of both coating and substrate. For example, optimizing the fatigue properties of Ti–6Al–4V porous-coated implants, becomes an interdisciplinary problem involving not only metallurgy but also surface properties and fracture mechanics.

CONCLUDING REMARKS

It should be evident that metallurgical principles guide our understanding of structure-property relationships in metallic implants, just as they would in the study of any metallic device. While this chapter's emphasis has been on mechanical properties (for the sake of specificity), other properties, in particular surface properties, are receiving increasing attention in relation to biological performance of implants.

Another point to remember is that the intrinsic material properties of metallic implants are not the sole determinant of implant performance and success. Existing implant metals and alloys have all been used in both successful and unsuccessful implant designs. The reasons for failures can include faulty or inappropriate use of the implant, surgical error, and inadequate mechanical design of the implant. Therefore, debates about which implant metal is "superior" often miss the point; implant design is a true multifaceted design problem in which the selection of materials is only a part—albeit an important part—of the total problem.

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2.3 POLYMERS

Susan A. Visser, Robert W. Hergenrother, and Stuart L. Cooper

Polymers are long-chain molecules that consist of a number of small repeating units. The repeat units or "mers" differ from the small molecules which were used in the original synthesis procedures, the monomers, in the loss of unsaturation or the elimination of a small molecule such as water or HCl during polymerization. The exact difference between the monomer and the mer unit depends on the mode of polymerization, as discussed later.

The wide variety of polymers includes such natural materials as cellulose, starches, natural rubber, and deoxyribonucleic acid (DNA), the genetic material of all living creatures. While these polymers are undoubtedly interesting and have seen widespread use in numerous applications, they are sometimes eclipsed by the seemingly endless variety of synthetic polymers that are available today.

The task of the biomedical engineer is to select a biomaterial with properties that most closely match those required for a particular application. Because polymers are long-chain molecules, their properties tend to be more complex than their short-chain counterparts. Thus, in order to choose a polymer type for a particular application, the unusual properties of polymers must be understood.

This chapter introduces the concepts of polymer characterization and property testing as they are applied to the selection of biomaterials. Examples of polymeric biomaterials currently used by the medical community are cited and discussed with regard to their solid-state properties and uses.

MOLECULAR WEIGHT

In polymer synthesis, a polymer is usually produced with a distribution of molecular weights. To compare the molecular

weights of two different batches of polymer, it is useful to define an average molecular weight. Two statistically useful definitions of molecular weight are the number average and weight average molecular weights. The number average molecular weight (M_n) is the first moment of the molecular weight distribution and is an average over the number of molecules. The weight average molecular weight (M_w) is the second moment of the molecular weight distribution and is an average over the weight of each polymer chain. Equations 1 and 2 define the two averages:

$$M_n = \frac{\Sigma N_i M_i}{\Sigma N_i} \quad (1)$$

$$M_w = \frac{\Sigma N_i M_i^2}{\Sigma N_i M_i}, \quad (2)$$

where N_i is the number of moles of species i, and M_i is the molecular weight of species i.

The ratio of M_w to M_n is known as the polydispersity index and is used as a measure of the breadth of the molecular weight distribution. Typical commercial polymers have polydispersity indices of 1.5–50, although polymers with polydispersity indices of less than 1.1 can be synthesized with special techniques. A molecular weight distribution for a typical polymer is shown in Fig. 1.

Linear polymers used for biomedical applications generally have M_n in the range of 25,000 to 100,000 and M_w from 50,000 to 300,000. Higher or lower molecular weights may be necessary, depending on the ability of the polymer chains to exhibit secondary interactions such as hydrogen bonding. The secondary interactions can give polymers additional strength. In general, increasing molecular weight corresponds to increasing physical properties; however, since melt viscosity also increases with molecular weight, processibility will decrease and an upper limit of useful molecular weights is usually reached.

SYNTHESIS

Methods of polymer preparation fall into two categories: addition polymerization (chain reaction) and condensation polymerization (stepwise growth). In addition polymerization, unsaturated monomers react through the stages of initiation, propagation, and termination to give the final polymer product. The initiators can be free radicals, cations, anions, or stereospecific catalysts. The initiator opens the double bond of the monomer, presenting another "initiation" site on the opposite side of the monomer bond for continuing growth. Rapid chain growth ensues during the propagation step until the reaction is terminated by reaction with another radical, a solvent molecule, another polymer, an initiator, or an added chain transfer agent.

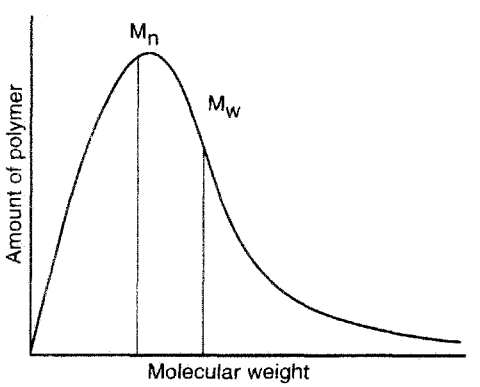


FIG. 1. Typical molecular weight distribution of a polymer.

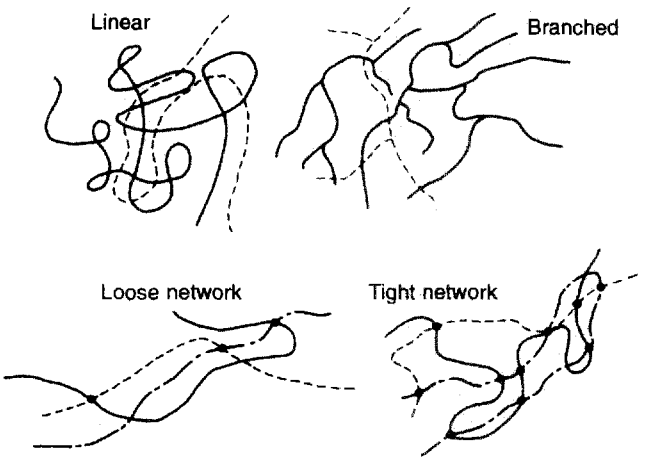


FIG. 2. Polymer arrangements. (From F. Rodriguez, *Principles of Polymer Systems*, Hemisphere Publ., 1982, p. 21, with permission.)

Condensation polymerization is completely analogous to condensation reactions of low-molecular-weight molecules. Two monomers react to form a covalent bond, usually with elimination of a small molecule such as water, hydrochloric acid, methanol, or carbon dioxide. The reaction continues until almost all of one type of reactant is used up.

The choice of polymerization method strongly affects the polymer obtained. In free radical polymerization, a type of addition polymerization, the molecular weights of the polymer chains are difficult to control with precision. Added chain transfer agents are used to control the average molecular weights, but molecular weight distributions are usually broad. In addition, chain transfer reactions with other polymer molecules in the batch can produce undesirable branched products (Fig. 2) that affect the ultimate properties of the polymeric material. In contrast, molecular architecture can be controlled very precisely in anionic polymerization. Regular linear chains with polydispersity indices of close to unity can be obtained.

Polymers produced by addition polymerization can be homopolymers—polymers containing only one type of repeat unit—or copolymers of two or more types of repeat units. Depending on the reaction conditions and the reactivity of each monomer type, the copolymers can be random, alternating, or block copolymers, as illustrated in Fig. 3. Random copolymers exhibit properties that approximate the weighted average of the two types of monomer units, whereas block copolymers

Homopolymer	–A–A–A–A–A–A–A–
Random copolymer	–A–B–B–A–B–A–B–
Alternating copolymer	–A–B–A–B–A–B–A–
Block copolymer	–A–A–A–A–B–B–B–

FIG. 3. Possible monomer arrangements in polymer materials.

tend to phase separate into a monomer-A-rich phase and a monomer-B-rich phase, displaying properties unique to each of the homopolymers.

Condensation polymerization can also result in copolymer formation. The properties of the condensation copolymer depend on three factors: the type of monomer units; the molecular weight of the polymer product, which can be controlled by the ratio of one reactant to another and by the time of polymerization; and the distribution of the molecular weight of the copolymer chains. The use of bifunctional monomers gives rise to linear polymers, while multifunctional monomers may be used to form covalently cross-linked networks.

Postpolymerization cross-linking of addition or condensation polymers is also possible. Natural rubber, for example, consists mostly of linear molecules that can be cross-linked to a loose network with 1–3% sulfur (vulcanization) or to a hard rubber with 40–50% sulfur (Fig. 2). In addition, physical, rather than chemical, cross-linking of polymers can be achieved in the presence of microscrystalline regions or through incorporation of ionic groups in the polymer (Fig. 4).

THE SOLID STATE

Tacticity

Polymers are long-chain molecules and, as such, are capable of assuming many conformations through rotation of valence bonds. The extended chain or planar zig-zag conformation of polypropylene is shown in Fig. 5. This figure illustrates the concept of tacticity. Tacticity refers to the arrangement of substituents (methyl groups in the case of polypropylene) around the extended polymer chain. Chains in which all substituents are located on the same side of the zigzag plane are isotactic, while syndiotactic chains have substituents alternating from side to side. In the atactic arrangement, the substituent groups appear at random on either side of the extended chain backbone.

Atactic polymers usually cannot crystallize, and an amorphous polymer results. Isotactic and syndiotactic polymers may crystallize if conditions are favorable. Crystalline polymers also possess a higher level of structure characterized by folded chain lamellar growth that results in the formation of spherulites. These structures can be visualized in a polarized light microscope.

Crystallinity

Polymers can be either amorphous or semicrystalline. They can never be completely crystalline owing to lattice defects that form disordered, amorphous regions. The tendency of a polymer to crystallize is enhanced by the small side groups and chain regularity. The presence of crystallites in the polymer usually leads to enhanced mechanical properties, unique thermal behavior, and increased fatigue strength. These properties make semicrystalline polymers (often referred to simply as crystalline polymers) desirable materials for biomedical applications.

Mechanical Properties

The tensile properties of polymers can be characterized by their deformation behavior (stress-strain response (Fig. 6). Amorphous, rubbery polymers are soft and reversibly extensible. The freedom of motion of the polymer chain is retained at a local level while a network structure resulting from chemical cross-links and chain entanglements prevents large-scale movement or flow. Thus, rubbery polymers tend to exhibit a lower modulus, or stiffness, and extensibilities of several hundred percent. Rubbery materials may also exhibit an increase of stress prior to breakage as a result of strain-induced crystallization assisted by molecular orientation in the direction of stress. Glassy and semicrystalline polymers have higher moduli and lower extensibilities.

The ultimate mechanical properties of polymers at large deformations are important in selecting particular polymers for biomedical applications. The ultimate strength of polymers is the stress at or near failure. For most materials, failure is catastrophic (complete breakage). However, for some semicrystalline materials, the failure point may be defined by the stress point where large inelastic deformation starts (yielding). The toughness of a polymer is related to the energy absorbed at failure and is proportional to the area under the stress-strain curve.

The fatigue behavior of polymers is also important in evaluating materials for applications where dynamic strain is applied. For example, polymers that are used in the artificial heart must be able to withstand many cycles of pulsating motion before failure. Samples that are subjected to repeated cycles of stress and release, as in a flexing test, fail (break) after a certain number of cycles. The number of cycles to failure decreases as the applied stress level is increased, as shown in Fig. 7 (see also Chapter 6.4). For some materials, a minimum stress exists below which failure does not occur in a measurable number of cycles.

Thermal Properties

In the liquid or melt state, a noncrystalline polymer possesses enough thermal energy for long segments of each polymer to move randomly (Brownian motion). As the melt is cooled, the temperature is eventually reached at which all long-range segmental motions cease. This is the glass transition temperature (T_g), and it varies from polymer to polymer. Poly-

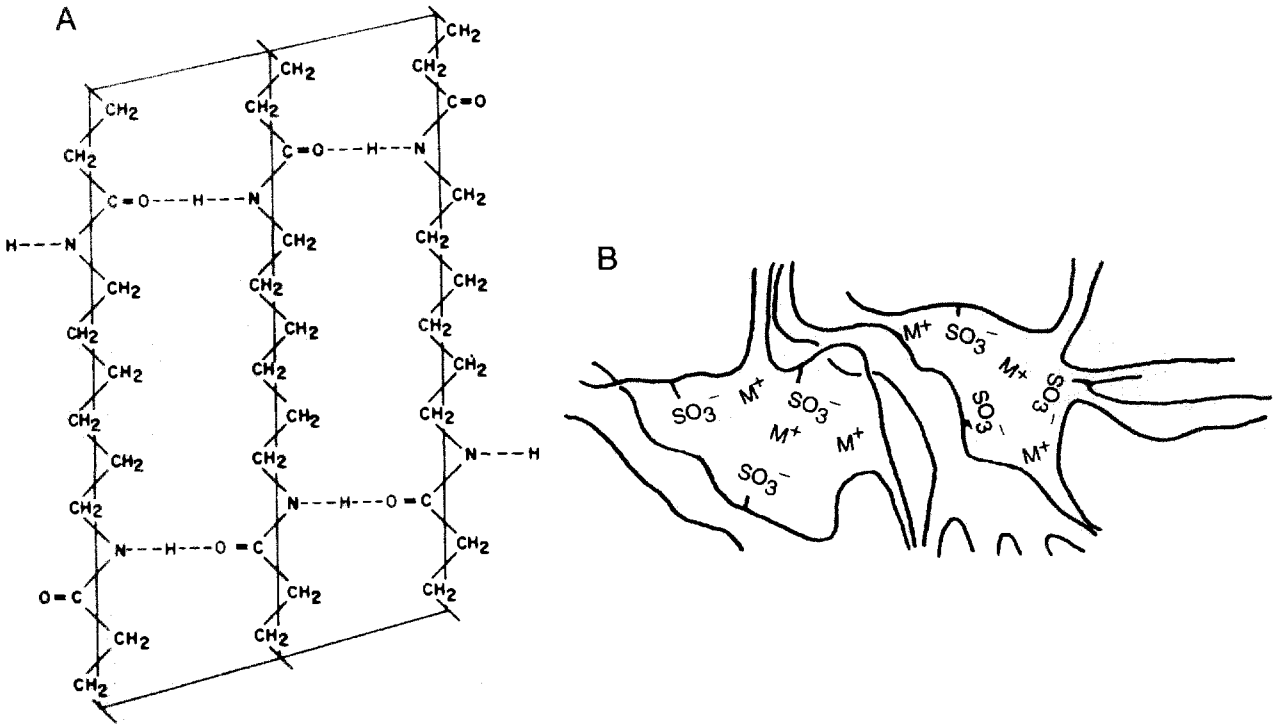


FIG. 4. (A) Hydrogen bonding in nylon 6,6 molecules in a triclinic unit cell: α-form. (From L. Mandelkern, *An Introduction to Macromolecules*, Springer-Verlag, 1983, p. 43, with permission.) (B) Ionic aggregation giving rise to physical cross-links in ionomers.

mers used below their T_g tend to be hard and glassy, while polymers used above their T_g are rubbery. Polymers with any crystallinity will also exhibit a melting temperaure (T_m) owing to melting of the crystalline phase. Thermal transitions in polymers can be measured by differential scanning calorimetry (DSC), as discussed in the section on characterization techniques.

The viscoelastic responses of polymers can also be used to classify their thermal behavior. The modulus versus temperature curves shown in Fig. 8 illustrate behaviors typical of linear amorphous, cross-linked, and semicrystalline polymers. The response curves are characterized by a glassy modulus below T_g of approximately 3×10^9 Pa. For linear amorphous polymers, increasing temperature induces the onset of the glass transition region where, in a 5–10°C temperature span, the modulus drops by three orders of magnitude, and the polymer is transformed from a stiff glass to a leathery material. The relatively

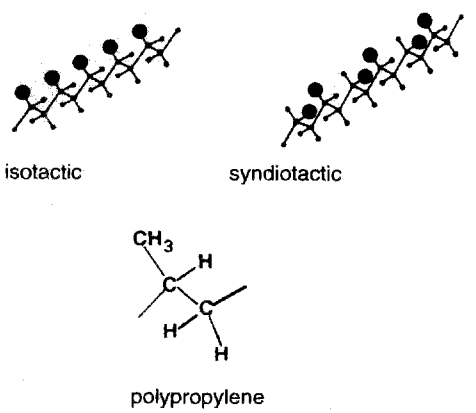


FIG. 5. Schematic of stereoisomers of polypropylene. (From F. Rodriguez *Principles of Polymer Systems*, Hemisphere Publ., 1982, p. 22, with permission.)

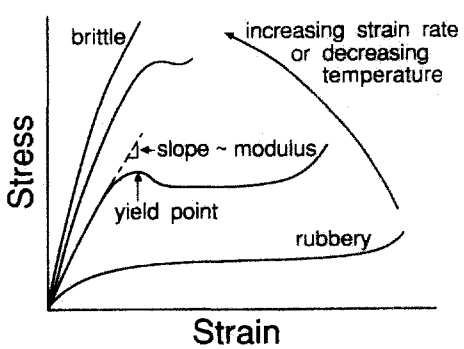


FIG. 6. Tensile properties of polymers.

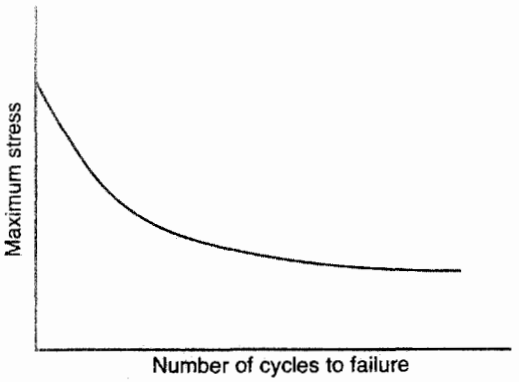


FIG. 7. Fatigue properties of polymers.

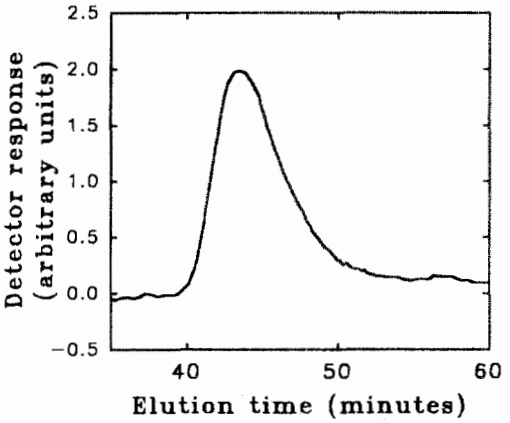


FIG. 9. A typical trace from a gel permeation chromatography run for a poly(tetramethylene oxide)/toluene diisocyanate-based polyurethane. The response of the ultraviolet detector is directly proportional to the amount of polymer eluted at each time point.

constant modulus region above T_g is the rubbery plateau region where long-range segmental motion is occurring but thermal energy is insufficient to overcome entanglement interactions that inhibit flow. This is the target region for many biomedical applications. Finally, at high enough temperatures, the polymer begins to flow, and a sharp decrease in modulus is seen over a narrow temperature range.

Crystalline polymers exhibit the same general features in modulus versus temperature curves as amorphous polymers; however, crystalline polymers possess a higher plateau modulus owing to the reinforcing effect of the crystallites. Crystalline polymers tend to be tough, ductile plastics whose properties are sensitive to processing history. When heated above their flow point, they can be melt processed and will become rigid again upon cooling.

Chemically cross-linked polymers exhibit modulus versus temperature behavior analogous to that of linear amorphous polymers until the flow regime is approached. Unlike linear polymers, chemically cross-linked polymers do not display flow behavior; the cross links inhibit flow at all temperatures below the degradation temperature. Thus, chemically cross-linked polymers cannot be melt processed. Instead, these materials are processed as reactive liquids or high-molecular-weight amorphous gums that are cross-linked during molding to give the desired product.

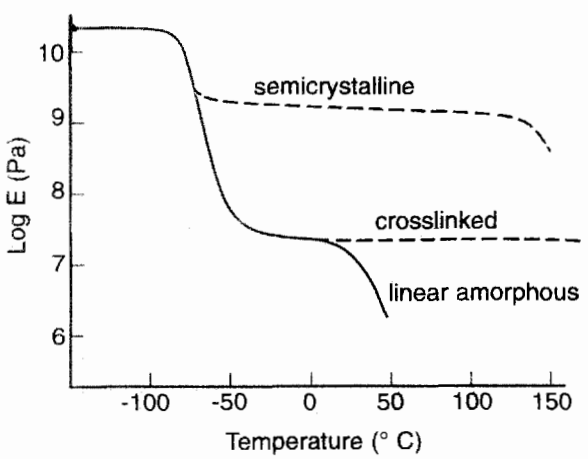


FIG. 8. Dynamic mechanical behavior of polymers.

Copolymers

In contrast to the thermal behavior of homopolymers discussed earlier, copolymers can exhibit a number of additional thermal transitions. If the copolymer is random, it will exhibit a T_g that approximates the weighted average of the T_gs of the two homopolymers. Block copolymers of sufficient size and incompatible block types will exhibit T_gs characteristic of each homopolymer but slightly shifted owing to incomplete phase separation.

CHARACTERIZATION TECHNIQUES

Determination of Molecular Weight

Gel permeation chromatography (GPC), a type of size exclusion chromatography, involves passage of a dilute polymer solution over a column of porous beads. High-molecular-weight polymers are excluded from the beads and elute first whereas lower molecular weight molecules pass through the pores of the bead, increasing their elution time. By monitoring the effluent of the column as a function of time using an ultraviolet or refractive index detector, the amount of polymer eluted during each time interval can be determined. Comparison of the elution time of the samples with those of monodisperse samples of known molecular weight allows the entire molecular weight distribution to be determined. A typical GPC trace is shown in Fig. 9.

Osmotic pressure measurements can be used to measure M_n. The principle of membrane osmometry is illustrated in

Fig. 10. A semipermeable membrane is placed between two chambers. Only solvent molecules flow freely through the membrane. Pure solvent is placed in one chamber, and a dilute polymer solution of known concentration is placed in the other chamber. The lowering of the activity of the solvent in solution with respect to that of the pure solvent is compensated by applying a pressure π on the solution. π is the osmotic pressure and is related to M_n by:

$$\frac{\pi}{c} = RT\left[\frac{1}{M_n} + A_2c + A_3c^2 + \cdots\right], \tag{3}$$

where c is the concentration of the polymer in solution, R is the gas constant, T is temperature, and A_2 and A_3 are virial coefficients relating to pairwise and triplet interactions of the molecules in solution. In general, a number of polymer solutions of decreasing concentration are prepared, and the osmotic pressure is extrapolated to zero:

$$\lim_{c\to 0}\frac{\pi}{c} = \frac{RT}{M_n}. \tag{4}$$

A plot of π/c versus c then gives as its intercept the number average molecular weight.

A number of other techniques, including vapor pressure osmometry, ebulliometry, cryoscopy, and end-group analysis can be used to determine the M_n of polymers up to molecular weights of about 40,000.

Light-scattering techniques are used to determine M_w. In dilute solution, the scattering of light is directly proportional to the number of molecules. The scattered intensity i_o observed at a distance r and an angle θ from the incident beam I_o is characterized by Rayleigh's ratio R_θ:

$$R_\theta = \frac{i_o r^2}{I_o}. \tag{5}$$

The Rayleigh ratio is related to M_w by:

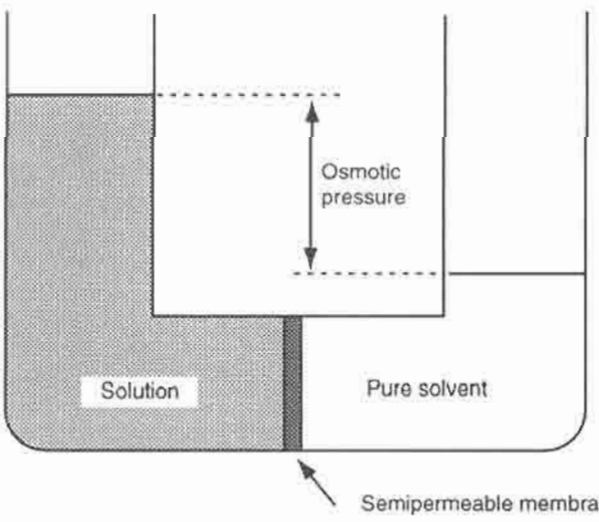


FIG. 10. The principle of operation of a membrane osmometer.

$$\frac{K_c}{R_\theta} = \frac{1}{M_w} + 2A_2c + 3A_2c^2 + \cdots. \tag{6}$$

A number of solutions of varying concentrations are measured, and the data are extrapolated to zero concentration to determine M_w.

Determination of Structure

Infrared (IR) spectroscopy is often used to characterize the chemical structure of polymers. Infrared spectra are obtained by passing infrared radiation through the sample of interest and observing the wavelength of the absorption peaks. These peaks are caused by the absorption of the radiation and its conversion into specific motions, such as C–H stretching. The infrared spectrum of a polyurethane is shown in Fig. 11, with a few of the bands of interest marked.

Nuclear magnetic resonance (NMR), in which the magnetic spin energy levels of nuclei of spin 1/2 or greater are probed, may also be used to analyze chemical composition. NMR is also used in a number of more specialized applications relating to local motions of polymer molecules.

Wide-angle X-ray scattering (WAXS) techniques are useful for probing the local structure of a semicrystalline polymeric solid. Under appropriate conditions, crystalline materials diffract X-rays, giving rise to spots or rings. According to Bragg's law, these can be interpreted as interplanar spacings. The interplanar spacings can be used without further manipulation or the data can be fit to a model such as a disordered helix or an extended chain. The crystalline chain conformation and atomic placements can then be accurately inferred.

Small-angle X-ray scattering (SAXS) is used in determining the structure of many multiphase materials. This technique requires an electron density difference to be present between two components in the solid and has been widely applied to morphological studies of copolymers and ionomers. It can probe features of 10–1000 Å in size. With appropriate modeling of the data, SAXS can give detailed structural information unavailable with other techniques.

Electron microscopy of thin sections of a polymeric solid can also give direct morphological data on a polymer of interest, assuming that (1) the polymer possesses sufficient electron density contrast or can be appropriately stained without changing the morphology and (2) the structures of interest are sufficiently large.

Mechanical and Thermal Property Studies

In stress-strain or tensile testing, a dog bone-shaped polymer sample is subjected to a constant elongation, or strain, rate, and the force required to maintain the constant elongation rate is monitored. As discussed earlier, tensile testing gives information about modulus, yield point, and ultimate strength of the sample of interest.

Dynamic mechanical analysis (DMA) provides information about the small deformation behavior of polymers. Samples are subjected to cyclic deformation at a fixed frequency in the range of 1–1000 Hz. The stress response is measured while the

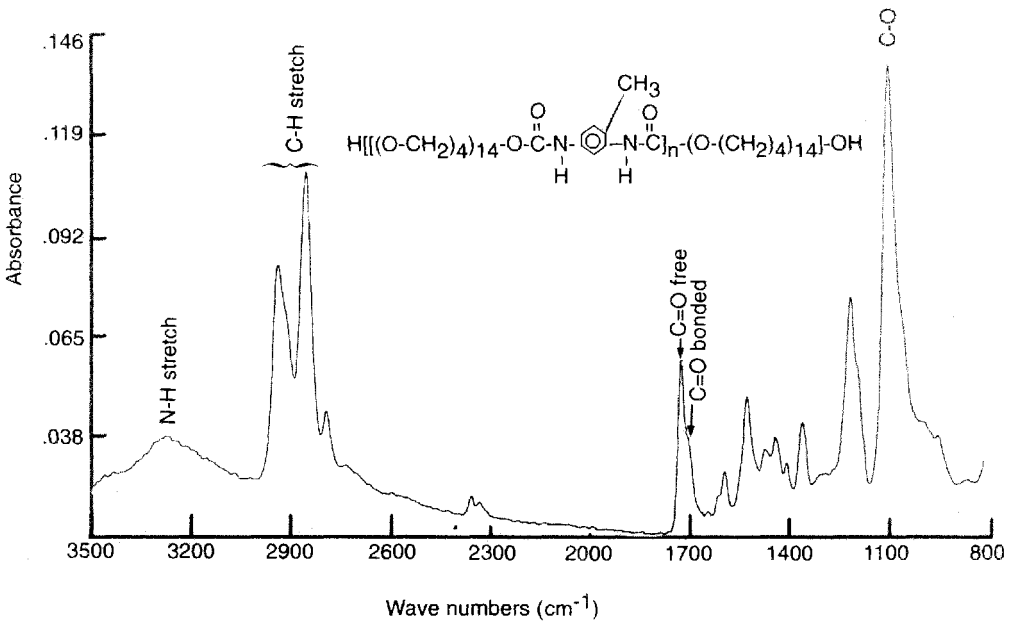


FIG. 11. Infrared spectrum of a poly(tetramethylene oxide)/toluene diisocyanate-based polyurethane.

cyclic strain is applied and the temperature is slowly increased (typically at 2–3°/min). If the strain is a sinusoidal function of time given by:

$$\varepsilon(\omega) = \varepsilon_0 \sin(\omega t), \tag{7}$$

where ε is the time-dependent strain, ε_0 is the strain amplitude, ω is the frequency of oscillation, and t is time, the resulting stress can be expressed by:

$$\sigma(\omega) = \sigma_0 \sin(\omega t + \delta), \tag{8}$$

where σ is the time-dependent stress, σ_0 is the amplitude of stress response, and δ is the phase angle between stress and strain. For Hookean solids, the stress and strain are completely in phase ($\delta = 0$), while for purely viscous liquids, the stress response lags by 90°. Real materials demonstrate viscoelastic behavior where δ has a value between 0° and 90°.

A typical plot of tan δ versus temperature will display maxima at T_g and at lower temperatures where small-scale motions (secondary relaxations) can occur. Additional peaks above T_g, corresponding to motions in the crystalline phase and melting, are seen in semicrystalline materials. DMA is a sensitive tool for characterizing polymers of similar chemical composition or for detecting the presence of moderate quantities of additives.

Differential scanning calorimetry is another method for probing thermal transitions of polymers. A sample cell and a reference cell are supplied energy at varying rates so that the temperatures of the two cells remain equal. The temperature is increased, typically at a rate of 10–20°/min over the range of interest, and the energy input required to maintain equality of temperature in the two cells is recorded. Plots of energy supplied versus average temperature allow determination of T_g, crystallization temperature (T_c), and T_m. T_g is taken as the temperature at which one half the change in heat capacity, ΔCp, has occurred. The T_c and T_m are easily identified, as shown in Fig. 12. The areas under the peaks can be quantitatively related to enthalpic changes.

Surface Characterization

Surface characteristics of polymers for biomedical applications are critically important. The surface composition is inevi-

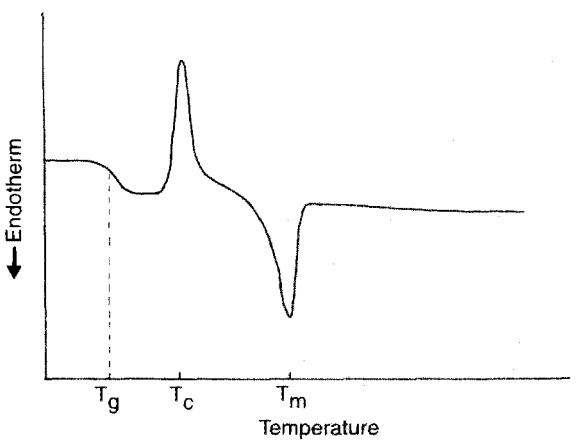
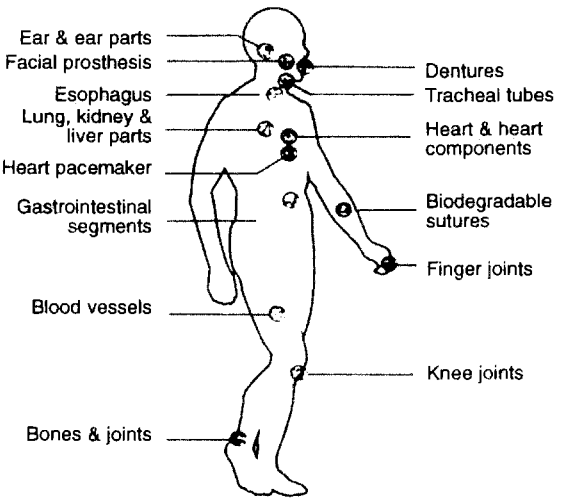


FIG. 12. Differential scanning calorimetry thermogram of a semicrystalline polymer.



Ear & ear parts: acrylic, polyethylene, silicone, poly(vinyl chloride) (PVC)
Dentures: acrylic, ultrahigh molecular weight polyethylene (UHMWPE), epoxy
Facial prosthesis: acrylic, PVC, polyurethane (PUR)
Tracheal tubes: acrylic, silicone, nylon
Heart & heart components: polyester, silicone, PVC
Heart pacemaker: polyethylene, acetal
Lung, kidney & liver parts: polyester, polyaldehyde, PVC
Esophagus segments: polyethylene, polypropylene (PP), PVC
Blood vessels: PVC, polyester
Biodegradable sutures: PUR
Gastrointestinal segments: silicones, PVC, nylon
Finger joints: silicone, UHMWPE
Bones & joints: acrylic, nylon, silicone, PUR, PP, UHMWPE
Knee joints: polyethylene

FIG. 13. Common clinical applications and types of polymers used in medicine. (From D. V. Rosato, in *Biocompatible Polymers, Metals, and Composites*, M. Szycher, ed., Technomic Publ., 1983, p. 1022, with permission.)

tably different from the bulk, and the surface of the material is generally all that is contacted by the body. The main surface characterization techniques for polymers are X-ray photoelectron spectroscopy (XPS), contact angle measurements, attenuated total reflectance Fourier transform infrared (ATR–FTIR) spectroscopy, and scanning electron microscopy (SEM). The techniques are discussed in detail in Chapter 1.3.

CLASSES OF POLYMERS USED IN MEDICINE

Many types of polymers are used for biomedical purposes. Figure 13 illustrates the variety of clinical applications for polymeric biomaterials. This section discusses some of the polymers used in medicine.

Homopolymers

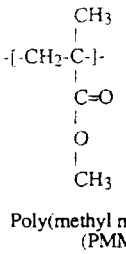
Homopolymers are composed of a single type of monomer. Figure 14 shows the repeat units of many of the homopolymers used in medicine.

Poly(methyl methacrylate) (PMMA) is a hydrophobic, linear chain polymer that is glassy at room temperature and may be more easily recognized by such trade names as Lucite or Plexiglas. It has very good light transmittance, toughness, and stability, making it a good material for intraocular lenses and hard contact lenses.

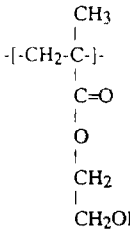
Soft contact lenses are made from the same family of polymers, with the addition of a $—CH_2OH$ group to the methyl methacrylate side group, resulting in 2-hydroxyethyl methacrylate (HEMA). The additional methylol group causes the polymer to be hydrophilic. For soft contact lenses, the poly(HEMA) is slightly cross-linked with ethylene glycol dimethyacrylate (EGDM) to prevent the polymer from dissolving when it is hydrated (Rodriguez, 1982). Fully hydrated, it is a swollen hydrogel. This class of polymers is discussed in more detail in Chapter 2.4.

Polyethylene (PE) is used in its high-density form in biomedical applications because low-density material cannot withstand sterilization temperatures. It is used in tubing for drains and catheters, and in very high-molecular-weight form as the acetabular component in artificial hips. The material has good toughness, resistance to fats and oils, and a relatively low cost.

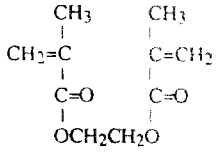
Polypropylene (PP) is closely related to PE and has high rigidity, good chemical resistance, and good tensile strength.



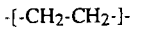
Poly(methyl methacrylate)
(PMMA)



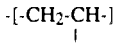
Poly(2-hydroxyethyl
methacrylate)
poly(HEMA)



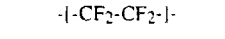
Ethylene glycol
dimethacrylate
(EGDM)



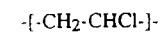
Polyethylene
(PE)



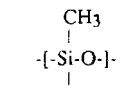
Polypropylene
(PP)



Poly(tetrafluoroethylene)
(PTFE)

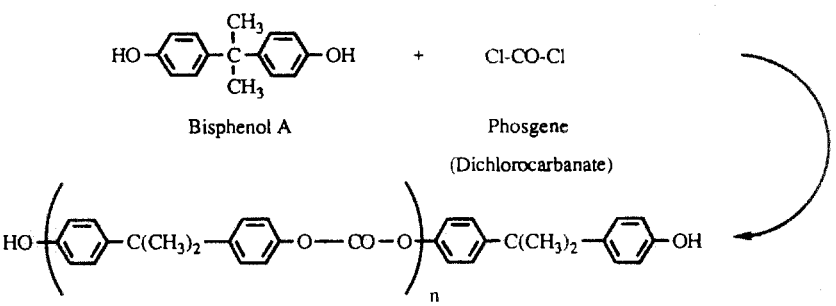


Poly(vinyl chloride)
(PVC)



Poly(dimethyl siloxane)
(PDMS)

Polycarbonate

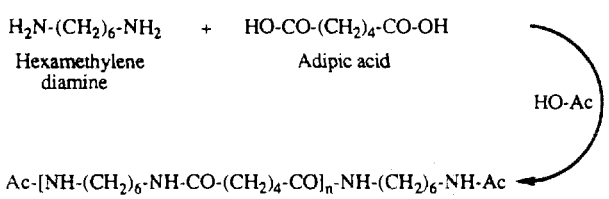


Bisphenol A

Phosgene
(Dichlorocarbanate)

Polycarbonate

Nylon



Hexamethylene
diamine

Adipic acid

Nylon 6,6

FIG. 14. Homopolymers used in medicine.

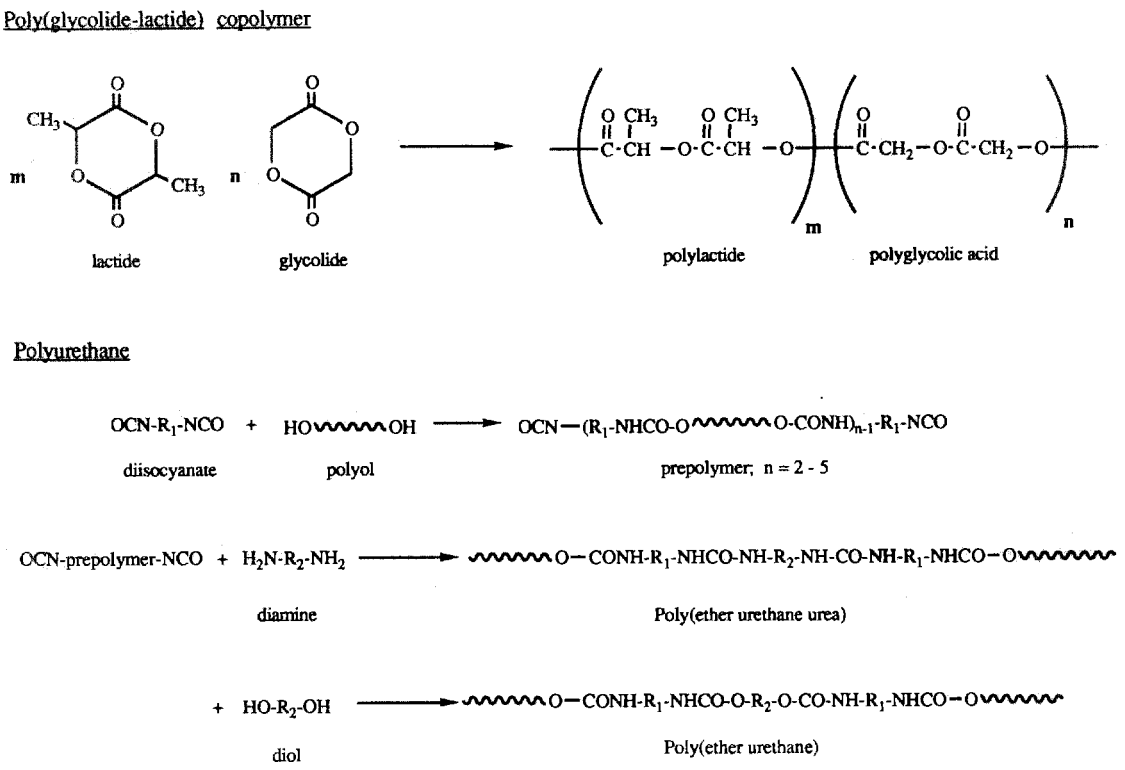


FIG. 15. Copolymers and their base monomers used in medicine.

Its stress cracking resistance is superior to that of PE, and it is used for many of the same applications as PE.

Poly(tetrafluoroethylene) (PTFE), also known as Teflon, has the same structure as PE, except that the hydrogen in PE is replaced by fluorine. PTFE is a very stable polymer, both thermally and chemically, and as a result it is very difficult to process. It is very hydrophobic and has excellent lubricity. In microporous (Gore-Tex) form, it is used in vascular grafts.

Poly(vinyl chloride) (PVC) is used mainly in tubing in biomedical applications. Typical tubing uses include blood transfusion, feeding, and dialysis. Pure PVC is a hard, brittle material, but with the addition of plasticizers, it can be made flexible and soft. PVC can pose problems for long-term applications because the plasticizers can be extracted by the body. While these plasticizers have low toxicities, their loss makes the PVC less flexible.

Poly(dimethyl siloxane) (PDMS) is an extremely versatile polymer. It is unique in that it has a silicon-oxygen backbone instead of a carbon backbone. Its properties are less temperature sensitive than other rubbers because of its lower T_g. PDMS is used in catheter and drainage tubing, in insulation for pacemaker leads, and as a component in some vascular graft systems. It is used in membrane oxygenators because of its high oxygen permability. Because of its excellent flexibility and stability, it is also used in a variety of prostheses such as finger joints, blood vessels, heart valves, breast implants, outer ears, and chin and nose implants (Rosato, 1983).

Polymerization of bisphenol A and phosgene produces polycarbonate, a clear, tough material. Its high impact strength dictates its use as lenses for eyeglasses and safety glasses, and housings for oxygenators and heart-lung bypass machine.

Nylon is the name given by Du Pont to a family of polyamides. Nylons are formed by the reaction of diamines with dibasic acids or by the ring opening polymerization of lactams. Nylons are used in surgical sutures.

Copolymers

Copolymers are another important class of biomedical materials. Fig. 15 shows two different copolymers used in medicine. Poly(glycolide lactide) (PGL) is a random copolymer used in resorbable surgical sutures. PGL polymerization occurs via a ring-opening reaction of a glycolide and a lactide, as illustrated in Fig. 15. The presence of ester linkages in the polymer backbone allows gradual hydrolytic degradation (resorption). In contrast to the natural resorbable suture material poly(glycolic acid), or catgut, a homopolymer, the PGL copolymer retains more of its strength over the first 14 days after implantation (Chu, 1983).

A copolymer of tetrafluoroethylene and hexafluoropropylene (FEP) is used in many applications similar to those of PTFE. FEP has a crystalline melting point near 265°C compared with 327°C for PTFE. This enhances the processibility of FEP compared with PTFE while maintaining the excellent chemical inertness and low friction characteristic of PTFE.

Polyurethanes are block copolymers containing "hard" and "soft" blocks. The "hard" blocks, having T_gs above room temperature and acting as glassy or semicrystalline reinforcing blocks, are composed of a diisocyanate and a chain extender. The diisocyanates most commonly used are 2,4-toluene diisocyanate (TDI) and methylene di(4-phenyl isocyanate) (MDI), with MDI being used in most biomaterials. The chain extenders are usually shorter aliphatic glycol or diamine materials with 2–6 carbon atoms. The "soft" blocks in polyurethanes are typically polyether or polyester polyols whose T_gs are much less than room temperature, allowing them to give a rubbery character to the materials. Polyether polyols are more commonly used for implantable devices because they are stable to hydrolysis. The polyol molecular weights tend to be on the order of 1000 to 2000.

Polyurethanes are tough elastomers with good fatigue and blood-containing properties. They are used in pacemaker lead insulation, vascular grafts, heart assist balloon pumps, and artificial heart bladders.

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2.4 HYDROGELS

Nikolaos A. Peppas

Hydrogels are water-swollen, cross-linked polymeric structures produced by the simple reaction of one or more monomers or by association bonds such as hydrogen bonds and strong van der Waals interactions between chains (Peppas, 1987). Hydrogels have received significant attention, especially in the past 30 years, because of their exceptional promise in biomedical applications. The classic book by Andrade (1976) offers some of the best work that was available prior to 1975. The more recent book by Peppas (1987) addresses the preparation, structure, and characterization of hydrogels. In this chapter, we concentrate on some features of the preparation of hydrogels, as well as characteristics of their structure and chemical and physical properties.

CLASSIFICATION AND BASIC STRUCTURE

Hydrogels may be classified in several ways, depending on their method of preparation, ionic charge, or physical structure features. Based on the method of preparation, they are (1) homopolymer hydrogels, (2) copolymer hydrogels, (3) multipolymer hydrogels, and (4) interpenetrating polymeric hydrogels. Homopolymer hydrogels are cross-linked networks of one type of hydrophilic monomer unit, whereas copolymer hydrogels are produced by cross-linking of two comonomer units, one of which must be hydrophilic. Multipolymer hydrogels are produced from three or more comonomers reacting together. Finally, interpenetrating polymeric hydrogels are produced by swelling a first network in a monomer and reacting the latter to form a second intermeshing network structure. Based on their ionic charges, hydrogels may be classified (Ratner and Hoffman, 1976) as (1) neutral hydrogels, (2) anionic hydrogels, (3) cationic hydrogels, and (4) ampholytic hydrogels. Based on physical structural features of the system, they can be classified as (1) amorphous hydrogels, (2) semicrystalline hydrogels, and (3) hydrogen-bonded structures. In amorphous hydrogels, the macromolecular chains are randomly arranged, whereas semicrystalline hydrogels are characterized by dense regions of ordered macromolecular chains (crystallites). Often, hydrogen bonds may be responsible for the three-dimensional structure formed.

Structural evaluation of hydrogels reveals that ideal networks are only rarely observed. Figure 1a shows an ideal macromolecular network (hydrogel) indicating tetrafunctional cross-links (junctions) produced by covalent bonds. However, the possibility exists of multifunctional junctions (Fig. 1b) or physical molecular entanglements (Fig. 1c) playing the role of semipermanent junctions. Hydrogels with molecular defects are always possible. Figures 1d and 1e indicate two such effects: unreacted functionalities with partial entanglements (Fig. 1d) and chain loops (Fig. 1e). Neither of these effects contributes to the mechanical or physical properties of a polymer network.

The terms "junction" and "cross-link" (an open circle symbol in Fig. 1d) indicate the connection points of several chains. This junction may be ideally a carbon atom, but it is usually a small chemical bridge [e.g., an acetal bridge in the case of poly(vinyl alcohol)] of molecular weight much smaller than that of the cross-linked polymer chains. In other situations, a junction may be an association of macromolecular chains caused by van der Waals forces, as in the case of the glycoproteinic network structure of natural mucus, or an aggregate

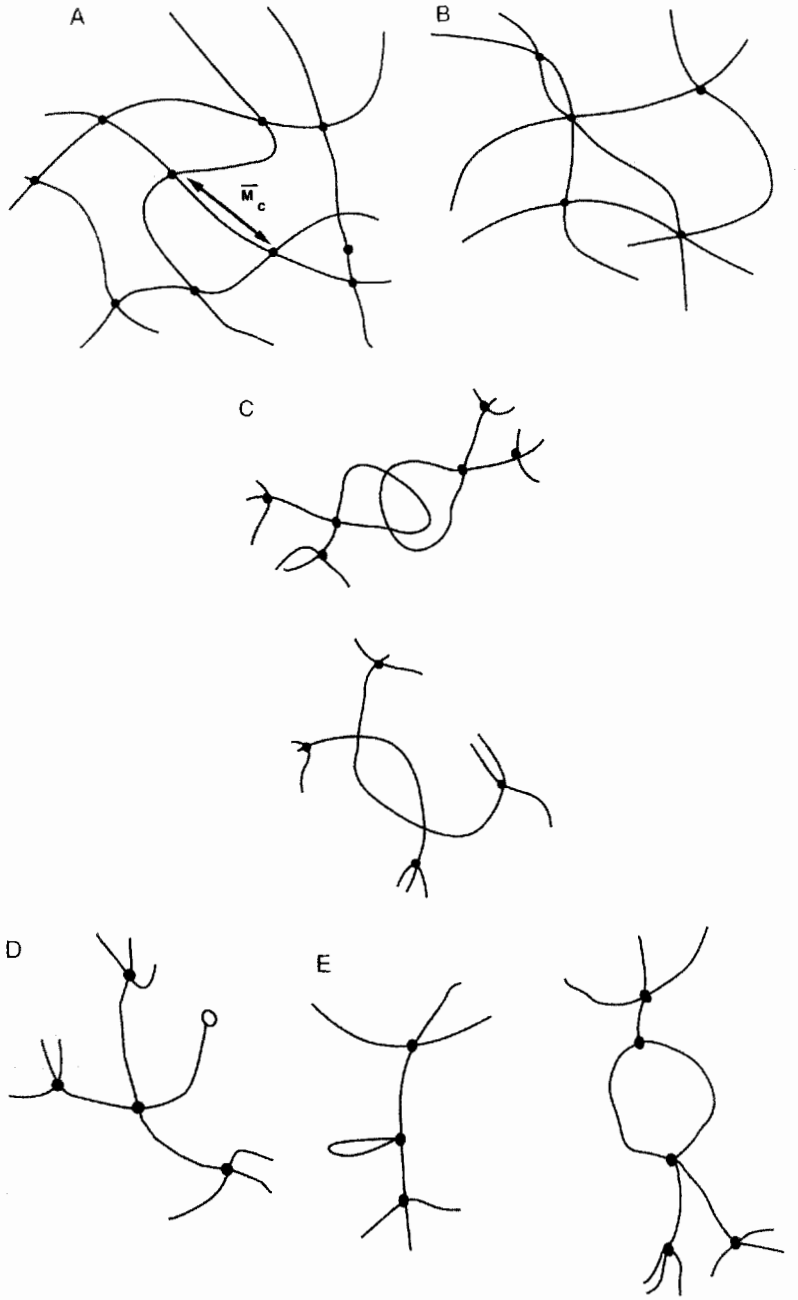

FIG. 1. (A) Ideal macromolecular network of a hydrogel. (B) Network with multifunctional junctions. (C) Physical entanglements in a hydrogel. (D) Unreacted functionality in a hydrogel. (E) Chain loops in a hydrogel.

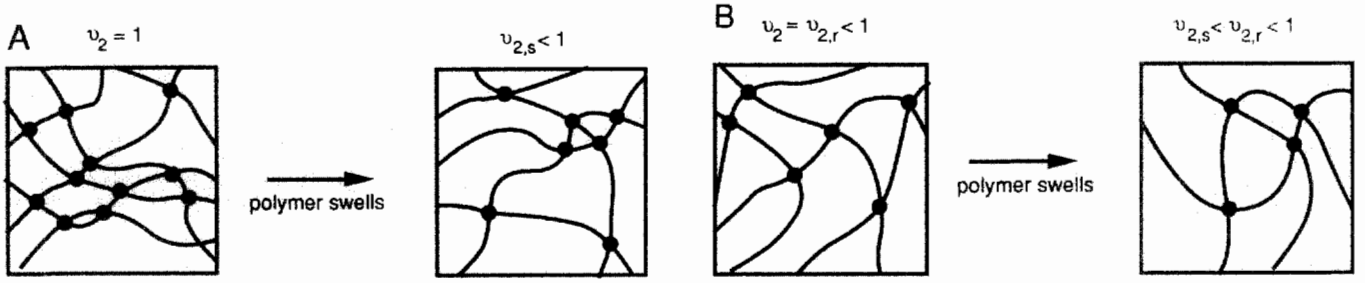

FIG. 2. (A) Swelling of a network prepared by cross-linking in dry state. (B) Swelling of a network prepared by cross-linking in solution.

formed by hydrogen bonds, as in the case of aged microgels formed in polymer solutions.

Finally, the structure may include effective junctions that can be either simple, physical entanglements of permanent or semipermanent nature, or ordered chains forming crystallites. Thus, the junctions should never be considered as a "volumeless point," the usual depiction applied when developing structural models for analysis of the cross-linked structure of hydrogels (Flory, 1953).

PREPARATION

Hydrogels are prepared by swelling cross-linked structures in water or biological fluids containing large amounts of water. In many situations, the water may be present during the initial formation of the cross-linked structure. There are many methods of preparing cross-linked hydrogels, such as irradiative cross-linking and chemical reactions.

Radiation reactions (Chapiro, 1962) utilize electron beams, gamma-rays, X-rays, or ultraviolet light to excite a polymer and produce a cross-linked structure. Chemical cross-linking requires the use of at least one difunctional, small-molecular-weight, cross-linking agent. This agent usually links two longer molecular weight chains through its di- or multifunctional groups. The second method is a copolymerization–cross-linking reaction between one or more abundant monomers and one multifunctional monomer that is present in very small quantities. A third variation of these techniques involves using a combination of monomer and linear polymeric chains that are cross-linked by means of an interlinking agent, as in the production of polyurethanes.

SWELLING BEHAVIOR

An integral part of the physical behavior of hydrogels is their swelling behavior in water, since upon preparation they must be brought in contact with water to yield the final, solvated network structure. Figure 2 shows one of the two possible processes of swelling. A dry, hydrophilic cross-linked network is placed in water. Then, the macromolecular chains interact with the solvent molecules owing to the relatively good thermodynamic compatibility. Thus, the network expands to the solvated state. The Flory–Huggins theory can be used to calculate thermodynamic quantities related to that mixing process (Flory, 1953).

This thermodynamic swelling force is counterbalanced by the retractive force of the cross-linked structure. The latter is usually described by the Flory rubber elasticity theory and its variations (Flory, 1953). Equilibrium is attained in a particular solvent at a particular temperature when the two forces become equal. The volume degree of swelling, Q (i.e., the ratio of the actual volume of a sample in the swollen state divided by its volume in the dry state) can then be determined.

Several researchers working with hydrogels, especially for biomedical applications, prefer to use other parameters to define the equilibrium swelling behavior. For example, Yasuda *et al.* (1969) propagated the use of the so-called hydration ratio, H, which has been accepted by those researchers who use hydrogels for contact lenses. Another definition is that of the weight degree of swelling, q, which is the ratio of the weight of the swollen sample over that of the dry sample (Flory, 1953).

In general, highly swollen hydrogels are those of cellulose derivatives, poly(vinyl alcohol), poly(*N*-vinyl 2-pyrrolidone) (PNVP), and poly(ethylene glycol), among others. Moderately and poorly swollen hydrogels are those of poly(hydroxyethyl methacrylate) (PHEMA) and many of its derivatives. Of course, one may copolymerize a basic hydrophilic monomer with other more or less hydrophilic monomers to achieve desired swelling properties.

Such processes have led to a wide range of swellable hydrogels, as Gregonis *et al.* (1976), Peppas (1987), and others have pointed out. Knowledge of the swelling characteristics of a polymer is of utmost importance in biomedical and pharmaceutical applications since the equilibrium degree of swelling influences (1) the solute diffusion coefficient through these hydrogels, (2) the surface properties and surface mobility, (3) the optical properties, especially in relation to contact lens applications, and (4) the mechanical properties.

DETERMINATION OF STRUCTURAL CHARACTERISTICS

The parameter that describes the basic structure of the hydrogel is the molecular weight between cross-links, $\overline{M}_c$, as shown in Figure 1a. This parameter defines the average molecular size between two consecutive junctions regardless of the

nature of those junctions. Additional parameters of importance in structural analysis of hydrogels are the cross-linking density, ρ_x, which is defined by Eq. 1, and the effective number of cross-links, ν_e, per original chain (Eq. 2).

$$\rho_x = \frac{1}{\bar{v}\overline{M}_c} \tag{1}$$

$$\nu_e = \left(\frac{\overline{M}_n}{\overline{M}_c}\right) - 1 \tag{2}$$

In these equations, $\bar{v}$ is the specific volume of the polymer (i.e., the reciprocal of the amorphous density of the polymer), and $\overline{M}_n$ is the initial molecular weight of the uncross-linked polymer.

PROPERTIES OF SOME BIOMEDICALLY AND PHARMACEUTICALLY IMPORTANT HYDROGELS

The multitude of hydrogels available leaves numerous choices for polymeric formulations. The best approach for developing a hydrogel with the desired characteristics is to correlate the macromolecular structures of the polymers available with the swelling and mechanical characteristics desired.

The most widely used hydrogel is water-swollen, cross-linked PHEMA, which was introduced as a biological material by Wichterle and Lim (1960). The PHEMA structure permits a water content similar to living tissue. The hydrogel is inert to normal biological processes, shows resistance to degradation, is permeable to metabolites, is not absorbed by the body, withstands heat sterilization without damage, and can be prepared in a variety of shapes and forms.

The swelling, mechanical, diffusional, and biomedical characteristics of PHEMA gels have been studied extensively. The properties of these hydrogels are dependent upon their method of preparation, polymer volume fraction, degree of cross-linking, temperature, and swelling agent.

Other hydrogels of biomedical interest include polyacrylamides. Tanaka (1979) has done extensive studies on the abrupt swelling and deswelling of partially hydrolyzed acrylamide gels with changes in swelling agent composition, curing time, degree of cross-linking, degree of hydrolysis, and temperature. These studies have shown that the ionic groups produced in an acrylamide gel upon hydrolysis give the gel a structure that shows a discrete transition in equilibrium swollen volume with environmental changes.

Discontinuous swelling in partially hydrolyzed polyacrylamide gels has been studied by Gehrke *et al.* (1986). They have utilized polyacrylamide gels in gel extraction processes as a method of concentrating dilute aqueous solutions. The solution to be concentrated is added to a small, unswollen gel particle. These gels then swell in water, often up to six times their original weight. The concentrated solution is then withdrawn from around the gel. Acid is added to shrink the gel and release the water; the gel particles are removed and treated with base; and the process is repeated. These gels may be used repeatedly for the same extraction process.

Besides HEMA and acrylamides, *N*-vinyl-2-pyrrolidone (NVP), methacrylic acid (MAA), methyl methacrylate (MMA), and maleic anhydride (MAH) have all been proven useful as monomers for hydrogels in biomedical applications. For instance, PNVP is used in soft contact lenses. Small amounts of MAA as a comonomer have been shown to dramatically increase the swelling of PHEMA polymers. Owing to the hydrophobic nature of MMA, copolymers of MMA and HEMA have a lower degree of swelling then pure PHEMA (Brannon-Peppas and Peppas, 1991). All of these materials have potential use in advanced technology applications, including biomedical separations, and biomedical and pharmaceutical devices.

APPLICATIONS

The physical properties of hydrogels make them attractive for a variety of biomedical and pharmaceutical applications. Their biocompatibility allows them to be considered for medical applications, whereas their hydrophilicity can impart desirable release characteristics to controlled and sustained release formulations.

Hydrogels exhibit properties that make them desirable candidates for biocompatible and blood-compatible biomaterials (Merrill *et al.*, 1987). Nonionic hydrogels for blood contact applications have been prepared from poly(vinyl alcohol), polyacrylamides, PNVP, PHEMA, and poly(ethylene oxide). Heparinized polymer hydrogels also show promise as materials for blood-compatible applications (Sefton, 1987).

One of the earliest biomedical applications of hydrogels was in contact lenses (Tighe 1976; Peppas and Yang, 1981) because of their relatively good mechanical stability, favorable refractive index, and high oxygen permeability.

Other applications of hydrogels include (Peppas, 1987) artificial tendon materials, wound-healing bioadhesives, artificial kidney membranes, articular cartilage, artificial skin, maxillofacial and sexual organ reconstruction materials, and vocal cord replacement materials.

Pharmaceutical hydrogel applications have become very popular in recent years. Pharmaceutical hydrogel systems can be classified into various types. The category of **equilibrium-swollen hydrogels** includes matrices that have a drug incorporated in them and are swollen to equilibrium. The category of **solvent-activated,** matrix-type, controlled-release devices comprises two important types of systems: swellable and swelling-controlled devices. In general, a system prepared by incorporating a drug into a hydrophilic, glassy polymer can be swollen when brought in contact with water or a simulant of biological fluids. This swelling process may or may not be the controlling mechanism for diffusional release, depending on the magnitude of the macromolecular relaxation of the polymer.

In **swelling-controlled release systems,** the bioactive agent is dispersed into the polymer to form nonporous films, disks, or spheres. Upon contact with an aqueous dissolution medium, a distinct front (interface) is observed that corresponds to the water penetration front into the polymer and separates the glassy from the rubbery (gel-like) state of the material. Under these conditions, the macromolecular relaxations of the polymer influence the diffusion mechanism of the drug through

the rubbery state. This water uptake can lead to considerable swelling of the polymer with a thickness that depends on time. The swelling process proceeds toward equilibrium at a rate determined by the water activity in the system and the structure of the polymer. If the polymer is cross-linked or of sufficiently high molecular weight (so that chain entanglements can maintain structural integrity), the equilibrium state is a water-swollen gel. The equilibrium water content of such hydrogels can vary up to more than 90%. If the dry hydrogel contains a water-soluble drug, the drug is essentially immobile in the glassy matrix, but begins to diffuse out as the polymer swells with water. Drug release thus depends on two simultaneous rate processes: water migration into the device and drug diffusion outward through the swollen gel. Since some water uptake must occur before the drug can be released, the initial burst effect frequently observed in matrix devices is moderated, although it may still be present. The continued swelling of the matrix causes the drug to diffuse increasingly easily, ameliorating the slow tailing off of the release curve. The net effect of the swelling process is to prolong and linearize the release curve. Additional discussion of controlled release systems for drug delivery can be found in Chapter 7.8.

Details of these experimental techniques have been presented by Korsmeyer and Peppas (1981) for poly(vinyl alchol) systems, and by Peppas (1981) for PHEMA systems and their copolymers.

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2.5 Bioresorbable and Bioerodible Materials

Joachim Kohn and Robert Langer

TYPES OF IMPLANTS

Since a degradable polymeric implant does not have to be removed surgically once it is no longer needed, degradable polymers are of value in short-term applications that require only the temporary presence of a polymeric implant. An additional advantage is that the use of degradable implants can circumvent some of the problems related to the long-term safety of permanently implanted devices. Some typical short-term applications are listed in Table 1. From a practical perspective, it is convenient to distinguish among four main types of degrad-

TABLE 1 Some "Short-Term" Medical Applications of Degradable Polymeric Biomaterials

Application	Comments
Sutures	The earliest, successful application of synthetic, degradable polymers in human medicine.
Drug delivery devices	One of the most widely investigated medical applications for degradable polymers.
Orthopedic fixation devices	Requires polymers of exceptionally high mechanical strength and stiffness.
Adhesion prevention	Requires polymers that can form soft membranes or films.
Temporary vascular grafts and stents	Only investigational devices are presently available. Blood compatibility is a major concern.

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2.7 NATURAL MATERIALS

Ioannis V. Yannas

Natural polymers offer the advantage of being very similar, often identical, to macromolecular substances which the biological environment is prepared to recognize and to deal with metabolically (Table 1). The problems of toxicity and stimulation of a chronic inflammatory reaction, which are frequently provoked by many synthetic polymers, may thereby be suppressed. Furthermore, the similarity to naturally occurring substances introduces the interesting capability of designing biomaterials which function biologically at the molecular, rather than the macroscopic, level. On the other hand, natural polymers are frequently quite immunogenic. Furthermore, because they are structurally much more complex than most synthetic polymers, their technological manipulation is much more elaborate. On balance, these opposing factors have conspired to lead to a substantial number of biomaterials applications in which naturally occurring polymers, or their chemically modified versions, have provided unprecedented solutions.

An intriguing characteristic of natural polymers is their ability to be degraded by naturally occurring enzymes, a virtual guarantee that the implant will be eventually metabolized by physiological mechanisms. This property may, at first glance, appear as a disadvantage since it detracts from the durability of the implant. However, it has been used to advantage in biomaterials applications in which it is desired to deliver a specific function for a temporary period of time, following which the implant is expected to degrade completely and to be disposed of by largely normal metabolic processes. Since, furthermore, it is possible to control the degradation rate of the implanted polymer by chemical cross-linking or other chemical modifications, the designer is offered the opportunity to control the lifetime of the implant.

A disadvantage of proteins on biomaterials is their frequently significant immunogenicity, which, of course, derives precisely from their similarity to naturally occurring substances. The immunological reaction of the host to the implant is directed against selected sites (antigenic determinants) in the protein molecule. This reaction can be mediated by molecules in solution in body fluids (immunoglobulins). A single such molecule (antibody) binds to single or multiple determinants on an antigen. The immunological reaction can also be mediated by molecules which are held tightly to the surface of immune cells (lymphocytes). The implant is eventually degraded. The reaction can be virtually eliminated provided that the antigenic determinants have been previously modified chemically. The immunogenicity of polysaccharides is typically

TABLE 1 General Properties of Certain Natural Polymers

	Polymer	Incidence	Physiological function
A. Proteins			
	Silk	Synthesized by arthropods	Protective cocoon
	Keratin	Hair	Thermal insulation
	Collagen	Connective tissues (tendon, skin, etc.)	Mechanical support
	Gelatin	Partly amorphous collagen	(Industrial product)
	Fibrinogen	Blood	Blood clotting
	Elastin	Neck ligament	Mechanical support
	Actin	Muscle	Contraction, motility
	Myosin	Muscle	Contraction, motility
B. Polysaccharides			
	Cellulose (cotton)	Plants	Mechanical support
	Amylose	Plants	Energy reservoir
	Dextran	Synthesized by bacteria	Matrix for growth of organism
	Chitin	Insects, crustaceans	Provides shape and form
	Glycosaminoglycans	Connective tissues	Conrributes to mechanical support
C. Polynucleotides			
	Deoxyribonucleic acids (DNA)	Cell nucleus	Direct protein biosynthesis
	Ribonucleic acids (RNA)	Cell nucleus	Direct protein biosynthesis

far lower than that of proteins. The collagens are generally weak immunogens relative to the majority of proteins.

Another disadvantage of proteins as biomaterials derives from the fact that these polymers typically decompose or undergo pyrolytic modification at temperatures below their melting point, thereby precluding the convenience of high-temperature thermoplastic processing methods, such as melt extrusion, during the manufacturing of the implant. However, processes for extruding these temperature-sensitive polymers at room temperature have been developed. Another serious disadvantage is the natural variability in structure of macromolecular substances which are derived from animal sources. Each of these polymers appears as a chemically distinct entity not only from one species to another (species specificity) but also from one tissue to the next (tissue specificity). This testimonial to the elegance of the naturally evolved design of the mammalian body becomes a problem for the manufacturer of implants, which are typically required to adhere to rigid specifications from one batch to the next. Consequently, relatively stringent control methods must be used for the raw material.

Most of the natural polymers in use as biomaterials today are constituents of the extracellular matrix (ECM) of connective tissues such as tendons, ligaments, skin, blood vessels, and bone. These tissues are deformable, fiber-reinforced composite materials of superior architectural sophistication whose main function in the adult animal appears to be the maintenance of organ shape as well as of the organism itself. In the relatively crude description of these tissues as if they were man-made composites, collagen and elastin fibers mechanically reinforce a "matrix" that primarily consists of protein–polysaccharides (proteoglycans) highly swollen in water. Extensive chemical bonding connects these macromolecules to each other, rendering these tissues insoluble and, therefore, impossible to characterize with dilute solution methods unless the tissue is chemically and physically degraded. In the latter case, the solubilized components are subsequently extracted and characterized by biochemical and physicochemical method. Of the various components of extracellular materials which have been used to fashion biomaterials, collagen is the one most frequently used.

Almost inevitably, the physicochemical processes used to extract the individual polymer from tissues, as well as subsequent deliberate modifications, alter the native structure, sometimes significantly. The following description emphasizes the features of the naturally occurring, or native, macromolecular structures. Certain modified forms of these polymers are also described.

STRUCTURE OF NATIVE COLLAGEN

Structural order in collagen, as in other proteins, occurs at several discrete levels of the structural hierarchy. The collagen in the tissues of a vertebrate occurs in at least ten different forms, each of these being dominant in a specific tissue. Structurally, these collagens share the characteristic triple helix, and variations among them are restricted to the length of the nonhelical fraction, the length of the helix itself, and the number and nature of carbohydrate attachments on the triple helix. The collagen in skin, tendon, and bone is mostly type I collagen. Type II collagen is predominant in cartilage, while type III collagen is a major constituent of the blood vessel wall as well as being a minor contaminant of type I collagen in skin. In contrast to these collagens, all of which form fibrils with the distinct collagen periodicity, type IV collagen, a constituent of the basement membrane which separates epithelial tissues from mesodermal tissues is largely nonhelical and does not form fibrils. We follow here the nomenclature which was proposed by W. Kauzmann (1959) to describe in a general way the

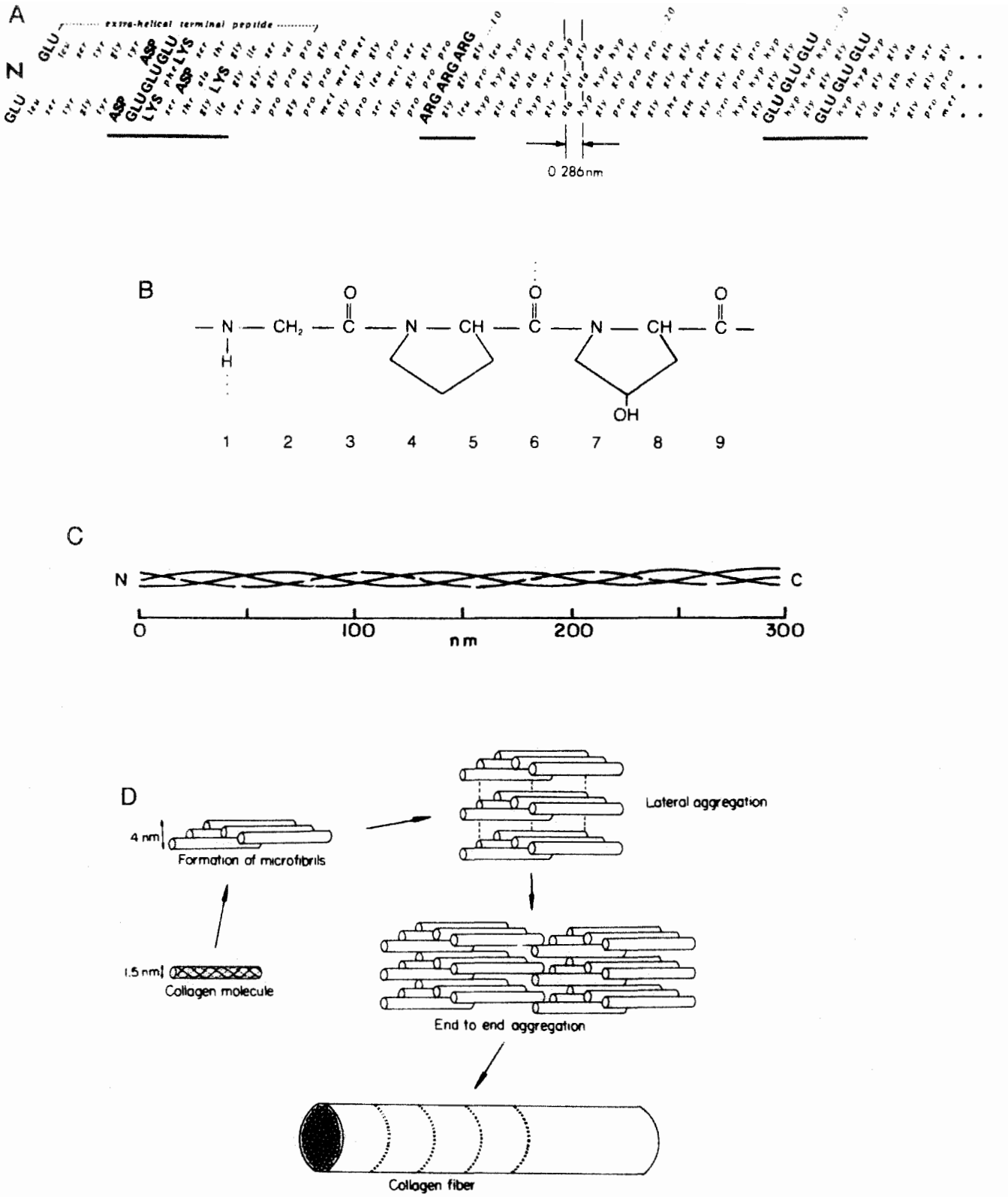


FIG. 1. Collagen, like other proteins, is distinguished by several levels of structural order. (A) Primary structure—the complete sequence of amino acids along each polypeptide chain. An example is the triple chain sequence of type I calf skin collagen at the N-end of the molecule. Roughly 5% of a complete molecule is shown. No attempt has been made to indicate the coiling of the chains. Amino acid residues participating in the triple helix are numbered, and the residue-to-residue spacing (0.286 nm) is shown as a constant within the triple helical domain, but not outside it. Bold capitals indicate charged residues which occur in groups (underlined) (Reprinted from J. A. Chapman and D. J. S. Hulmes, in *Ultrastructure of the Connective Tissue Matrix*, A Ruggeri and P. M. Motta, eds., Martinus Nijhoff, 1984, Chap. 1, Fig. 1, p. 2, with permission.)

structural order in proteins, and we specialize it to the case of type I collagen (Fig. 1).

The primary structure denotes the complete sequence of amino acids along each of three polypeptide chains as well as the location of interchain cross-links in relation to this sequence. Approximately one-third of the residues are glycine and another quarter or so are proline or hydroxyproline. The structure of the bifunctional interchain cross-link is the relatively complex condensation product of a reaction involving lysine and hydroxylysine residues; this reaction continues as the organism matures, thereby rendering the collagens of older animals more difficult to extract.

The secondary structure is the local configuration of a polypeptide chain that results from satisfaction of stereochemical angles and hydrogen-bonding potential of peptide residues. In collagen, the abundance of glycine residues (Gly) plays a key configurational role in the triplet Gly-X-Y, where X and Y are frequently proline or hydroxyproline, respectively, the two amino acids that direct the chain configuration locally by the rigidity of their ring structures. On the other hand, the absence of a side chain in glycine permits the close approach of polypeptide chains in the collagen triple helix. The tertiary structure refers to the global configuration of the polypeptide chains; it represents the pattern according to which the secondary structures are packed together within the complete macromolecule and it constitutes the structural unit that can exist as a physicochemically stable entity in solution, namely, the triple helical collagen molecule.

In type I collagen, two of the three polypeptide chains have identical amino acid composition, consist of 1056 residues, and are termed a1(I) chains, while the third has a different composition; it consists of 1038 residues and is termed a2(I). The three polypeptide chains fold to produce a left-handed helix while the three-chain supercoil is actually right-handed with an estimated pitch of about 100 nm (30–40 residues). The helical structure extends over 1014 of the residues in each of the three chains, leaving the remaining residues at the ends (telopeptides) in a nonhelical configuration. The residue spacing is 0.286 nm and the length of the helical portion of the molecule is, therefore, about 1014×0.286 or 290 nm.

The fourth-order or quaternary structure denotes the repeating supermolecular unit structure, comprising several molecules packed in a specific lattice, which constitutes the basic element of the solid state (microfibril). Collagen molecules are packed in a quasi-hexagonal lattice at an interchain distance of about 1.3 nm which shrinks considerably when the microfibril is dehydrated. Adjacent molecules in the microfibril are approximately parallel to the fibril axis; they all point in the same direction along the fibril and are staggered regularly, giving rise to the well-known D-period of collagen, about 64 nm, which is visible in the electron microscope. Higher levels of order, eventually leading to gross anatomical features which can be readily seen with the naked eye, have been proposed but there is no agreement on their definition.

PHYSICAL MODIFICATIONS OF THE NATIVE STRUCTURE OF COLLAGEN

Crystallinity in collagen can, according to Fig. 1, be detected at two discrete levels of structural order: the tertiary (triple helix) (Fig. 1C) and the quaternary (lattice of triple helices) (Fig. 1D). Each of these levels of order corresponds, interestingly enough, to a separate melting transformation. A solution of collagen triple helices is thus converted to the randomly coiled gelatin by heating above the helix-coil transition temperature, which is approximately 37°C for bovine collagen, or by exceeding a critical concentration of certain highly polarizable anions, e.g., bromide or thiocyanate, in the solution of collagen molecules. Infrared spectroscopic procedures, based on helical marker bands in the mid- and far infrared, have been developed to assay the gelatin content of collagen in the solid or semisolid states in which collagen is commonly used as an implant. Since implanted gelatin is much more rapidly degradable than collagen, these assays are essential tools for quality control of collagen-based biomaterials. Frequently such biomaterials have been processed under manufacturing conditions which may threaten the integrity of the triple helix.

Collagen fibers also exhibit a characteristic banding pattern

(B) Secondary structure—the local configuration of a polypeptide chain. The triplet sequence Gly-Pro-Hyp illustrates elements of collagen triple-helix stabilization. The numbers identify peptide backbone atoms. The conformation is determined by *trans* peptide bonds (3-4, 6-7, and 9-1); fixed rotation angle of bond in proline ring (4-5); limited rotation of proline past the C=O group (bond 5-6); interchain hydrogen bonds (dots) involving the NH hydrogen at position 1 and the C=O at position 6 in adjacent chains; and the hydroxy group of hydroxyproline, possibly through water-bridged hydrogen bonds. (Reprinted from K. A. Piez and A. H. Reddi, eds., *Extracellular Matrix Biochemistry*. Elsevier, 1984, Chap. 1, Fig. 1.6, p. 7, with permission.) (C) Tertiary structure—the global configuration of polypeptide chains, representing the pattern according to which the secondary structures are packed together within the unit substructure. A schematic view of the type I collagen molecule, a triple helix 300 nm long. (Reprinted from K. A. Piez and A. H. Reddi, eds., *Extracellular Matrix Biochemistry*, Elsevier, 1984, Chap. 1, Fig. 1.22, p. 29, with permission.) (D) Quaternary structure—the unit supermolecular structure. The most widely accepted unit is one involving five collagen molecules (microfibril). Several microfibrils aggregate end to end and also laterally to form a collagen fiber which exhibits a regular banding pattern in the electron microscope with a period of 65 nm. (Reprinted from M. E. Nimni, ed., *Collagen*, Vol. I, *Biochemistry*. CRC Press, Boca Raton, 1988, Chap. 1, Fig. 10, p. 14, with permission.)

with a period of 65 nm (quarternary structure). This pattern is lost reversibly when the pH of a suspension of collagen fibers in acetic acid is lowered below 4.25 ± 0.30. Transmission electron microscopy or small-angle X-ray diffraction can be used to determine the fraction of fibrils which possess banding as the pH of the system is altered. During this transformation, which appears to be a first-order thermodynamic transition, the triple helical structure remains unchanged. Changes in pH can, therefore, be used to selectively abolish the quarternary structure while maintaining the tertiary structure intact.

This experimental strategy has made it possible to show that the well-known phenomenon of blood platelet aggregation by collagen fibers (the reason for using collagen sponges as hemostatic devices) is a specific property of the quarternary rather than the tertiary structure. Thus collagen which is thromboresistant *in vitro* has been prepared by selectively "melting out" the packing order of helices while preserving the triple helices themselves. Figure 2 illustrates the banding pattern of such collagen fibers. Notice that short segments of banded fibrils persist even after very long treatment at low pH, occasionally interrupting long segments of nonbanded fibrils (Fig. 2, inset).

The porosity of collagenous implants normally makes an indispensable contribution to its performance. A porous structure provides an implant with two critical functions. First, pore channels are ports of entry for cells migrating from adjacent tissues into the bulk of the implant or for the capillary suction of blood from a hemorrhaging blood vessel nearby. Second, pores endow a solid with a frequently enormous specific surface which is made available either for specific interactions with invading cells (e.g., collagen-glycosaminoglycan (CG) copolymers which induce regeneration of skin in burned patients) or for interaction with coagulation factors in blood flowing into the device (e.g., hemostatic sponges).

Pores can be incorporated by first freezing a dilute suspension of collagen fibers and then inducing sublimation of the ice crystals by exposing the suspension to a low-temperature vacuum. The resulting pore structure is a negative replica of the network of ice crystals (primarily dendrites). It follows that control of the conditions for ice nucleation and growth can lead to a large variety of pore structures (Fig. 3).

In practice, the average pore diameter decreases with decreasing temperature of freezing while the orientation of pore channel axes depends on the magnitude of the heat flux vector during freezing. In experimental implants, the mean pore diameter has ranged between about 1 and 800 mm; pore volume fractions have ranged up to 0.995; the specific surface has been varied between about 0.01 and 100 m^2/g dry matrix; and the orientation of axes of pore channels has ranged from strongly uniaxial to highly radial. The ability of collagen-glycosaminoglycans to induce regeneration of tissues such as skin and nerve depends critically, among other factors, on the adjustment of the pore structure to desired levels, e.g., about 20–125 μm for skin regeneration and less than 10 μm for sciatic nerve regeneration. Determination of pore structure is based on principles of stereology, the discipline which allows the quantitative statistical properties of three-dimensional implant structures to be related to those of two-dimensional projections, e.g., sections used for histological analysis.

CHEMICAL MODIFICATION OF COLLAGEN

The primary structure of collagen is made up of long sequences of some 20 different amino acids. Since each amino acid has its own chemical identity, there are 20 types of pendant side groups, each with its own chemical reactivity, attached to the polypeptide chain backbone. As examples, there are carboxylic side groups (from glutamic acid and aspartic acid residues), primary amino groups (lysine, hydroxylysine, and arginine residues), and hydroxylic groups (tyrosine and hydroxylysine). The collagen molecule is therefore subject to modification by a large variety of chemical reagents. Such versatility comes with a price: Even though the choice of reagents is large, it is imporant to ascertain that use of a given reagent has led to modification of a given fraction of the residues of a certain amino acid in the molecule. This is equivalent to proof that a reaction has proceeded to a desired "yield." Furthermore, proof that a given reagent has attacked only a specific type of amino acid, rather than all amino acid residue types carrying the same functional group, also requires chemical analysis.

Historically, the chemical modification of collagen has been practiced in the leather industry (since about 50% of the protein content of cowhide is collagen) and in the photographic gelatin industry. Today, the increasing use of collagen in biomaterials applications has provided renewed incentive for novel chemical modification, primarily in two areas. First, implanted collagen is subject to degradative attack by collagenases, and chemical cross-linking is a well-known means of decelerating the degradation rate. Second, collagen extracted from an animal source elicits production of antibodies (immunogenicity). Although it is widely accepted that collagen elicits synthesis of a far smaller concentration of antibodies than other proteins (e.g., albumin), treatment with specific reagents, including enzymatic treatment, is occasionally used to reduce the immunogenicity of collagen.

Collagen-based implants are normally degraded by collagenases, naturally occurring enzymes which attack the triple helical molecule at a specific location. Two characteristic products result, namely, the N-terminal fragment which amounts to about two thirds of the molecule, and the one-quarter C-terminal fragment. Both of these fragments become spontaneously transformed (denatured) to gelatin at physiological temperatures via the helix-coil transition and the gelatinized fragments are then cleaved to oligopeptides by naturally occurring enzymes which degrade several other tissue proteins (nonspecific proteases).

Collagenases are naturally present in healing wounds and are credited with a major role in the degradation of collagen fibers at the site of trauma. At about the same time that degradation of collagen and of other ECM components proceeds in the wound bed, these components are being synthesized *de novo* by cells in the wound bed. Eventually, new architectural arrangements, such as scar tissue, are synthesized. While it is not a replica of the intact tissue, scar tissue forms a stable endpoint to the healing process, and forms a tissue barrier between adjacent organs which allows the healed organ to continue functioning at a nearly physiological level. The combined process of collagen degradation and scar synthesis is

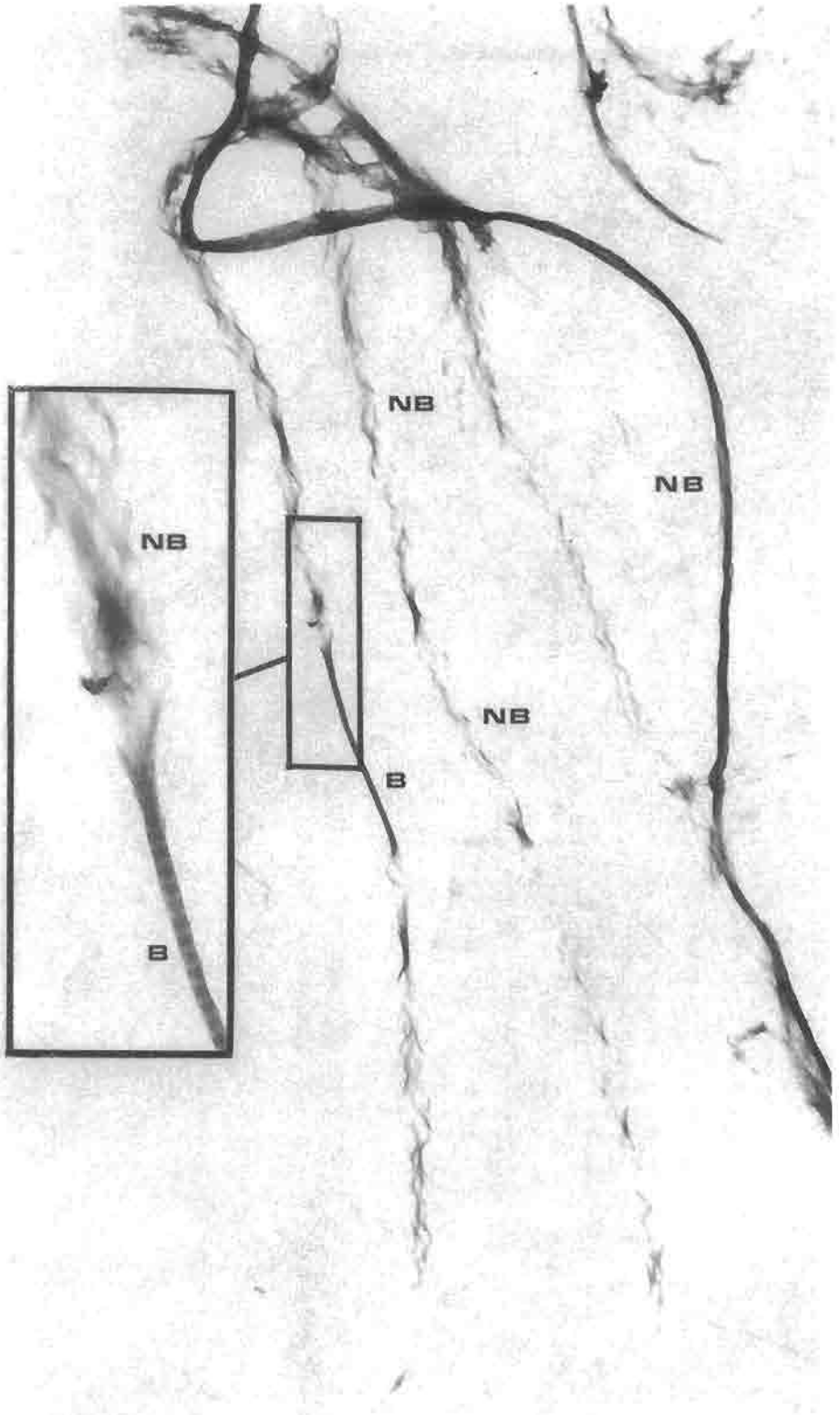


FIG. 2. Following exposure to pH below 4.25 ± 0.30, the banding pattern of type I bovine hide collagen practically disappears. Short lengths of banded collagen (B) do, however, persist next to very long lengths of nonbanded collagen (NB) which has tertiary but not quaternary structure. This preparation does not include platelet aggregation provided that the fibers are prevented from recrystallizing to form banded structures when the pH is adjusted to neutral in order to perform the platelet assay. Stained with 0.5 wt.% phosphotungstic acid. Banded collagen period, about 65 nm. ×12,750. Inset: ×63,750. (Reprinted from M. J. Forbes, M. S. dissertation, Massachusetts Institute of Technology, 1980, courtesy of MIT.)

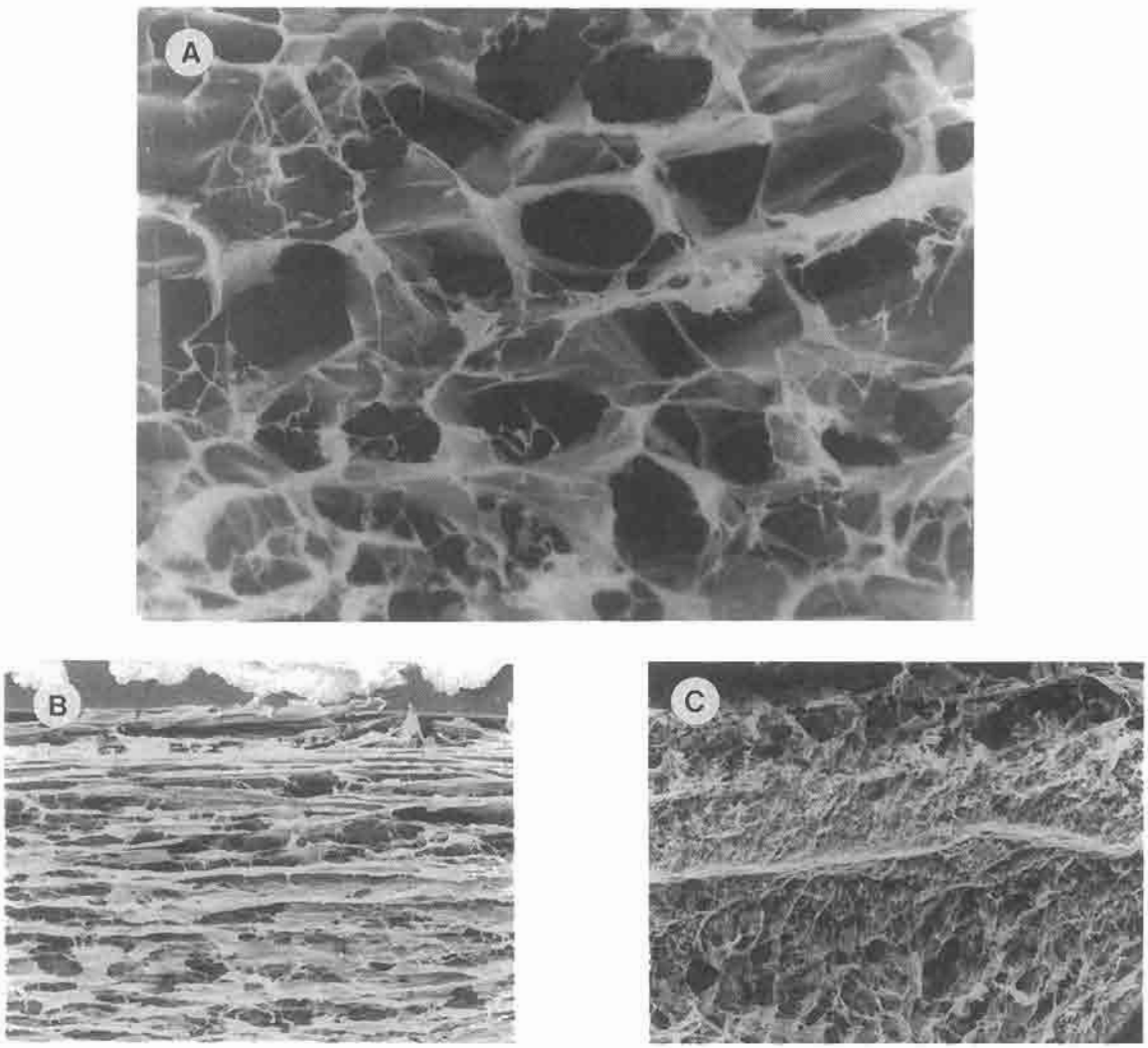


FIG. 3. Illustration of the variety of porous structures which can be obtained with collagen-GAG copolymers by adjusting the kinetics of crystallization of ice to the appropriate magnitude and direction. Pores form when the ice dendrites are eventually sublimed. Scanning electron microscopy. (Courtesy of MIT.)

often referred to as remodeling. One of the frequent challenges in the design of collagen implants is to modify collagen chemically in a way which either accelerates or slows down the rate of its degradation at the implantation site to a desired level.

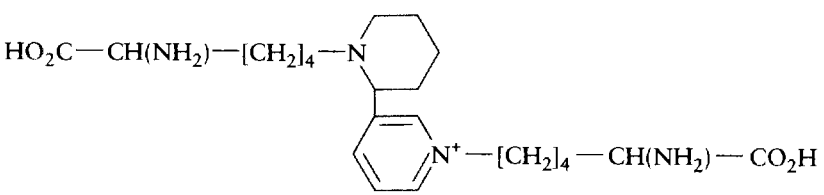
An effective method for reducing the degradation rate of collagen by naturally occurring enzymes is chemical cross-linking. A very simple self-cross-linking procedure, dehydrative cross-linking, is based on the fact that removal of water below about 1 wt.% insolubilizes collagen as well as gelatin by inducing formation of interchain peptide bonds. The nature of the cross-links formed can be inferred from the results of studies using chemically modified gelatins. Gelatin which had been modified either by esterification of the carboxylic groups of aspartyl–glutamyl residues or by acetylation of the ε-amino groups of lysyl residues remained soluble in aqueous solvents after exposure of the solid protein to high temperature, while unmodified gelatins lost their solubility. Insolubilization of collagen and gelatin following severe dehydration has been, accordingly, interpreted as the result of drastic removal of the aqueous product of a condensation reaction which led to the formation of interchain amide links. The proposed mechanism is consistent with results, obtained by titration, showing that the number of free carboxylic groups and free amino groups in collagen are both significantly decreased following high-temperature treatment.

Removal of water to the extent necessary to achieve a density of cross-links in excess of 10^{-5} moles of cross-links/g dry gelatin, which corresponds to an average molecular weight between cross-links, M_c, of about 70 kDa, can be achieved within hours by exposure to temperatures in excess of 105°C

under atmospheric pressure. The possibility that the cross-linking achieved under these conditions is caused by a pyrolytic reaction has been ruled out. Furthermore, chromatographic data have shown that the amino acid composition of collagen remains intact after exposure to 105°C for several days. In fact, it has been observed that gelatin can be cross-linked by exposure to temperatures as low as 25°C provided that a sufficiently high vacuum is present to achieve the drastic moisture removal which appears to drive the cross-linking reaction.

Exposure of highly hydrated collagen to temperatures in excess of about 37°C is known to cause reversible melting of the triple helical structure, as described earlier. The melting point of the triple helix increases with the collagen-diluent ratio from 37°C, the helix-coil transition of the infinitely dilute solution, to about 120°C for collagen swollen with as little as 20% wt. diluent and up to about 210°C, the melting point of anhydrous collagen. Accordingly, it is possible to cross-link collagen using the drastic dehydration procedure described earlier without loss of the triple helical structure. It is sufficient to adjust the moisture content of collagen to a low enough level prior to exposure to the high temperature levels required for rapid dehydration.

Dialdehydes have been long known in the leather industry as effective tanning agents and in histological laboratories as useful fixatives. Both of these applications are based on the reaction between the dialdehyde and the ε-amino group of lysyl residues in the protein, which induces formation of interchain cross-links. Glutaraldehyde cross-linking is a relatively widely used procedure. The nature of the cross-link formed has been the subject of controversy, primarily because of the complex, apparently polymeric, character of this reagent. Considerable evidence supports the proposed anabilysine structure, which is derived from two lysine side chains and two molecules of glutaraldehyde:



Evidence for other mechanisms has been presented. Compared with other aldehydes, glutaraldehyde has shown itself to be a particularly effective cross-linking agent, as judged, for example, by its ability to increase the cross-link density. The M_c values provide the experimenter with a series of collagens in which the enzymatic degradation rate can be studied over a wide range, thereby affording implants which effectively disappear from tissue between a few days and several weeks following implantation. Although the mechanism of the reaction between glutaraldehyde and collagen at neutral pH is understood in part, the reaction in acidic media has not been studied extensively. Evidence that covalent cross-linking is involved comes from measurements of the equilibrium tensile modulus of films that have been treated to induce cross-linking and have subsequently been gelatinized by treatment in 1 *M* NaCl at 70°C. Under such conditions, only films which have been converted into a three-dimensional network support an equilibrium tensile force; by contrast, uncross-linked specimens dissolve readily in the hot medium.

The immunogenicity of the collagen used in implants is significant and has been studied assiduously using laboratory preparations. However, the clinical significance of such immunogenicity has been shown to be very low, and is often considered to be negligible. This immense simplification of the immunological problem of using collagen as a biomaterial was recognized a long time ago by manufacturers of collagen-based sutures. The apparent reason for the low antigenicity of type I collagen stems from the small species difference among type I collagens (e.g., cow vs. human). Such similarity is, in turn, probably understandable in terms of the inability of the triple helical configuration to incorporate the substantial amino acid substitutions which characterize species differences with other proteins. The relative constancy of the structure of the triple helix among the various species is, in fact, the reason why collagen is sometimes referred to as a "successful" protein in terms of its evolution or, rather, the lack of it.

In order to modify the immunogenicity of collagen, it is useful to consider the location of its antigenic determinants, i.e., the specific chemical groups which are recognized as foreign by the immunological system of the host animal. The configurational (or conformational) determinants of collagen depend on the presence of the intact triple helix and, consequently, are abolished when collagen is denatured into gelatin; the latter event (see earlier discussion) occurs spontaneously after the triple helix is cleaved by a collagenase. Gelatinization exposes the sequential determinant of collagen over the short period during which gelatin retains its macromolecule character, before it is cleared away following attack by one of several non-specific proteases. Controlling the stability of the triple helix during processing of collagen, therefore, prevents the display of the sequential determinants.

Sequential determinants also exist in the nonhelical end (telopeptide region) of the collagen molecule and this region has been associated with most of the immunogenicity of collagen-based implants. Several enzymatic treatments have been devised to cleave the telopeptide region without destroying the triple helix. Treating collagen with glutaraldehyde not only reduces its degradation rate by collagenase but also appears to reduce its antigenicity as well. The mechanism of this effect is not well understood. Certain applications of collagen-based biomaterials are shown in Table 2.

TABLE 2 Certain Applications of Collagen-Based Biomaterials

Application	Physical state
Sutures	Extruded tape (Schmitt, 1985)
Hemostatic agents	Powder, sponge, fleece (Stengel *et al.*, 1974; Chvapil, 1979)
Blood vessels	Extruded collagen tube, processed human or animal blood vessel (Nimni, 1988)
Heart valves	Processed porcine heart valve (Nimni, 1988)
Tendon, ligaments	Processed tendon (Piez, 1985)
Burn treatment (dermal regeneration)	Porous collagen-glycosaminoglycan (GAG) polymer[a] (Yannas *et al.*, 1981, 1982, and 1989)
Peripheral nerve regeneration	Porous collagen-GAG copolymer (Chang and Yannas, 1992)
Meniscus regeneration	Porous collagen-GAG copolymers (Stone *et al.*, 1989)
Intradermal augmentation	Injectable suspension of collagen particles (Piez, 1985)
Gynecological applications	Sponges (Chvapil, 1979)
Drug-delivery systems	Various forms (Stenzel *et al.*, 1974, Chvapil, 1979)

[a]See also Chapter 7.10.

PROTEOGLYCANS AND GLYCOSAMINOGLYCANS

Glycosaminoglycans (GAGs) occur naturally as polysaccharide branches of a protein chain, or protein core, to which they are covalently attached via a specific oligosaccharide link. The entire branched macromolecule, which has been described as having a "bottle brush" configuration, is known as a proteoglycan and has a molecular weight of about 10^3 kDa.

The structure of GAGs can be generically described as that of an alternating copolymer, the repeat unit consisting of a hexosamine (glucosamine or galactosamine) and of another sugar (galactose, glucuronic acid or iduronic acid). Individual GAG chains are known to contain occasional substitutions of one uronic acid for another; however, the nature of the hexosamine component remains invariant along the chain. There are other deviations from the model of a flawless alternating copolymer, such as variations in sulfate content along the chain. It is, nevertheless, useful for the purpose of getting acquainted with the GAGs to show their typical (rather, typified) repeat unit structure, as in Fig. 4. The molecular weights of GAGs are in the range of 5–60 kDa, with the exception of hyaluronic acid, the only GAG which is not sulfated; it exhibits molecular weights in the range of 50–500 kDa. Sugar units along GAG chains are linked by α or β glycosidic bonds and are 1, 3, or 1, 4 (Fig. 4). There are several naturally occurring enzymes which degrade specific GAGs, the most well-known being hyaluronidase. These enzymes are primarily responsible for the physiological turnover rate of GAGs, which is in the range of 2–14 days.

The nature of the oligosaccharide link appears to be identical for the GAGs, except for keratan sulfate, and is a galactosyl–galactosyl–xylose, with the latter glycosidically linked to the hydroxyl group of serine in the protein core.

The very high molecular weight of hyaluronic acid is the basis of most uses of this GAG as a biomaterial: almost all applications make use of the exceptionally high viscosity and the facility to form gels which characterize this polysaccharide. Hyaluronic acid gels have found considerable use in ophthalmology because they facilitate cataract surgery as well as retinal reattachment. Other uses of this GAG reported are the treatment of degenerative joint dysfunction in horses and experimental treatment of certain orthopedic dysfunctions in humans. On the other hand, sulfated GAGs are anionically charged and can induce precipitation of collagen at acidic pH levels, a process which yields collagen–GAG coprecipitates that can be subsequently freeze dried and covalently cross-linked to yield biomaterials which have been shown capable of inducing regeneration of skin (dermis), peripheral nerve, and the meniscus of joints (Table 2).

ELASTIN

Elastin is the least soluble protein in the body, consisting as it does of a three-dimensional cross-linked network. It can be extracted from tissues by dissolving and degrading all adjacent substances. It appears to be highly amorphous and thus eludes elucidation of its structure by crystallographic methods. Fortunately, it exhibits ideal rubber elasticity and it thus becomes possible to study certain features of the macromolecular network. For example, mechanical measurements have shown that the average number of amino acid units between cross-links is 71–84. Insoluble elastic preparations can be degraded by the enzyme elastase but the soluble preparations made this way have not yet been used extensively as biomaterials.

GRAFT COPOLYMERS OF COLLAGEN AND GLYCOSAMINOGLYCANS

The preceding discussion has focused on the individual macromolecular components of ECM. By contrast, naturally occurring ECMs are insoluble networks comprising several macromolecular components. Several types of ECMs are known to play critical roles during organ development. During the past several years certain analogs of ECMs have been synthesized and have been studied as implants. This section summarizes the evidence for the unusual biological activity of a small number of ECM analogs.

In the 1970s it was discovered that a highly porous graft copolymer of type I collagen and chondroitin 6-sulfate was capable of modifying dramatically the kinetics and mechanism of healing of full-thickness skin wounds in rodents (Yannas *et al.*, 1977). In the adult mammal, full-thickness skin wounds

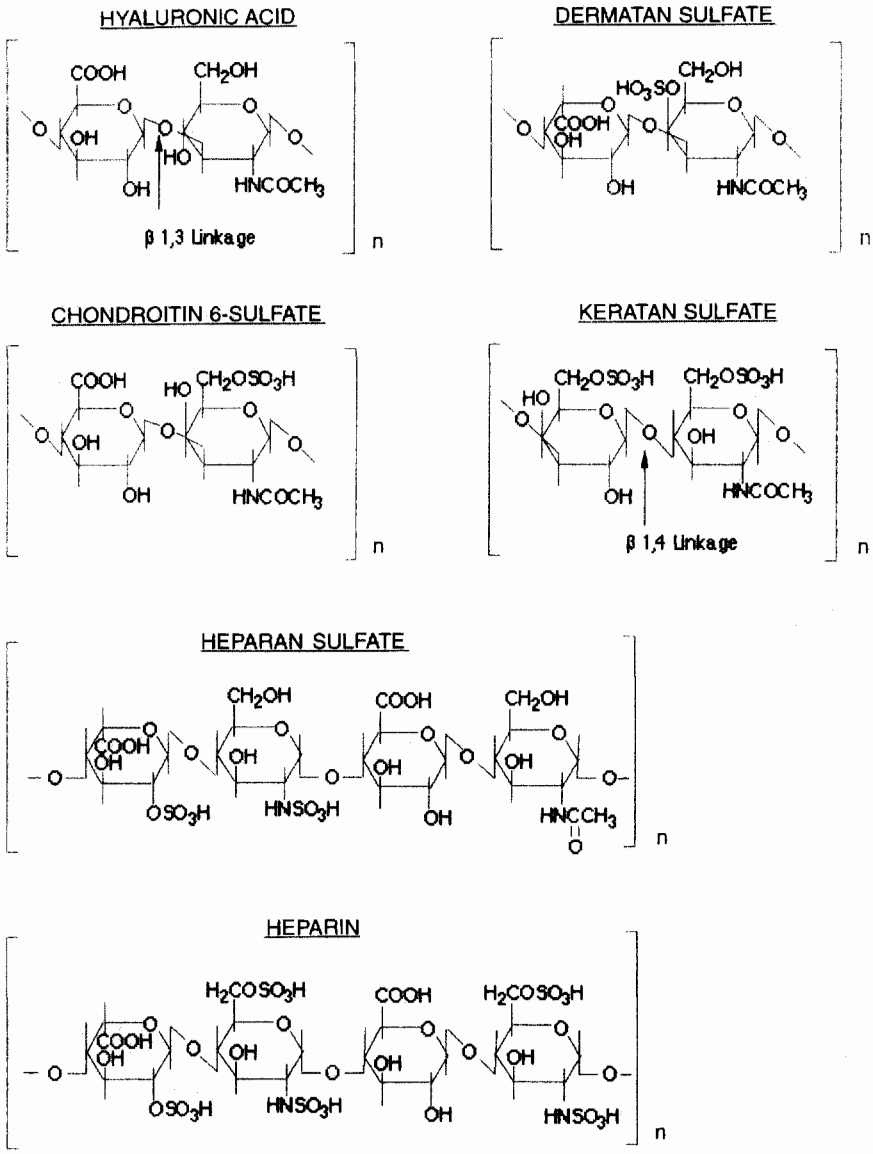


FIG. 4. Repeat units of glycosaminoglycans. (Reprinted for J. E. Siebert, 1987, with permission.)

represent areas that are demonstrably devoid of both epidermis and dermis, the outer and inner layers of skin, respectively. Such wounds normally close by contraction of wound edges and by synthesis of scar tissue. Previously, collagen and various glycosaminoglycans, each prepared in various forms such as powder and films, had been used to cover such deep wounds without observing a significant modification in the outcome of the wound healing process (compare the historical review of Schmitt, 1985).

Surprisingly, grafting of these wounds with the porous CG copolymer on guinea pig wounds blocked the onset of wound contraction by several days and led to synthesis of new connective tissue within about 3 weeks in the space occupied by the copolymer (Yannas *et al.*, 1981, 1982). The copolymer underwent substantial degradation under the action of tissue collagenases during the 3-week period, at the end of which it had degraded completely at the wound site. Studies of the connective tissue synthesized in place of the degraded copolymer eventually showed that the new tissue was distinctly different from scar and was very similar, though not identical, to physiological dermis. In particular, new hair follicles and new sweat glands had not been synthesized. This marked the first instance where scar synthesis was blocked in a full-thickness skin wound of an adult mammal and, in its place, a physiological dermis had been synthesized. That this result was not confined to guinea pigs was confirmed by grafting the same copoly-

mer on full-thickness skin wounds in other adult mammals, including pigs (Butler *et al.*, 1995) and, most importantly, human victims of massive burns (Burke *et al.*, 1981).

Although a large number of CG copolymers were synthesized and studied as grafts, it was observed that only one possessed the requisite activity to modify dramatically the wound healing process in skin. The structure of the CG copolymer required specification at two scales: at the nanoscale, the average molecular weight of the cross-linked network which was required to induce regeneration of the dermis was described by an average molecular weight between cross-links of 12,500 ± 5,000; at the microscale, the average pore diameter was between 20 and 120 μm. Relatively small deviations from these structural features, either at the nanoscale or the microscale, led to loss of activity (Yannas *et al.*, 1989). In view of the nature of its unique activity this biologically active macromolecular network has been referred to as skin regeneration template (SRT). (See also Chapter 7.10.)

The regeneration of dermis was followed by regeneration of a quite different organ, the peripheral nerve (Yannas *et al.*, 1987; Chang and Yannas, 1992). This was accomplished using a distinctly different ECM analog, termed nerve regeneration template (NRT). Although the chemical composition of the two templates was identical there were significant differences in other structural features. NRT degrades considerably slower than SRT (about 6 weeks for NRT compared to about 2 weeks for SRT) and is also characterized by a much smaller average pore diameter (about 5 μm compared to 20–120 μm for SRT). A third ECM analog was shown to induce regeneration of the knee meniscus in the dog (Stone *et al.*, 1990). The combined findings showed that the activity of individual ECM analogs was organ specific. It also suggested that other ECM analogs, still to be discovered, could induce regeneration of organs such as a kidney or the pancreas.

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2.8 Composites

Harold Alexander

The word "composite" means "consisting of two or more distinct parts." At the atomic level, materials such as metal alloys and polymeric materials could be called composite materials in that they consist of different and distinct atomic groupings. At the microstructural level (about 10^{-4} to 10^{-2} cm), a metal alloy such as a plain-carbon steel containing ferrite and pearlite could be called a composite material since the ferrite and pearlite are distinctly visible constituents as observed in the optical microscope. At the molecular and microstructural level, tissues such as bone and tendon are certainly composites with a number of levels of hierarchy.

In engineering design, a composite material usually refers to a material consisting of constituents in the micro- to macrosize range, favoring the macrosize range. For the purpose of discussion in this chapter, composites can be considered to be materials consisting of two or more chemically distinct constituents, on a macroscale, having a distinct interface separating them. This definition encompasses the fiber and particulate composite materials of primary interest as biomaterials. Such composites consist of one or more discontinuous phases embedded within a continuous phase. The discontinuous phase is usually harder and stronger than the continuous phase and is called the rein-

CHAPTER

6

Degradation of Materials in the Biological Environment

ARTHUR J. COURY, ROBERT J. LEVY, CARL R. MCMILLIN, YASHWANT PATHAK, BUDDY D. RATNER, FREDERICK J. SCHOEN, DAVID F. WILLIAMS, AND RACHEL L. WILLIAMS

6.1 INTRODUCTION

Buddy D. Ratner

The biological environment is surprisingly harsh and can lead to rapid or gradual breakdown of many materials. Superficially, one might think that the neutral pH, low salt content, and modest temperature of the body would constitute a mild environment. However, many special mechanisms are brought to bear on implants to break them down. These are mechanisms that have evolved over millennia specifically to rid the living organism of invading foreign substances and they now attack contemporary biomaterials.

First, consider that, along with the continuous or cyclic stress many biomaterials are exposed to, abrasion and flexure may also take place. This occurs in an aqueous, ionic environment that can be electrochemically active to metals and plasticizing (softening) to polymers. Then, specific biological mechanisms are invoked. Proteins adsorb to the material and can enhance the corrosion rate of metals. Cells secrete powerful oxidizing agents and enzymes that are directed at digesting the material. The potent degradative agents are concentrated between the cell and the material where they act, undiluted by the surrounding aqueous medium.

To understand the biological degradation of implant materials, synergistic pathways should be considered. For example, the cracks associated with stress crazing open up fresh surface area to reaction. Swelling and water uptake can similarly increase the number of sites for reaction. Degradation products can alter the local pH, stimulating further reaction. Hydrolysis of polymers can generate more hydrophilic species, leading to polymer swelling and entry of degrading species into the bulk of the polymer. Cracks might also serve as sites for the initiation of calcification.

Biodegradation is a term that is used in many contexts. It can be used for reactions that occur over minutes or over years. It can be engineered to happen at a specific time after implantation, or it can be an unexpected long-term consequence of the severity of the biological environment. Implant materials can solubilize, crumble, become rubbery, or become rigid with time. The products of degradation may be toxic to the body, or they may be designed to perform a pharmacologic function. Degradation is seen with metals, polymers, ceramics, and composites. Thus, biodegradation as a subject is broad in scope, and rightfully should command considerable attention for the biomaterials scientist. This section introduces biodegradation issues for a number of classes of materials, and provides a basis for further study on this complex but critical subject.

6.2 CHEMICAL AND BIOCHEMICAL DEGRADATION OF POLYMERS

Arthur J. Coury

Biodegradation is the chemical breakdown of materials by the action of living organisms which leads to changes in physical properties. It is a concept of vast scope, ranging from decomposition of environmental waste involving microorganisms to host-induced deterioration of biomaterials in implanted medical devices. Yet it is a precise term, implying that specific biological processes are required to effect such changes (Williams, 1989). This chapter, while grounded in biodegradation, addresses other processes that contribute to the often complex mechanisms of polymer degradation. Its focus is the unintended chemical breakdown, in the body, of synthetic solid-phase polymers. (See Chapter 2.5 for a description of systems engineered to break down in the body.)

POLYMER DEGRADATION PROCESSES

Polymeric components of implantable devices are generally reliable for their intended lifetimes. Careful selection and exten-

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TABLE 1 Typical Operations on an Injection-Moldable Polymer Biomaterial

Polymer: Synthesis, extrusion, pelletizing
Pellets: Packaging, storage, transfer, drying
Components: Injection molding, post-mold finishing, cleaning, inspecting, packaging, storage
Device: Fabrication, storage (presterilization), cleaning, inspecting, packaging, storage (packaged), sterilization, storage (sterile), shipment, storage (preimplant), implantation, operation in body

sive preclinical testing of the compositions, fabricated components, and devices usually establish functionality and durability. However, with chronic, indwelling devices, it is infeasible during qualification to match all implant conditions in real time for years or decades of use. The accelerated aging, animal implants, and statistical projections employed cannot expose all of the variables which may cause premature deterioration of performance. The ultimate measure of the acceptability of a material for a medical device is its functionality for the device's intended lifetime as ascertained in human postimplant surveillance.

No polymer is totally impervious to the chemical processes and mechanical action of the body. Generally, polymeric biomaterials degrade because body constituents attack the biomaterials directly or through other device components or the intervention of external factors.

Numerous operations are performed on a polymer from the time of its synthesis to its use in the body (see, e.g., Table 1). Table 2 lists mechanisms of physical and chemical deterioration, which may occur alone or in concert at various stages of a polymer's history. Moreover, a material's treatment prior to implant may predispose it to stable or unstable end-use behavior (Brauman *et al.*, 1981; Greisser *et al.*, 1994). A prominent example of biomaterial degradation caused by preimplant processing is the gamma irradiation sterilization of ultrahigh-molecular-weight polyethylene used in total joint prostheses. The process generates free radicals within the material which react with oxygen to produce undesirable oxidation products. Chain oxidation and scission can occur for periods of months to years, causing loss of strength and embrittlement with limited shelf life (McKellop *et al.*, 1995; Furman and Li, 1995; Weaver *et al.*, 1995). It is crucially important, therefore, that appropriate and rigorous processing and characterization protocols be followed for all operations (Coury *et al.*, 1988).

After a device has been implanted, adsorption and absorption processes occur. Polymeric surfaces in contact with body fluids immediately adsorb proteinaceous components, and the bulk begins to absorb soluble components such as water, proteins, and lipids. Cellular elements subsequently attach to the surfaces and initiate chemical processes. With biostable components, this complex interplay of factors is of little functional consequence. At equilibrium fluid absorption, there may be some polymer plasticization, causing dimensional and mechanical property changes (Coury *et al.*, 1988). On the surface, a powerful acute attack by cells and many chemical agents, including enzymes, will have been substantially withstood. With the resolution of this acute inflammatory phase, a fibrous capsule will likely have formed over the device, and the rate of release of powerful chemicals from activated cells will have markedly decreased.

For those polymers subjected to chemical degradation *in vivo*, few if any reports have comprehensively described the multistep processes and interactions that comprise each mechanism. Rather, explant analysis and occasionally metabolite evaluation is used to infer reaction pathways. The analysis of chemically degraded polymers has almost always implicated either hydrolysis or oxidation as an essential component of the process.

HYDROLYTIC BIODEGRADATION

Structures of Hydrolyzable Polymers

Hydrolysis is the scission of susceptible molecular functional groups by reaction with water. It may be catalyzed by acids, bases, salts, or enzymes. It is a single-step process in which the rate of chain scission is directly proportional to the rate of initiation of the reaction (Schnabel, 1981). A polymer's susceptibility to hydrolysis is the result of its chemical structure, its morphology, its dimensions, and the body's environment.

In a commonly used category of hydrolyzable polymeric

TABLE 2 Mechanisms Leading to Degradation of Polymer Properties[a]

Physical	Chemical
Sorption	Thermolysis
Swelling	Radical scission
Softening	Depolymerization
Dissolution	Oxidation
Mineralization	Chemical
Extraction	Thermooxidative
Crystallization	Solvolysis
Decrystallization	Hydrolysis
Stress cracking	Alcoholysis
Fatigue fracture	Aminolysis, etc.
Impact fracture	Photolysis
	Visible
	Ultraviolet
	Radiolysis
	Gamma rays
	X-rays
	Electron beam
	Fracture-induced radical reactions

[a]Some degradation processes may involve combinations of two or more individual mechanisms.

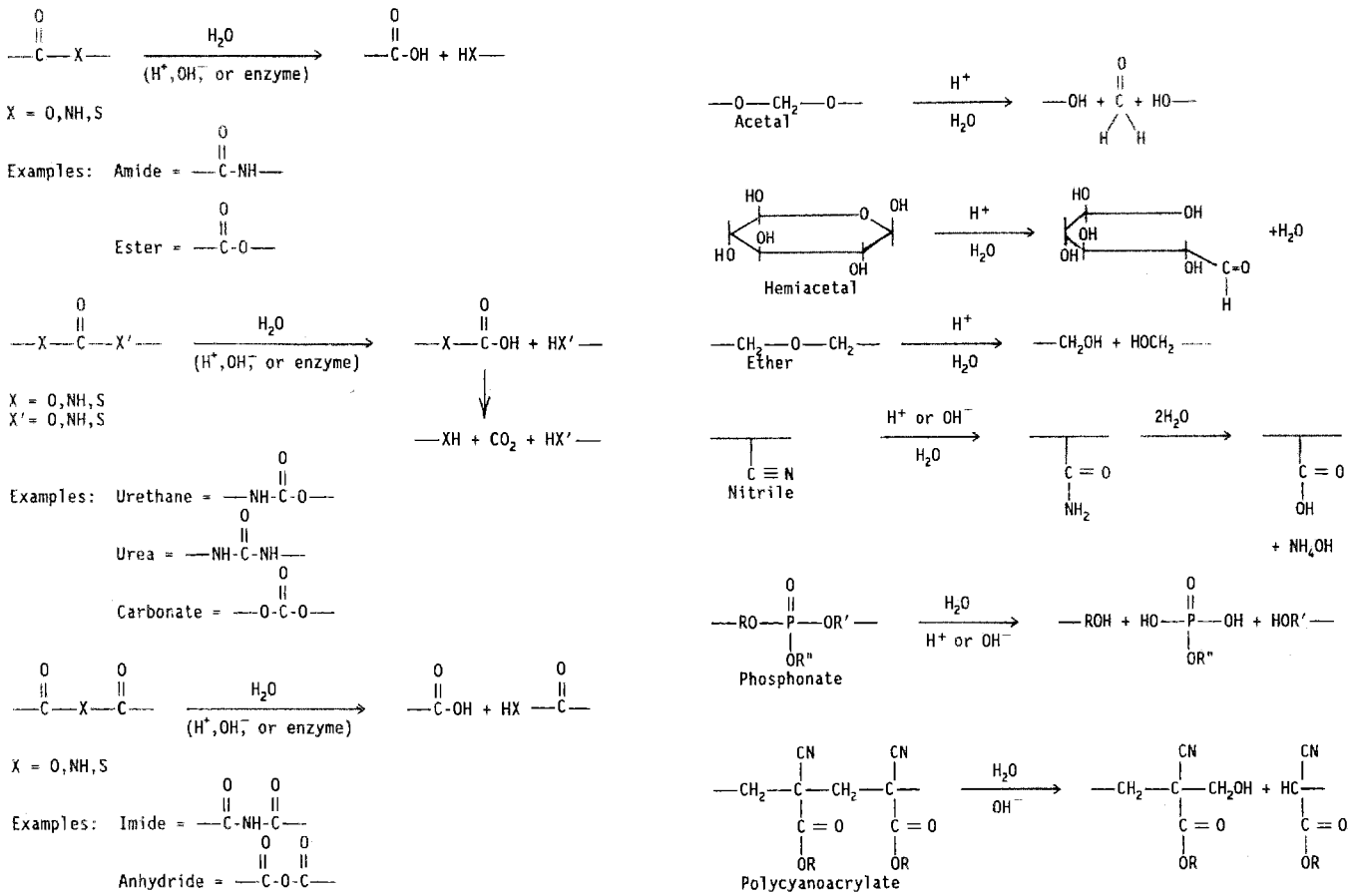


FIG. 1. Hydrolyzable groups in polymer biomaterials.

biomaterials, functional groups consist of carbonyls bonded to heterochain elements (O, N, S). Examples include esters, amides, and carbonates (Fig. 1). Other polymers containing groups such as ether, acetal, nitrile, phosphonate, or active methylenes, hydrolyze under certain conditions (Fig. 1). Groups that are normally very stable to hydrolysis are indicated in Fig. 2.

The rate of hydrolysis tends to increase with a high proportion of hydrolyzable groups in the main or side chain, other polar groups which enhance hydrophilicity, low crystallinity, low or negligible cross-link density, a high ratio of exposed surface area to volume and, very likely, mechanical stress. Porous hydrolyzable structures undergo especially rapid property loss because of their large surface area. Factors that tend to suppress hydrolysis kinetics include hydrophobic moieties (e.g., hydrocarbon or fluorocarbon), cross-linking, high crystallinity due to chain order, thermal annealing or orientation, low stress, and compact shape. While the molecular weight of linear polymers per se may not have a great effect on degradation rate, physical property losses may be retarded for a given number of chain cleavage events with relatively high-molecular-weight polymers. Property loss caused by chain cleavage

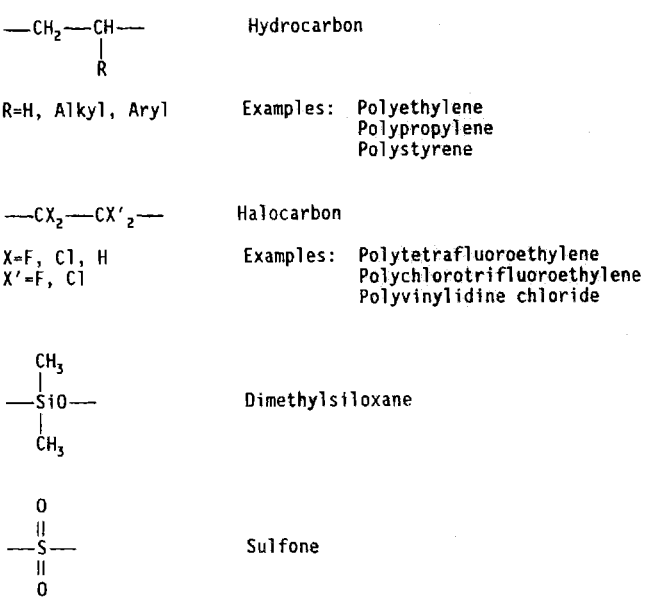


FIG. 2. Groups highly stable to hydrolysis.

is more pronounced in polymers with weak intermolecular bonding forces.

Host-Induced Hydrolytic Processes

The body is normally a highly controlled reaction medium. Through homeostasis, the normal environment of most implants is maintained at isothermal (37°C), neutral (pH 7.4), aseptic, and photoprotected aqueous steady state. By *in vitro* standards, these conditions appear mild. However, complex interactions of humoral and cellular components of body fluids involving activators, receptors, inhibitors, etc. produce aggressive responses to any foreign bodies through the processes of adhesion, chemical reaction, and particulate transport.

Several scenarios leading to hydrolysis in the host can be considered. First, essentially neutral water is capable of hydrolyzing certain polymers (e.g., polyglycolic acid) at a significant rate (Chapter 2.5 and Zaikov, 1985). However, this simple mechanism is unlikely to be significant in polymer compositions selected for long-term *in vivo* biostability.

Next, ion-catalyzed hydrolysis offers a likely scenario in body fluids. Extracellular fluids contain ions such as: H^+, OH^-, Na^+, Cl^-, HCO_3^-, PO_4^{-3}, K^+ Mg^{2+}, Ca^{2+} and SO_4^{2-}. Organic acids, proteins, lipids, lipoproteins, etc. also circulate as soluble or colloidal components. It has been shown that certain ions (e.g., PO_4^{3-}) are effective hydrolysis catalysts, enhancing, for example, reaction rates of polyesters by several orders of magnitude (Zaikov, 1985). Ion catalysis may be a surface effect or a combined surface-bulk effect, depending on the hydrophilicity of the polymer. Very hydrophobic polymers (e.g., those containing <2% water of saturation) absorb negligible concentrations of ions. Hydrogels, on the other hand, which can absorb large amounts of water (>15% by weight) are essentially "sieves," allowing significant levels of ions to be absorbed with consequent bulk hydrolysis via acid, base, or salt catalysis.

Localized pH changes in the vicinity of the implanted device, which usually occur during acute inflammation or infection, can cause catalytic rate enhancement of hydrolysis (Zaikov, 1985). Organic components, such as lipoproteins, circulating in the bloodstream or in extracellular fluid, appear to be capable of transporting catalytic inorganic ions into the polymer bulk by poorly defined mechanisms.

Enzymes generally serve a classic catalytic function, altering reaction rate (via ion or charge transfer) without being consumed, by modifying activation energy but not thermodynamic equilibrium. While enzymes function in extracellular fluids, they are most effectively transferred onto target substrates by direct cell contact (e.g., during phagocytosis). Hydrolytic enzymes or hydrolases (e.g., proteases, esterases, lipases, glycosidases) are named for the molecular structures they affect. They are cell-derived proteins which act as highly specific catalysts for the scission of water-labile functional groups.

Enzymes contain molecular chain structures and develop conformations that allow "recognition" of chain sequences (receptors) on biopolymers. Complexes form between segments of the enzyme and the biopolymer substrate which result in enhanced bond cleavage rates. Lacking the recognition sequences of susceptible natural polymers, most synthetic polymers are more resistant to enzymatic degradation. Nevertheless, comparative studies have shown some enhancement of hydrolysis rates by enzymes, particularly with synthetic polyesters and polyamides (Zaikov, 1985; Smith *et al.*, 1987; Kopecek *et al.*, 1983). Apparently the enzymes can recognize and interact with structural segments of the polymers, or more accurately, of the polymers coated with serum proteins, to initiate their catalytic action *in vivo* (Pitt, 1992).

Enzymes with demonstrated effects on hydrolysis rates can be quite selective in the presence of several hydrolyzable functional groups. For example, polyether urethane ureas and polyester urethane ureas exposed to hydrolytic enzymes (an esterase, cholesterol esterase, and a protease, elastase) were observed for rate and site of hydrolysis. Enzyme catalysis was clearly observed for the ester groups while the hydrolytically susceptible urea, urethane, and ether groups did not show significant hydrolysis as indicated by release of radiolabeled degradation products (Santerre *et al.*, 1994; Labow *et al.*, 1995).

Many enzymes exert predominantly a surface effect because of their great molecular size, which prevents absorption. Even hydrogels [e.g., poly(acrylamide)], which are capable of absorbing certain proteins, have molecular weight cutoffs for absorption well below those of such enzymes. However, as the degrading surface becomes roughened or fragmented, enzymatic action may be enhanced as a result of increased surface area if the substrates remain accessible to phagocytic cells that contain the active enzymes. Implanted devices that are in continuous motion relative to neighboring tissue can provoke inflammation, stimulating enzyme release.

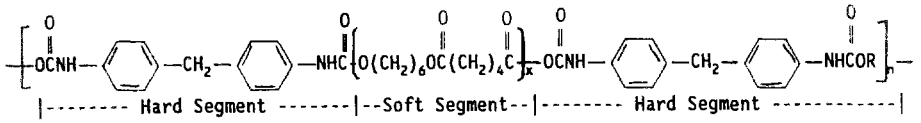
Hydrolysis: Preclinical and Clinical Experience

A discussion of *in vivo* responses of several prominent polymer compositions known to be susceptible to hydrolysis follows. The structures of these polymers are described in Chapter 2.3.

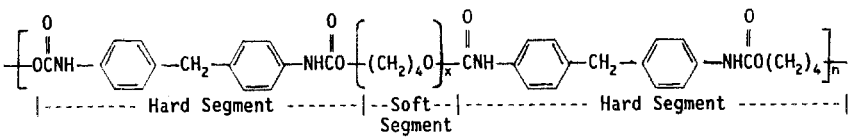
Polyesters

Poly(ethylene terephthalate) (PET), in woven, velour, or knitted fiber configurations, remains a primary choice of cardiovascular surgeons for large-diameter vascular prostheses, arterial patches, valve sewing rings, etc. It is a strong, flexible, polymer, stabilized by high crystallinity as a result of chain rigidity and orientation and is often considered to be biostable. Yet, over several decades, there have been numerous reports of long-term degeneration of devices *in vivo,* owing to breakage of fibers and device dilation. The proposed causes have been structural defects, processing techniques, handling procedures, and hydrolytic degradation (Cardia *et al.*, 1989).

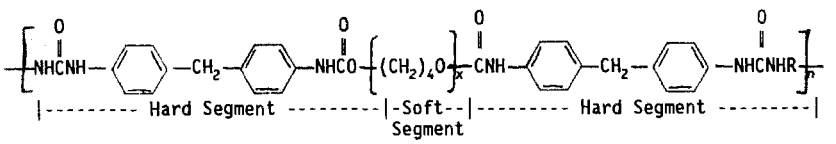
Systematic studies of PET implants in healthy dogs have shown slow degradation rates, which were estimated to be



Polyester urethane (e.g., Surgitek, Meme Mammary Prosthesis Covering)



Polyether urethane (eg., Dow Pellethane 2363 Series)



Polyether urethane urea (eg., Ethicon Biomer)

FIG. 3. Structure of implantable polyester urethane, polyether urethane, and polyether urethane urea.

equivalent to those in humans. For woven patches implanted subcutaneously, a mean total absorption time by the body of 30 ± 7 years, with 50% deterioration of fiber strength in 10 ± 2 years was projected. In infected dogs, however, where localized pH dropped to as low as 4.8, degradation was enhanced exponentially, with complete loss of properties within a few months (Zaikov, 1985). Human implant retrieval studies have shown significant evidence of graft infection (Vinard *et al.*, 1991). Besides the obvious pathological consequences of infection, the enhanced risk of polymer degradation is a cause for concern.

Aliphatic polyesters are most often intended for use as biodegradable polymers, with polycaprolactone, for example, undergoing a significant decrease in molecular weight as indicated by a drop of 80–90% in relative viscosity within 120 weeks of implant (Kopecek *et al.*, 1983).

Polyester Urethanes

The earliest reported implants of polyurethanes, dating back to the 1950s, were cross-linked, aromatic polyester urethane foam compositions (Blais, 1990; Bloch *et al.*, 1972). Their use in plastic and orthopedic reconstructive surgery initially yielded promising results. Acute inflammation was low. Tissue ingrowth promoted thin fibrous capsules. However, within months, they were degraded and fragmented, producing untoward chronic effects (Bloch *et al.*, 1972). Foci of initial degradation are generally considered to be the polyadipate ester soft segments which undergo hydrolysis (Fig. 3). By comparison, corresponding polyether urethanes are very resistant to hydrolysis, although more susceptible to oxidation (see the section on oxidative biodegradation). Whether such hydrolytically degraded polyester urethanes subsequently produce meaningful levels of aromatic amines (suspected carcinogens) by hydrolysis of urethane functions *in vivo* is currently an unresolved subject of considerable debate (Szycher *et al.*, 1991; Blais, 1990).

It is noteworthy that polyester urethane foam-coated silicone mammary implants have survived as commercial products until recently (Blais, 1990), despite their known tendency to degrade. Apparently the type of fibrous capsules formed on devices containing degradable foam were favored by some clinicians over those caused by smooth-walled silicone implants. In large devices, unstabilized by tissue ingrowth, the frictional effects of sliding may cause increased capsule thickness and contraction (Snow *et al.*, 1981) along with extensive chronic inflammation.

Polyamides

Nylon 6 (polycaproamide) and nylon 6,6 [poly(hexamethylene adipamide)] contain a hydrolyzable amide connecting group, as do proteins. These synthetic polymers can absorb 9–11% water, by weight, at saturation. It is predictable, then, that they degrade by ion-catalyzed surface and bulk hydrolysis (Fig. 1). In addition, hydrolysis due to enzymatic catalysis leads to surface erosion (Zaikov, 1985). Quantitatively, nylon 6,6 lost 25% of its tensile strength after 89 days, and 83% after 726 days in dogs (Kopecek, 1983). An example of polyamide degradation of particular consequence involved the *in vivo*

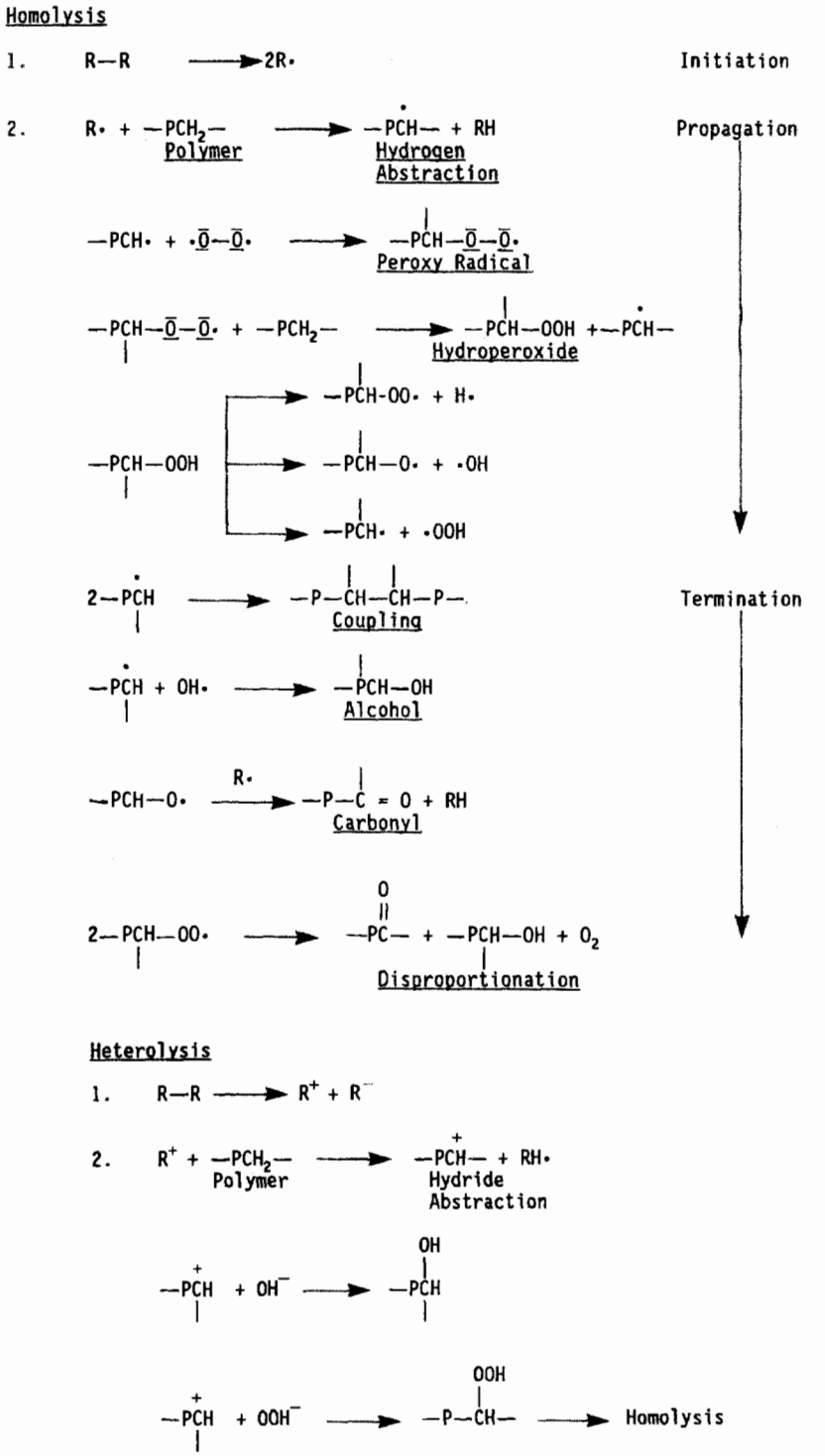


FIG. 4. Proposed homolytic chain reaction and heterolytic oxidation mechanisms.

fragmentation of the nylon 6 tail string of an intrauterine contraceptive device. This string consisted of nylon 6-coated nylon 6 multifilaments. The combination of fluid absorption (>10%) and hydrolysis was claimed to produce environmental stress cracking. The cracked coating allegedly provided a pathway for bacteria to travel from the vagina into the uterus, resulting in significant pelvic inflammatory disease (Hudson and Crugnola, 1987).

Degradation of a polyarylamide intended for orthopedic use (the fiber-reinforced polyamide from *m*-xylylene diamine

and adipic acid) was also shown in a rabbit implant study. [Although the material provoked a foreign body reaction comparable to a polyethylene control, surface pitting associated with resolving macrophages was noted at 4 weeks and became more pronounced by 12 weeks. This result was not predicted since polyarylamides are very resistant to solvents and heat (Finck *et al.*, 1995).]

Polyamides with long aliphatic hydrocarbon chain segments (e.g., polydodecanamide) are more hydrolytically stable than shorter chain nylons and correspondingly degrade slower *in vivo*.

Polyalkylcyanoacrylates

This class of polymers, used as tissue adhesives, is noteworthy as a rare case in which carbon–carbon bonds are cleaved by hydrolysis (Fig. 1). This occurs because the methylene ($—CH_2—$) hydrogen in the polymer is highly activated inductively by electron-withdrawing neighboring groups. Formation of the polymer adhesive from monomers is base catalyzed, with adsorbed water on the adherend being basic enough to initiate the reaction.

Catalysts for equilibrium reactions affect the reverse, as well as the forward reaction. Therefore, water associated with tissue can induce polycyanoacrylate hydrolysis by a "reverse Knoevenagel" reaction (Fig. 1). More basic conditions and (as suggested by *in vitro* cell culture or implant studies) enzymatic processes are much more effective. In chick embryo liver culture (a rich source of a variety of enzymes), methyl cyanoacrylate degraded much faster than in culture medium alone. In animal implants, methyl cyanoacrylate was extensively degraded within 4–6 months (Kopecek, 1983). Higher alkyl (e.g., butyl) homologs degraded slower than the methyl homolog and were less cytotoxic (Hegyeli, 1973).

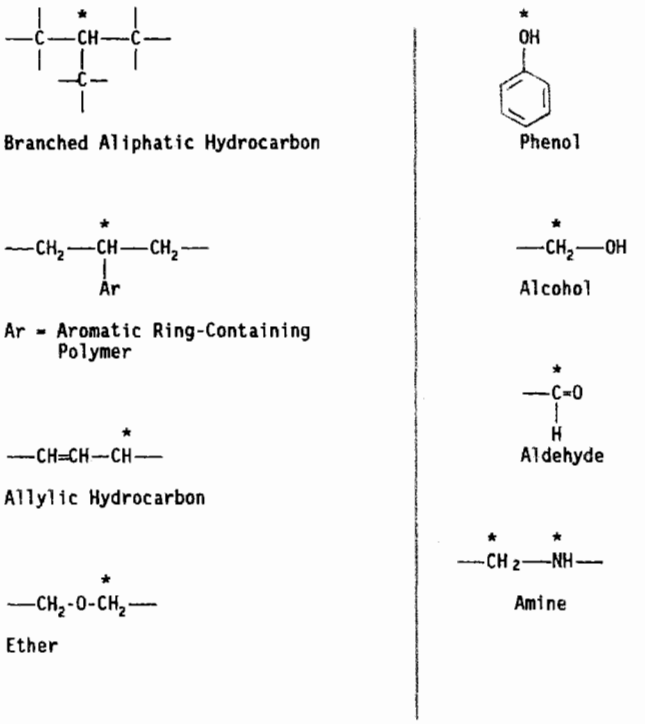


FIG. 5. Readily oxidizable functional groups (* is site of homolysis or heterolysis).

OXIDATIVE BIODEGRADATION

Oxidation Reaction Mechanisms and Polymer Structures

While much is known about the structures and reaction products of polymers susceptible to oxidative biodegradation, confirmation of the individual reaction steps has not yet been demonstrated analytically. Still, mechanistic inferences are possible from extensive knowledge of physiological oxidation processes and polymer oxidation *in vitro*.

The polymer oxidation processes to be discussed may be consistent with a homolytic chain reaction or a heterolytic mechanism. Species such as carbonyl, hydroxyl, and chain scission products are detectable. Classic initiation, propagation, and termination events for homolysis and ionic heterolytic processes are detailed in Fig. 4.

Except for the nature of susceptible functional groups, the hydrolysis resistance principles stated in the section on the structures of hydrolyzable polymers are valid for predicting relative oxidation resistance of polymers. Sites favored for initial oxidative attack, consistent with a homolytic or heterolytic pathway, are those that allow abstraction of an atom or ion and provide resonance stabilization of the resultant radical or ion. Figure 5 provides a selection of readily oxidized groups and the atom at which initial attack occurs. In Fig. 6, examples of radical and ion stabilization by resonance in ether and branched hydrocarbon structures are provided. Peroxy, carbonyl, and other radical intermediates are stabilized by similar resonance delocalization of electrons from the elements C, O, H, or N.

Two general categories of oxidative biodegradation, based on the source of initiation of the process, are direct oxidation by the host and device or external environment-mediated oxidation.

Direct Oxidation by Host

In these circumstances, host-generated molecular species effect or potentiate oxidative processes directly on the polymer. Current thinking, based on solid analytical evidence, is that such reactive molecules are derived from activated phagocytic cells responding to the injury and properties of the foreign body at the implant site (Zhao *et al.*, 1991). These cells, which originate in the bone marrow and populate the circulatory system and connective tissues, are manifest as two types, the neutrophils (polymorphonuclear leukocytes, PMNs) and the monocytes. The latter can differentiate into macrophage and foreign body giant cell (FBGC) phenotypes.

Much work is under way to elucidate the sequence of events

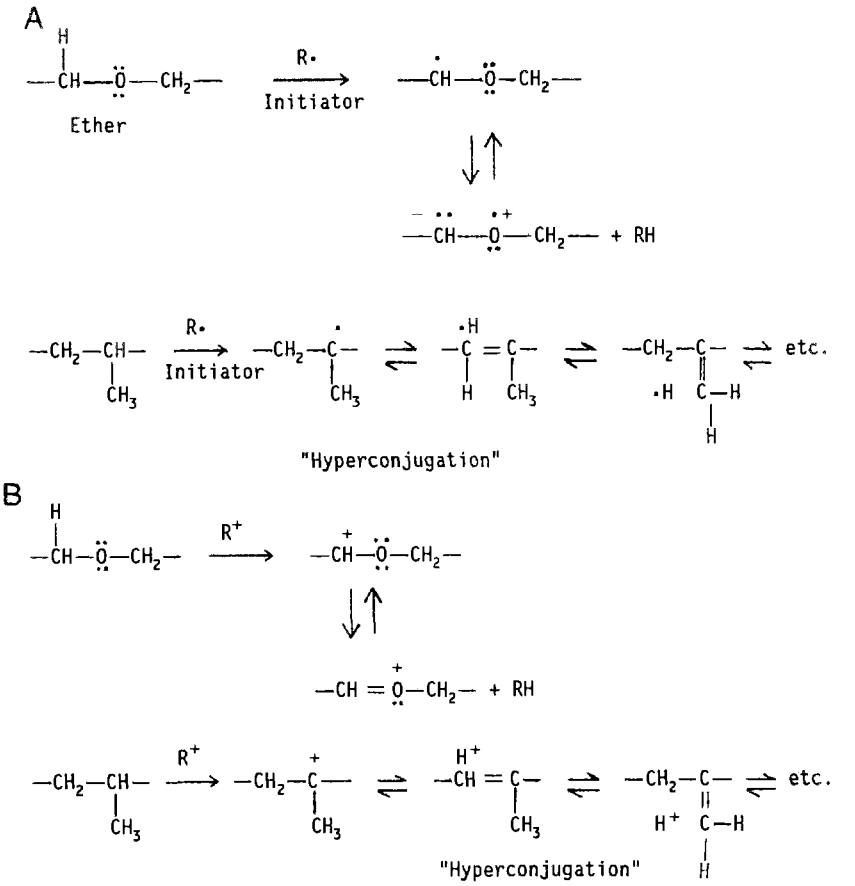


FIG. 6. (A) Resonance stabilization of ether and hydrocarbon radicals. (B) Resonance stabilization of ether and hydrocarbon cations.

leading to phagocytic oxidation of biomaterials. Certain important processes of wound healing in the presence of biologically derived foreign bodies such as bacteria and parasites, are showing some relevance to biomaterial implants (Northrup, 1987).

Neutrophils, responding to chemical mediators at the wound site, mount a powerful but transient chemical attack within the first few days of injury (Northrup, 1987; Test and Weiss, 1986). Chemically susceptible biomaterials may be affected if they are in close apposition to the wound site (Sutherland *et al.*, 1993). Activated macrophages subsequently multiply and subside within days at a benign wound site or in weeks if stimulants such as toxins or particulates are released at the site. Their fusion products, foreign body giant cells, can survive for months to years on the implant surface. Macrophages also remain resident in collagenous capsules for extended periods.

While we recognize that the mechanism of cellular attack and oxidation of biomaterials is as yet unconfirmed, the following discussion attempts to provide logical biological pathways to powerful oxidants capable of producing known degradation products.

Both PMNs and macrophages metabolize oxygen to form a superoxide anion ($O_2^{\cdot-}$). This intermediate can undergo trans-

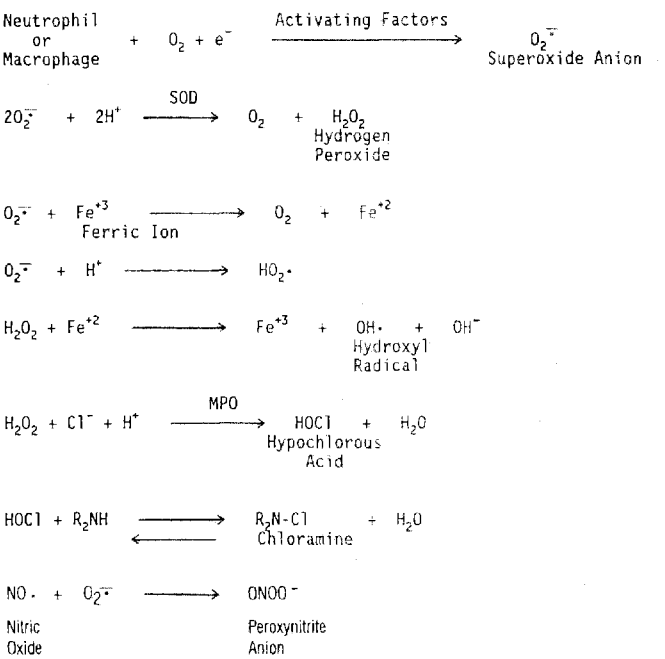


FIG. 7. Generation of potential oxidants by phagocytic processes.

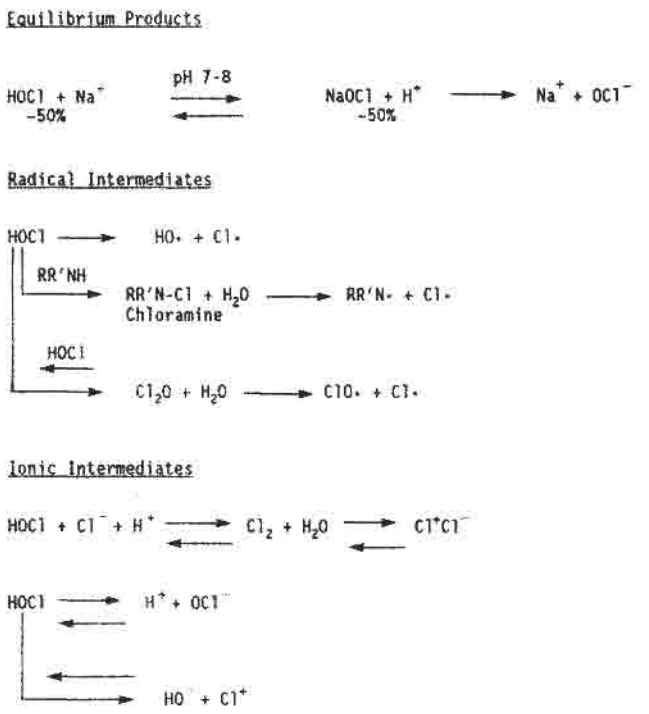


FIG. 8. Hypochlorous acid: formation and potential reaction intermediates.

formation to more powerful oxidants, or, conceivably, can initiate homolytic reactions on the polymer. Superoxide dismutase (SOD), a ubiquitous peroxidase enzyme, can catalyze the conversion of superoxide to hydrogen peroxide, which, in the presence of myeloperoxidase (MPO), derived from PMNs, is converted to hypochlorous acid (HOCl). A potent biomaterial oxidant in its own right (Coury *et al.*, 1987), hypochlorite can oxidize free amine functionality (e.g., in proteins) to chloramines that can perform as long-lived sources of chlorine oxidant (Test and Weiss, 1986, Figs. 7, 8). Hypochlorite can oxidize other substituted nitrogen functional groups (amides, ureas, urethanes, etc.) with potential chain cleavage of these groups.

The following paragraphs describe potential cooperative reactions involving acquired peroxidase and free ferrous ions. Macrophages contain essentially no MPO, so their hydrogen peroxide is not normally converted to HOCl. However, PMN-derived MPO can bind securely to foreign body surfaces (Locksley *et al.*, 1982), and serve as a catalyst reservoir for macrophage- or FBGC-derived HOCl production. If free ferrous ion, which is normally present in negligible quantities in the host, is released to the implant site by hemolysis or other injury, it can catalyze the formation of the powerfully oxidizing hydroxyl radical via the Haber–Weiss cycle (Klebanoff, 1982; Fig. 7).

Figure 8 shows radical and ionic intermediates of HOCl that may initiate biomaterial oxidation. Figure 9 is a diagram showing a leukocyte phagocytic process which employs endogenous MPO catalysis of HOCl formation. In a more general sense, the MPO may come from within or outside of the cell.

The foregoing discussion of sources of direct oxidation focused primarily on acute implant periods in which bursts of PMN activity followed by macrophage activity normally resolve within weeks. However, since the foreign body subsequently remains implanted, a sustained, if futile attempt to phagocytose an implanted device provides a prolonged release of chemicals onto the biomaterial. This phenomenon, called

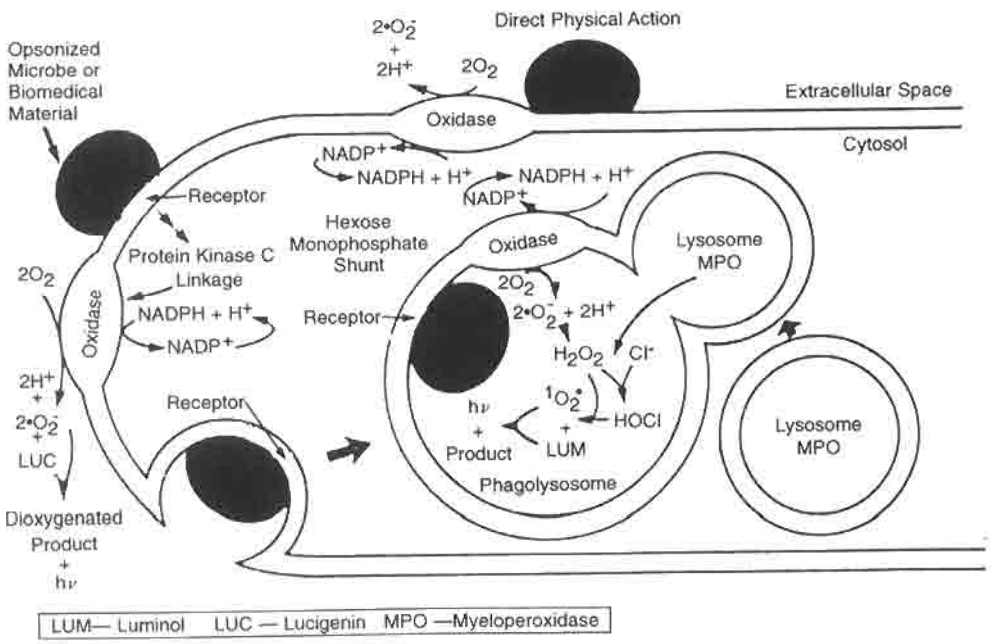


FIG. 9. Activation of phagocyte redox metabolism: chemiluminigenic probing with luminol and lucigenin. From R. C. Allen, personal communication.

TABLE 3 Characteristics of Polyether Urethanes That Cracked *in Vivo*

Components contained residual processing and/or applied mechanical stresses/strains
Components were exposed to a medium of viable cellular and extracellular body constituents
Polymers had oxidatively susceptible (aliphatic ether) groups
Analysis of polymers showed surface oxidation products

exocytosis, occurs over months to possibly years (Zhao *et al.*, 1990) and results primarily from the macrophage-FBGC line. It can contribute to long-term chemical degradation of the polymer.

The oxidation processes induced by phagocytes are the result of oxidants produced by general foreign body responses, not direct receptor–ligand catalysis by oxidase enzymes. Attempts to degrade oxidatively susceptible polymers by direct contact with oxidase enzymes have generally been unsuccessful (Santerre *et al.*, 1994; Sutherland *et al.*, 1993).

Macrophages mediate other processes, such as fibrous capsule formation around the device. Their release of cellular regulatory factors stimulates fibroblasts to populate the implant site and produce the collagenous sheath. Any knowledge of the effects of such factors as fibroblasts or fibrous capsules on rates and mechanisms of polymer degradation is, at this time, extremely rudimentary.

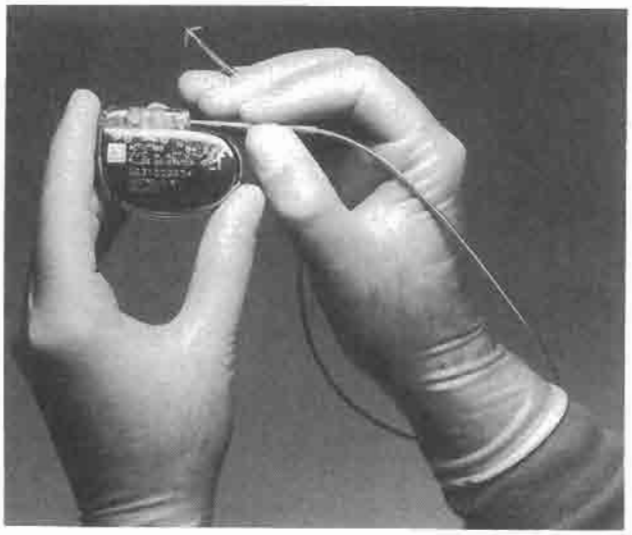


FIG. 10. Cardiac pacemaker with polyurethane lead, tine, and connector. Courtesy of Medtronic, Inc.

Stress Cracking

An important category of host-induced biodegradation with an oxidative component is stress cracking as manifest in polyether methane elastomers. It differs from classic environmental stress cracking (ESC), which involves a susceptible material at a critical level of stress in a medium which may permeate, but does not dissolve, the polymer. Classic ESC is not accompanied by significant chemical degradation (Stokes, 1988). Instead,

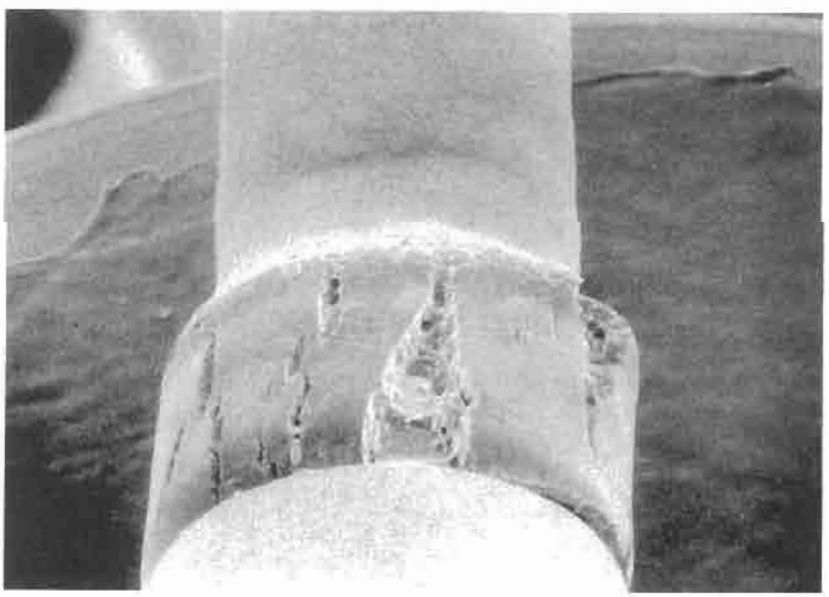


FIG. 11. Pellethane 2463-80A tubing with high applied radial stress showing total breach.

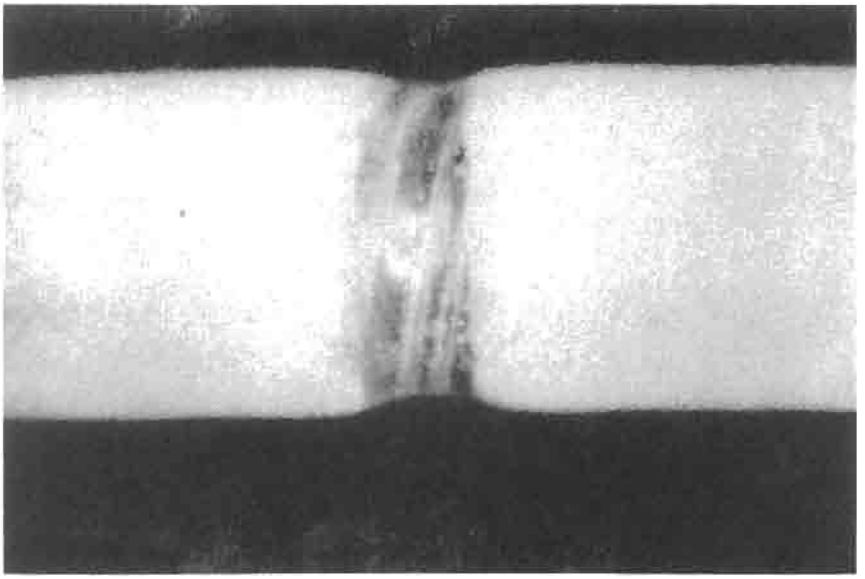


FIG. 12. Pellethane 2363-80A tubing showing "frosting" due to stress from tight ligature.

stress cracking of polyurethanes is characterized by surface attack of the polymer and by chemical changes induced by relatively specific *in vivo* or *in vitro* oxidizing conditions. Conditions relevant to stress cracking of certain polyether urethane compositions are stated in Table 3.

Recent information on the stress cracking of polyether urethanes and polyether urethane ureas (e.g., Fig. 3) has provided insights that may be valid for these and other compositions that can be oxidized (e.g., polypropylene; Altman *et al.*, 1986; polyethylenes, Wasserbauer *et al.*, 1990; Zhao *et al.*, 1995).

Polyether urethanes, which are resistant to hydrolysis *in vivo*, are used as connectors, insulators, tines, and adhesives for cardiac pacemakers and neurological stimulators (Fig. 10). They have performed with high reliability in chronic clinical

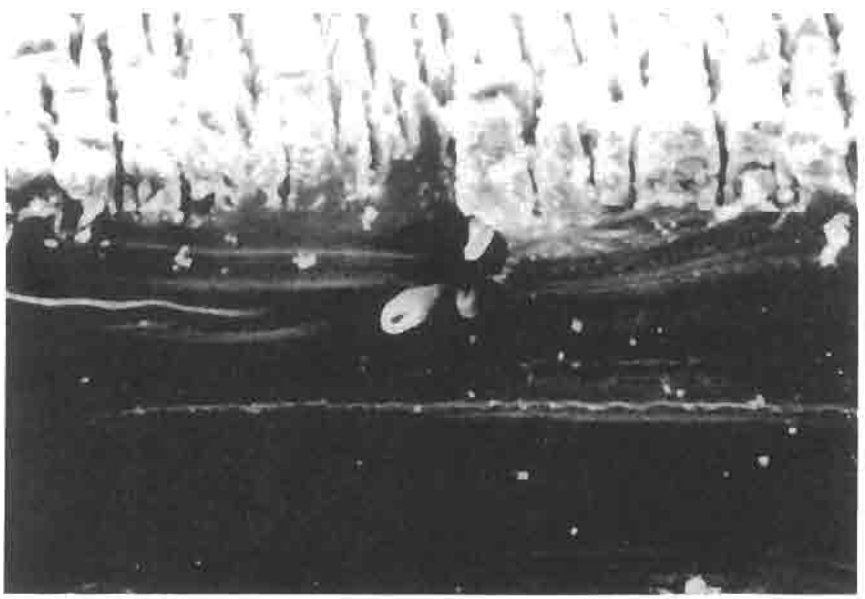


FIG. 13. Stress crack pattern (frosting) near tight ligature. ×14.

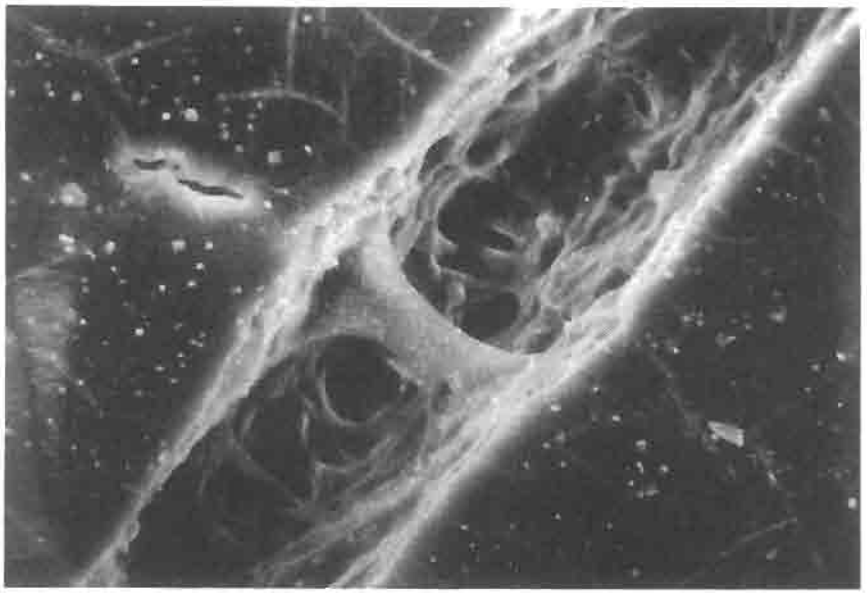


FIG. 14. Single stress crack with rough walls and "tie fibers" indicative of ductile fracture. ×700.

applications since 1975. Certain polyether urethane pacing leads have displayed surface cracks in their insulation after residence times *in vivo* of months to years. These cracks are directly related in frequency and depth to the amount of residual stress (Figs. 11, 12) and the ether (soft segment) content of the polyurethane (Coury *et al.*, 1987).

Morphologically, the cracks display regular patterns predominately normal to the force vectors, with very rough walls, occasionally with "tie fibers" bridging the gaps, indicative of ductile rather than brittle fracture (Figs. 13, 14). Infrared analysis indicates that oxidation does not take place detectably in the bulk, only on the surface, where extensive loss of ether functionality (1110 cm^{-1}) and enhanced absorption in the hydroxyl and carbonyl regions are observed (Stokes *et al.*, 1987). Possible mechanisms for the oxidative degradation of ethers are presented in Fig. 15.

In a seminal study, Zhao *et al.* (1990) placed polyurethane tubing in cages permeable to fluids and cells under strain (therefore under high initial stress, which was subject to subsequent stress relaxation), and implanted them in rats. In certain cases, antiinflammatory steroids or cytotoxic polymers were coimplanted in the cages. Implants of up to 15 weeks were retrieved. The only prestressed samples to crack were those that did not reside in the cages with the coimplants. The authors concluded that adherent cells caused the stress cracking, and cell necrosis or deactivation inhibited crack induction.

Subsequently, viable phagocytic cells were implicated as a cause of crack initiation *in vivo* (Zhao *et al.*, 1991). By removing adherent foreign body giant cells after implantation of a curved polyether urethane urea film in a wire cage for up to 10 weeks, exposed "footprints" showed localized surface cracking, on the order of several microns deep and wide. Adjacent areas of polymer, which were devoid of attached cells, were not cracked. Owing to relatively low stresses in the implanted film, deep crack propagation was not observed.

In vitro studies of strained (Stokes, 1988) and unstrained polyether urethane films (Phua *et al.*, 1987; Bouvier *et al.*, 1991; Ratner *et al.*, 1988) using oxidants, enzymes, etc., have sought to duplicate *in vivo* stress cracking. Although some surface chemical degradation with products similar to those seen *in vivo* was demonstrated, stress crack morphology was not closely matched *in vitro* until recently, in two studies. A test which involves immersing stressed polyether urethane tubing in a medium of glass wool, hydrogen peroxide, and cobalt chloride produces cracks which duplicate those produced *in vivo* but with rate acceleration of up to seven times (Zhao *et al.*, 1995). In another study, comparable crack patterns were produced when specimens of stressed tubing in rats were compared with those incubated with PMNs in culture (Sutherland *et al.*, 1993). Moreover, this study revealed a difference in chemical degradation products with time of implant which correlated with products from oxidants generated primarily by PMNs (HOCl) and macrophages ($ONOO^-$). Early implant times, activated PMNs, and HOCl caused preferential decrease in the urethane oxygen stretch peak while longer implant times and $ONOO^-$ caused selective loss of the aliphatic ether stretch peak (by infrared spectroscopy).

Taken together, the foregoing observations are consistent with a two-step mechanism for stress cracking *in vivo*. This hypothesis, as yet unproven, is under investigation. In the first step, surface oxidation induces very shallow, brittle microcracks. The second step involves propagation of the cracks in which specific body fluid components act on the formed cracks to enhance their depth and width without inducing major detectable bulk chemical reactions. Should this hypothesis prove

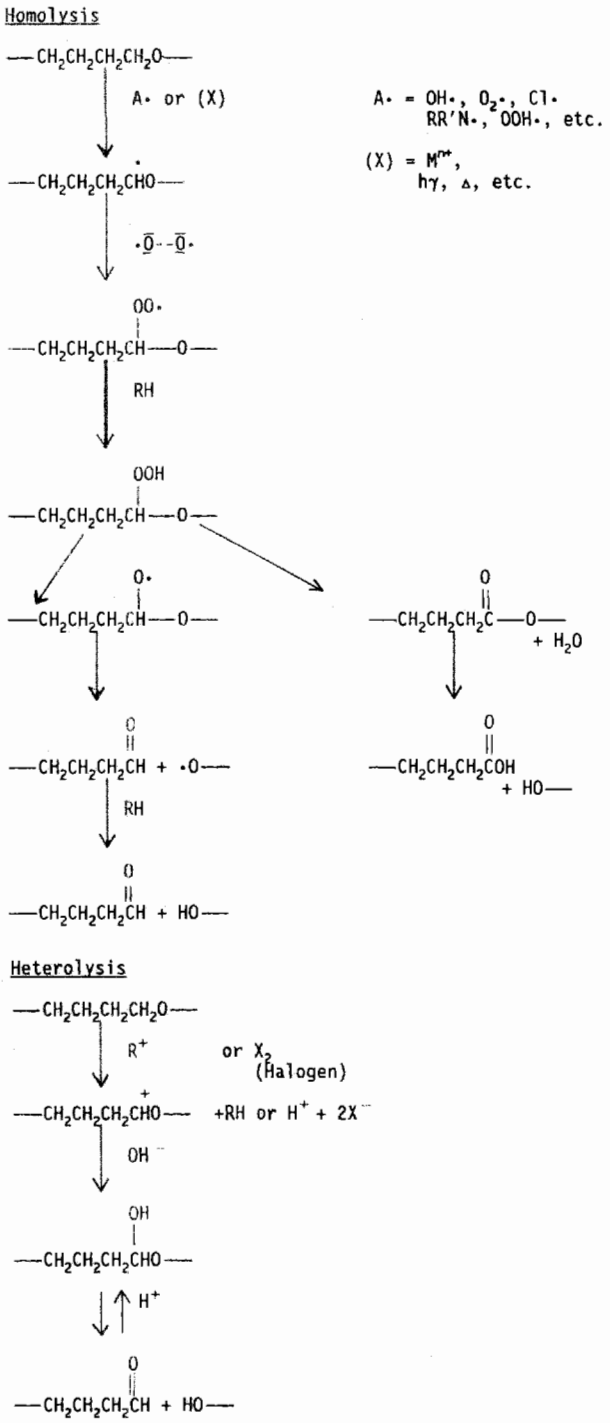


FIG. 15. Pathways for oxidative fragmentation of polyethers.

correct, the term "oxidation-initiated stress cracking" would be reasonably descriptive.

Stress cracking has been controlled by reducing residual stress, isolating the polymer from cell contact (Tang *et al.*, 1994), protecting the polymer from stress cracking media, or using stress crack-resistant (in the case of urethanes, ether-free) polymers (Takahara *et al.*, 1994; Coury *et al.*, 1990). Stress cracking is next compared with another type of degradation, metal ion-induced oxidation.

Device or Environment-Mediated Oxidation

Metal Ion-Induced Oxidation

A process of oxidative degradation that has, thus far, only been reported clinically for polyether urethane pacemaker leads, requires, as does stress cracking, a very specific set of conditions. The enabling variables and fracture morphology are quite different from stress cracking, although oxidative degradation products are similar. Biodegradation of implanted devices through stress cracking always occurs on polymer surfaces exposed to cells and provides characteristic rough-walled fissures (indicative of ductile fracture) oriented perpendicular to the stress vector (Figs. 11–14). Metal ion-induced oxidation takes place on the enclosed inner surfaces of pacing lead insulation near corroded metallic components and their entrapped corrosion products. Smooth crack walls and microscopically random crack orientation is indicative of brittle fracture (Figs. 16, 17). Macroscopically, crack patterns that track metal component configurations may be present (Fig. 18). Degradation products which may be found deeper in the bulk than with stress cracking, again are indicative of brittle fracture.

This phenomenon, called metal ion-induced oxidation, has been confirmed by *in vitro* studies in which polyether urethanes were aged in metal ion solutions of different standard oxidation potentials. Above an oxidation potential of about +0.77, chemical degradation was severe. Below that oxidation potential, changes in the polymer that are characteristic of simple plasticization were seen (Coury *et al.*, 1987; Table 4). This technique also showed that metal ion-induced oxidation was proportional to the ether content of the polyurethane (Coury *et al.*, 1987; Table 5).

The effect of various metals on oxidation *in vitro* and *in vivo* has also been studied. Different metallic components of pacing lead conductors were sealed in polyether urethane (Dow Pellethane 2363-80A) lead tubing and immersed in 3% hydrogen peroxide at 37°C for up to 6 months (Stokes *et al.*, 1987) or implanted in rabbits for up to 2 years (Stokes *et al.*, 1990). Both techniques resulted in corroded metals and degraded tubing lumen surfaces, under certain conditions, within 30 days. *In vivo*, the interaction of body fluids with cobalt and its alloys, in particular, resulted in oxidative cracking of the polymer.

The metal ion-induced oxidation process clearly involves corrosion of metallic elements to their ions and subsequent oxidation of the polymer. In operating devices, the metal ion may be formed by solvation, galvanic corrosion, or chemical or biochemical oxidation (Fig. 19). In turn, these metal ions develop oxidation potentials that may well be enhanced in body fluids over their standard half-cell potentials. As strong oxidants, they produce intermediates or attack the polymer to initiate the chain reaction (Fig. 20). Metal ion-induced oxidation is, therefore, the result of a highly complex interaction of the device, the polymer, and the body.

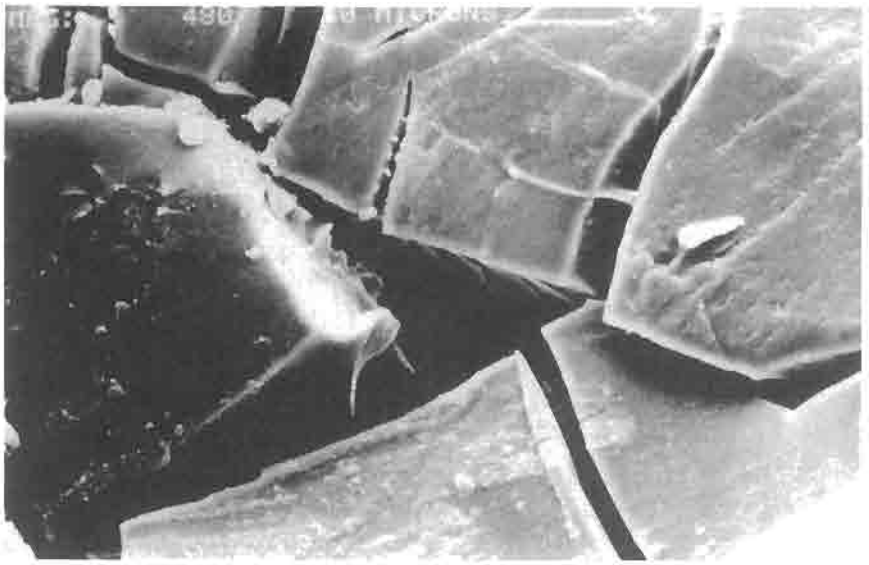


FIG. 16. Random crack pattern of Pellethane 2363-80A lead insulation caused by metal ion-induced oxidation. ×480.

Should metal ion-induced oxidation be a possibility in an implanted device, several approaches are available to control this problem. They are not universally applicable, however, and should be incorporated only if functionality and biocompatibility are retained. Potentially useful techniques include using corrosion-resistant metals, "flushing" corrosive ions away from the susceptible polymer, isolating the metals and polymer from electrolyte solutions, incorporating appropriate antioxidants, and using oxidation-resistant polymers if available.

Recently, polyurethane elastomers with enhanced oxidation stability have been developed. They are segmented, ether- and ester-free polymers with unconventional soft segments, including, for example, hydrogenated polybutadiene, polydimethylsiloxane, polycarbonate, and dimerized fat acid derivatives (Takahara *et al.*, 1991, 1994; Coury *et al.*, 1990; Pinchuk *et al.*,

FIG. 17. Smooth crack wall indicative of brittle fracture caused by metal ion-induced oxidation. ×830.

FIG. 18. Crack pattern on inner lumen of polyether urethane lead insulation tracking coil indicative of metal ion-induced oxidation. ×100.

1991; Kato *et al.*, 1995; Ward *et al.*, 1995). In implant tests, they have shown reduced tendency to stress crack, and some of them have shown high resistance to metal ion oxidants *in vitro*.

Oxidative Degradation Induced by External Environment

Under very limited circumstances the body can transmit electromagnetic radiation that may affect the integrity of implanted polymers. For example, the cornea and vitreous humor of the eye as well as superficial skin layers allow the passage of long-wave (320–400 nanometer) "ultraviolet A" radiation. Absorption of ultraviolet radiation causes electron excitation that can lead to photo-oxidative degradation. This process has been suggested in the breakdown of polypropylene components of intraocular lens (Altman *et al.*, 1986).

In maxillofacial exo- and, very likely, endoprostheses, elastomers may undergo undesirable changes in color and physical properties as a consequence of exposure to natural sunlight-frequency radiation (Craig *et al.*, 1980). Photo-oxidation mechanisms involving the urethane function of aromatic polyether- or polyester urethanes are shown in Fig. 21. Antioxidants and ultraviolet absorbers provide limited protection for these materials.

TABLE 4 Effect of Metal Ion Oxidation Potential on Properties of Polyetherurethane (Pellethane 2363-80A)[a]

Aqueous solution	Standard oxidation potential	Change in tensile strength (%)	Change in elongation (%)
$PtCl_2$	Ca +1.2	−87	−77
$AgNO_3$	+0.799	−54	−42
$FeCl_3$	+0.771	−79	−10
Cu_2Cl_2	+0.521	−6	+11
$Cu_2(OAc)_2$	+0.153	−11	+22
$Ni(OAc)_2$	−0.250	−5	+13
$Co(OAc)_2$	−0.277	+1	+13

[a]Conditions: 0.1 *M* solutions/90°C/35 days vs. controls aged in deionized water; ASTM (D-1708) microtensile specimens; specimens were tested wet.

TABLE 5 Effect of Ether Content of Polyether Urethane on Susceptibility to Metal Ion-Induced Oxidation[a]

Polyetherurethane	Polyether content	Change in tensile strength (%)	Change in elongation (%)
Pellethane 2363-80A	High	−54	−42
Pellethane 2363-55D	Low	−23	−10
Model segmented polyurethane	None	+9	+3

[a]Conditions: 0.1 *M* $AgNO_3$/90°C/35 days vs. controls aged in deionized water; ASTM (D-1708) microtensile specimens.

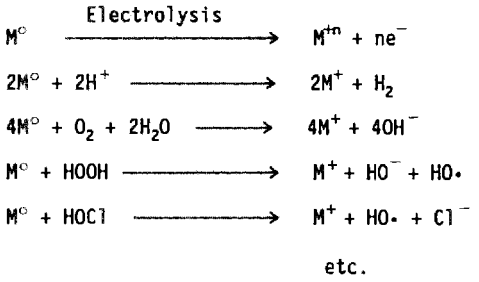


FIG. 19. Formation of metal ion from metal.

CONCLUSION

Polymers that are carefully chosen for use in implanted devices generally serve effectively for their intended lifetimes if they are properly processed and device–material–host interactions are adequately addressed. In certain limited circumstances, unintended hydrolytic or oxidative biodegradation occurs. This may be induced by direct attack by the host or via the intermediacy of the device or the outside environment. With susceptible polymers, protective measures can be taken to ensure extended efficacy, although new, biodegradation-resistant polymers, which are on the horizon, will require less protection. Knowledge of biodegradation mechanisms and the employment of appropriate countermeasures will promote the continued growth in compositions and uses of polymers as implantable biomaterials.

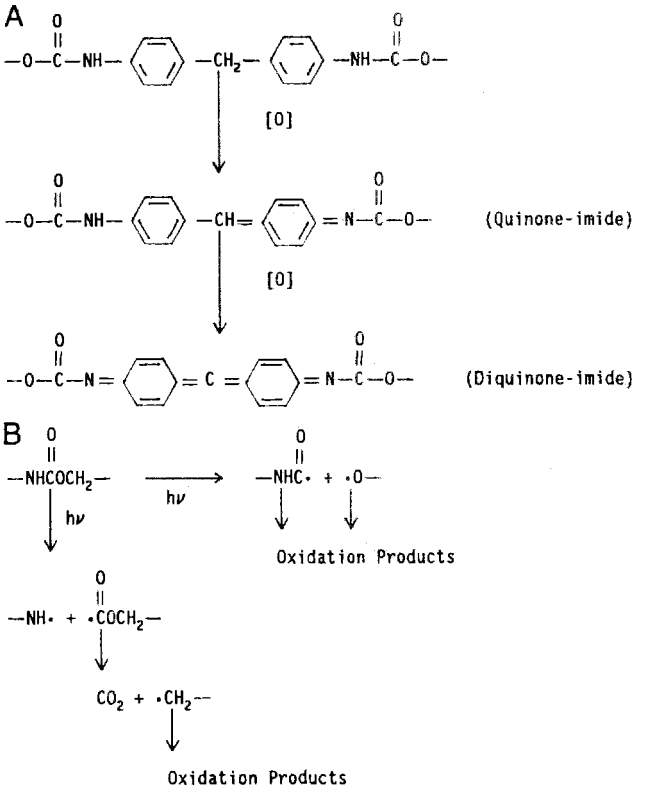


FIG. 21. Photo-oxidative reactions of aromatic polyurethanes. (A) Formation of quinone-imide from aromatic polyurethane. (From A. J. Coury *et al.*, *J. Biomater. Appl.* 3, 1988.) (B) Photolytic cleavage of urethane link. (From S. K. Brauman *et al.*, *Ann. Biomed. Eng.* 9, 1981.)

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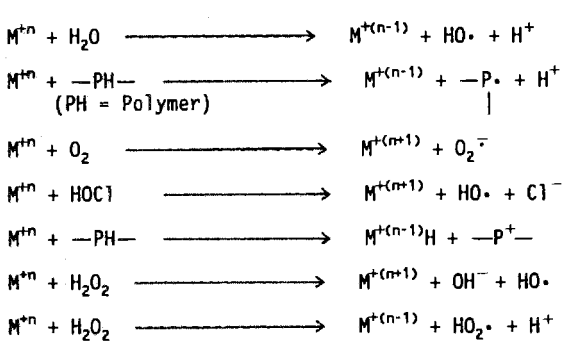

FIG. 20. Initiation of oxidation pathways by metal ion.

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CHAPTER

7

Application of Materials in Medicine and Dentistry

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7.1 INTRODUCTION

Jack E. Lemons

Synthetic biomaterials have been evaluated and used for a wide range of medical and dental applications. From the earliest uses (~1000 B.C.) of gold strands as soft tissue sutures for hernia repairs, silver and gold as artificial crowns, and gemstones as tooth replacements (inserted into bone and extending into the oral cavity), biomaterials have evolved to standardized formulations. Since the late 1930s, high-technology polymeric and ceramic substrates have played a central role in expending the application of biomaterial devices.

Most students enter the biomaterials discipline with a strong interest in applications. Critical to understanding these applications is the degree of success and failure and, most important, what can be learned from a careful evaluation of this history. The following chapters present topics across the spectrum of applications, ranging from blood contact and cardiovascular devices to drug delivery and sensors for diagnostic purposes. A central emphasis is the correlation of application limits with the basic properties of the various biomaterials and devices and how it might be possible to extend and improve existing applications. One goal for future applications of devices is to extend functional longevities by a factor of four (to 80 or more years) so that the need for revisions and replacements will be minimized.

More extended literature on applications can be found in the numerous books that have been written by professionals within the various fields, and more recently, by the edited versions of conferences that are available through the professional societies and government agencies. To obtain this literature, the reader is referred to the computer-based (MedLine or equivalent) methods for initial surveys within discipline areas. This will provide an extensive list of books and standard reference materials that should complement the basic information contained here.

7.2 CARDIOVASCULAR APPLICATIONS

Paul Didisheim and John T. Watson

Over the past 30 years, major advances have been made in using biomaterials to develop cardiovascular devices. Table 1 lists some of these devices and their annual use. However, the materials used in the fabrication of these devices have been primarily designed for nonmedical applications rather than specifically synthesized for medical purposes. In addition to having the required mechanical properties, both the materials and the devices made from them must be biocompatible (Didisheim and Watson, 1989; Webster, 1988). (Chapters 3.3.2., 3.3.3.), i.e., they must not provoke undesirable responses or complications during use.

Blood–Material Interactions

Blood–material interactions include any interaction between a material or device and blood or any component of blood, resulting in effects on the device or on the blood or on any organ or tissue. The effects commonly occur in various combinations, since there is considerable synergism among them. Such effects may or may not have clinically significant or undesirable consequences.

Classification of Blood–Material Interactions

A. Those which primarily affect the material or device and which may or may not have an undesirable effect on the subject.

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7.5 ADHESIVES AND SEALANTS

Dennis C. Smith

According to a definition of the American Society for Testing and Materials, an adhesive is a substance capable of holding materials together by surface attachment. Inherent in the concept of adhesion is the fact that a bond that resists separation is formed between the substrates or surfaces (adherends) comprising the joint and work is required to separate them.

"Adhesive" is a general term that covers designations such as cement, glue, paste, fixative and bonding agent used in various areas of adhesive technology. Adhesive systems may comprise one- or two-part organic and/or inorganic formulations that set or harden by several mechanisms.

Commercial adhesive systems are often designed to result in only a thin layer of adhesive for efficient bonding of the two surfaces since thick layers may contain weakening defects such as air voids or contaminants. Such systems may be low-viscosity liquids. In other situations where, for example, the surfaces to be joined are irregular, gap-filling qualities are required of the bonding agent. These systems may be solid–liquid (filled) adhesives or viscous liquids and are usually referred to as cements, glues, or sealants. Thus, the term "sealant" implies not only that good bonding and gap-filling characteristics are present in the material, but also that the bonded join is impervious, for example, to penetration by water. Since most adhesives, including biomaterials, are used to joint dissimilar materials that are subjected to a variety of physical, mechanical, and chemical stresses, good resistance to environmental degradative processes, including biodegradation, is essential.

The applications of adhesive biomaterials range from soft (connective) tissue adhesives used both externally to temporarily fix adjunct devices such as colostomy bags and internally for wound closure and sealing, to hard (calcified) tissue adhesives used to bond prosthetic materials to teeth and bone on a more permanent basis. All of these biological environments are hostile, and a major problem in the formulation of medical and dental adhesives is to develop a material that will be easy to manipulate, interact intimately with the tissue to form a strong bond, and also be biocompatible. Over the past two decades, more success at a clinical level has been achieved in bonding to hard tissues than to soft tissues.

More details on the background of adhesion and adhesives can be found in recent texts (Kinloch, 1987; Skeist, 1990; Lee, 1991a,b; Pizzi and Mittal, 1994).

HISTORICAL OVERVIEW

Wound closure by means of sutures extends back many centuries. The idea of using an adhesive is more recent but dates back to at least 1787 when it was noted "that many workmen glue their wounds with solid glue dissolved in water" (Haring, 1972). Hide glue is similar to gelatin, which itself derives from collagen. Other biological adhesives such as blood and egg white have also been known for centuries; however, first attempts to develop adhesives with specific chemical structures began in the late 1940s and 1950s.

Natural materials such as cross-linked gelatin and thrombin-plasma were investigated, but a major stimulus was provided by the discovery in 1951 of methyl 2-cyanoacrylate by Coover *et al.* (1972). This clear liquid monomer and its higher homologs (ethyl, butyl, octyl, etc.) were found to polymerize rapidly in the presence of moisture or blood, giving rapid hemostasis and highly adherent films. Extensive clinical and laboratory investigations on the cyanoacrylates took place in the 1960s and 1970s (Matsumoto, 1972), but problems of manipulation and biocompatibility, including reports of cancer in laboratory animals, have limited their current use to surface applications on oral mucosa and life-threatening arteriovenous situations.

The discovery of the adhesive properties of the cyanoacrylates prompted numerous studies on synthetic adhesive systems designed to interact with tissue protein side chain groups to achieve chemical bonding (Cooper *et al.*, 1972). Few systems have been found to possess the requisite combination of biocompatibility, ease of manipulation, and effectiveness. As a result of this experience and the more strictly controlled regulatory situation of today, little new research is being done on novel tissue adhesives. Work has been reported on synthetic polymerizable systems containing the reactive cyanoacrylate or isocyanate groups, but attention has been more focused clinically on materials on a natural basis. Some studies still continue on the gelatin–resorcinol–formaldehyde (GRF) combination (Cooper *et al.*, 1972; Chopin *et al.*, 1989; Nakayama *et al.*, 1994) but the main emphasis has been on fibrin glues derived from a fibrinogen–thrombin combination (Schlag and Redl, 1987).

As with soft tissues, interest in adhesive bonding to calcified tissues as a replacement for, or supplementation to, gross mechanical fixation such as screws has developed mainly in this century and particularly in the past 30 years. Fixation of orthopedic joint components by a cement dates back at least to Gluck (1891), and retention of metal or ceramic inlays and crowns on teeth by dental cements to about 1880. The development of acrylic room temperature polymerizing (cold-curing) systems for dental filling applications in the 1950s led to their use as dental cements and later to their application for fixation of hip joint components by Charnley and Smith (Charnley, 1970; Smith, 1971). These situations involved bonding by mechanical interlocking into surface irregularities. In the case of tooth restorations, leakage along the bonded interface developed. This so-called microleakage led to an intensive effort over the past 30 years to develop adhesive dental cements and

filling (restorative) materials (Phillips and Ryge, 1961; Smith, 1991, 1994).

Bonding materials and techniques are now a major component of clinical dentistry (Neuse and Mizrahi, 1994). Effective clinical bonding of polymerizable fluid dimethacrylate monomers and composite formulations to dental enamel, the most highly calcified (98%) tissue in the body, has been achieved by using phosphoric acid etching of the surface (the "acid-etch" technique). Bonding to tooth dentin is currently achieved by using acidic primer monomeric systems containing functional groups such as polycarboxylate or polyphosphate and hydrophilic monomers such as hydroxy ethyl methacrylate (Asmussen and Hansen, 1993; Johnson *et al.*, 1991; Vanherle *et al.*, 1993). Similar materials have been investigated for adhesion to bone, which is compositionally similar to dentin (Lee and Brauer, 1989).

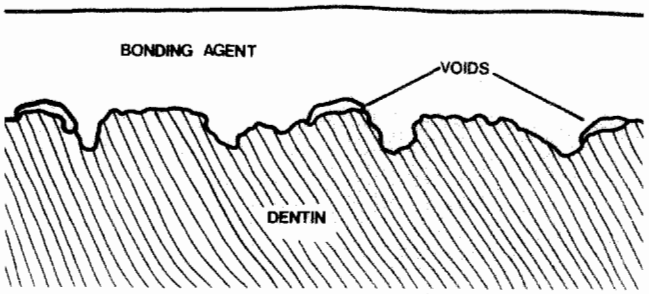

FIG. 1. Diagrammatic representation of mechanical interlocking by a cement to tooth dentin. Note voids at interface due to imperfect adaption.

BACKGROUND CONCEPTS

As indicated previously, significant advances in adhesive biomaterials have occurred over the past 30–40 years as real progress has taken place in the science and technology of adhesion and adhesives. This development is continuing since the fundamental aspects of the formation of adhesive bonds at interfaces are not yet fully understood even though successful application of adhesives in technically demanding situations has been achieved.

Experience and, to some extent, theory have shown that severe hostile environments such as biological milieu may require specific surface pretreatments for the surfaces being joined in addition to selection of an adhesive with appropriate characteristics. Such surface pretreatments may involve cleaning or etching processes designed to remove contaminants and expose wettable surfaces and may require the application of primers to achieve specific chemical reactivity at the surface. These procedures are a reflection of the need for intimate interfacial contact between the bonding agent and the adherends in order to form adhesive bonds across the interface. These adhesive forces must hold the materials together throughout the required service life of the joint. However, it must also be appreciated that the factors of the design of an adhesive joint, the applied loads, and the service environment it must withstand will all affect its mechanical performance and life expectancy (Kinloch, 1987).

The establishment of intimate molecular contact between the adhesive and adherend requires, ideally, the adhesive and/or primer to (1) exhibit a zero or near zero contact angle when liquid (2) have a low viscosity during bonding and (3) be able to displace air and contaminants during application. As discussed elsewhere in this volume (Chapters 1.3 and 9.7) surface wetting to achieve these requirements involves an understanding of wetting equilibria on clean, high-energy surfaces, the kinetics of spreading of the adhesive, and the minimization of surface contaminants, including moisture, during the bonding process.

Four main mechanisms of adhesion at the molecular level have been proposed: (1) mechanical interlocking, (2) adsorption (including chemical bonding), (3) diffusion theory, and (4) electronic theory. More complex interpretations have been proposed (Schulz and Nardin, 1994) but the validity of each theory is influenced by the system under consideration.

Mechanical Interlocking

This adhesion involves the penetration of the bonding agent into surface irregularities or porosity in the substrate surface. Gross examples of this mechanism include the retention of dental filling materials in mechanically prepared tooth cavities and of crowns by dental cements on teeth (Fig. 1) and the fixation of artificial joint components by acrylic bone cement (Fig. 2). Even apparently smooth surfaces are pitted and rough at the microscopic level, and strong bonding can arise with an adhesive that can penetrate at this level. The use of primers (chemical pretreatments) can create surface irregularities or porosities at the microscopic level, or can deposit porous layers that similarly provide effective micromechanical interlocking. Examples include the etching of dental enamel by 35–40% phosphoric acid (Fig. 3) and primer treatment of tooth dentin with acidic agents (Fig. 4). In each case the unpolymerized bonding agent penetrates 5–50 μm into the surface, creating numerous resin "tags" that provide a strong bond.

Adsorption Theory

This theory postulates that if intimate interfacial molecular contact is achieved, interatomic and intermolecular forces will establish a strong joint. Such forces include van der Waals and hydrogen bonds, donor–acceptor bonds involving acid–base interactions, and primary bond (ionic, covalent, metallic) formation (chemisorption). Numerous studies have suggested that secondary bonds (van der Waals and hydrogen bonds) alone are sufficient to establish strong bonding. However, where environmental attack is severe (e.g., by water as in biological systems), the formation of primary bonds across the interface seems to be essential.

Evidence of such bond formation has been found for commercial adhesives, particularly as a result of the use of chemical primers (e.g., silane coupling agents) on ceramics (Kinlock,

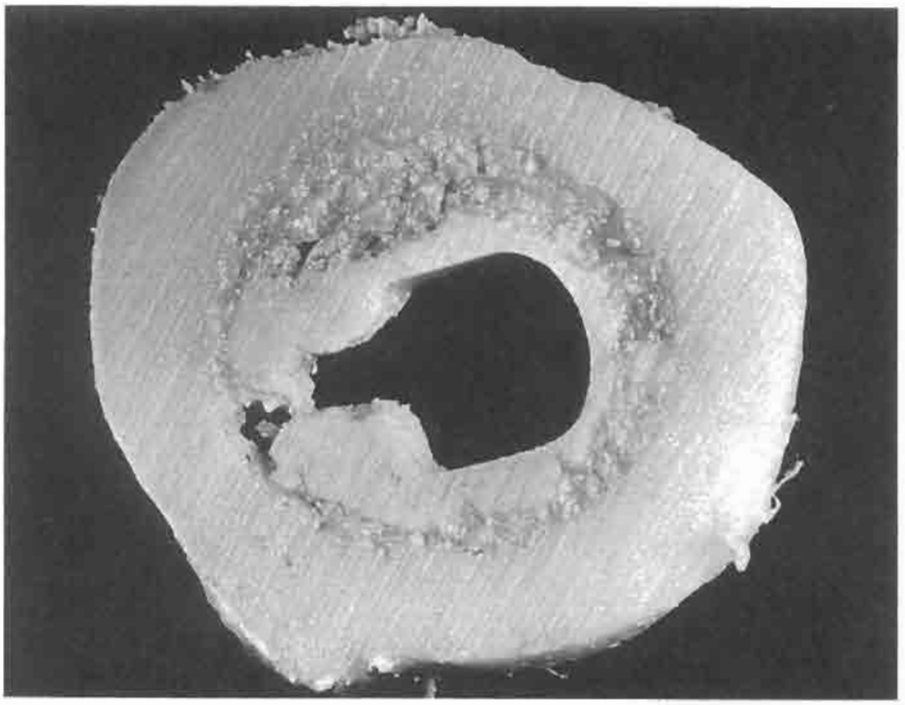

FIG. 2. Section through femur after removal of stem of hip prosthesis showing mechanical interlocking by bone cement into cancellous bone. (After J. Charnley, personal communication.)

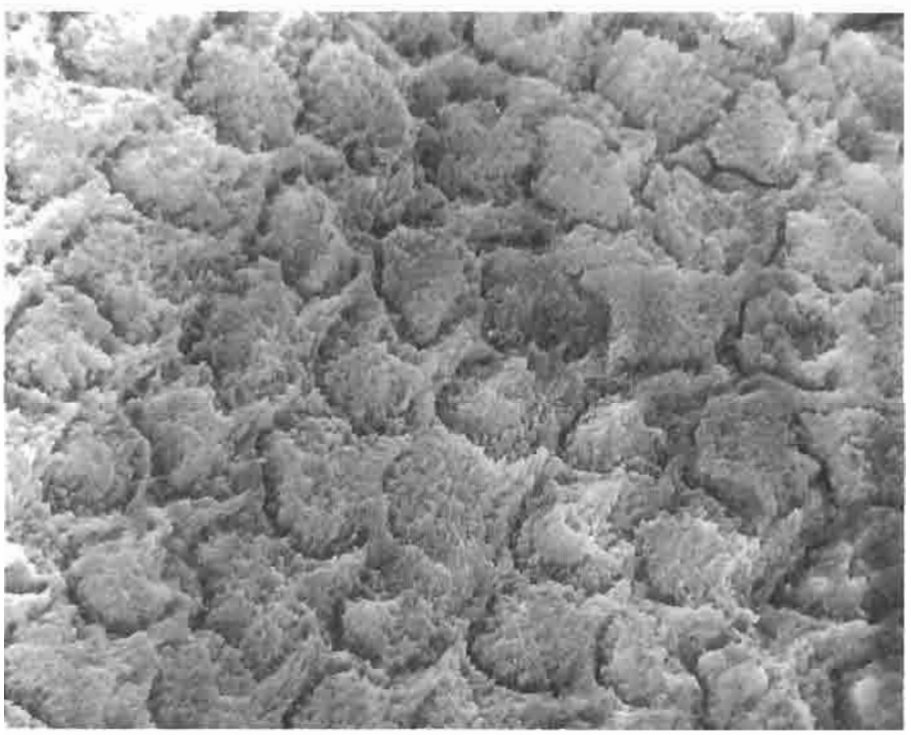

FIG. 3. Dental enamel etched by 30-sec treatment with 35% phosphoric acid showing prismatic structure. Prisms are about 5 μm in diameter.

FIG. 4. Treatment of dentin surface by acidic primer showing demineralized collagen fibers in surface zone.

1987; Schulz and Nardin, 1994). In the biomedical field, the polyacrylic acid-based dental cements (zinc polycarboxylate and glass ionomer cements) (Fig. 5) have been shown to undergo carboxylate bonding with Ca in enamel and dentin (Smith, 1994). Silane primers are used also to form bonds between dental resin adhesives and dental ceramics. Primary bond formation has also been postulated in several reactive dentin bonding systems (Asmussen and Hansen, 1993), but no unequivocal evidence for this has yet been presented (Eliades, 1993).

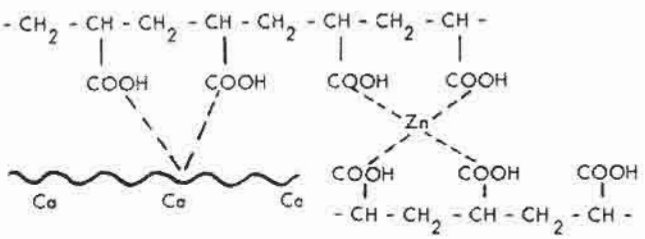

FIG. 5. Diagrammatic representation of setting of zinc polyacrylate and bonding to calcific surface.

Diffusion Theory

This theory states that the intrinsic adhesion of polymers to substrates and each other involves mutual diffusion of polymer molecules or segments across the interface. This can occur only when sufficient chain mobility is present. The application of this theory is limited to specific situations. Diffusion of polymers into intimate contact with metallic or ceramic surfaces may in fact result in enhanced adsorption or even micromechanical interlocking as a source of improved bonding. This concept (and others) has led to the idea of an "interphase" that is formed between adhesive and substrate which influences bonding behavior.

Electronic Theory

Electronic theory postulates that electronic transfer between adhesive and adherent may lead to electrostatic forces that result in high intrinsic adhesion. Such interactions may arise in certain specialized situations, but for typical adhesive–substrate interfaces, any electrical double layer generated does not contribute significantly to the observed adhesion (Kinlock 1987; Schulz and Nardin, 1994).

The evidence available at present suggests that for most biological adhesives, adsorption phenomena or micromechanical interlocking account for the bond formation and behavior observed. Since few practical surfaces, especially tissues, are completely smooth and nonporous, it is likely that both mechanisms exist in practical clinical situations, with one or the other predominating according to the type of adhesive system, surface preparation technique, and bonding environment.

COMPOSITION AND CHARACTERISTICS OF ADHESIVE BIOMATERIALS

Soft Tissue Adhesives

Most soft tissue adhesives are intended to be temporary, that is, they are removed or degrade when wound healing is sufficiently advanced for the tissue to maintain its integrity. Effective adhesion can be obtained on dry skin or wound surfaces by using wound dressing strips with acrylate-based adhesives. However, on wound surfaces that are wet with tissue fluid or blood, the adhesive must be able to be spread on such wet surfaces, provide adequate working time, develop and maintain adhesion, desirably provide hemostasis, facilitate wound healing, and maintain biocompatibility. Positive antimicrobial action would be an additional advantage.

Few, if any, systems comply with all these requirements. Currently, there are two principal systems in clinical use—cyanoacrylate esters and fibrin sealants. Another glue based on a gelatin–resorcinol–formaldehyde combination still receives limited use. An interesting but still experimental system based on polypeptides from marine organisms (mussel adhesive) does not seem to have developed into practical use.

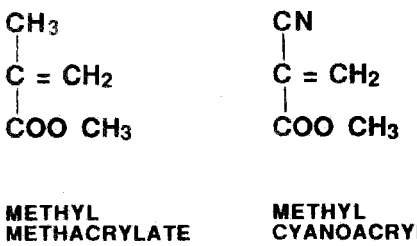

FIG. 6. Structure of methyl cyanoacrylate and methyl methacrylate.

Cyanoacrylate Esters

These esters are fluid, water-white monomers that polymerize rapidly by an anionic mechanism in the presence of weak bases such as water or NH_2 groups. Initially, methyl cyanoacrylate (Fig. 6) was used but in the past decade isobutyl and *n*-butyl cyanoacrylate have been found more acceptable. The higher cyanoacrylates spread more rapidly on wound surfaces and polymerize more rapidly in the presence of blood. Furthermore, they degrade more slowly over several weeks, in contrast to the methyl ester, which hydrolyzes rapidly, yielding formaldehyde that results in an acute inflammatory response.

These materials achieve rapid hemostasis as well as a strong bond to tissue. However, the polymer film is somewhat brittle and can be dislodged on mobile tissue, and the materials can be difficult to apply on large wounds. Because of adverse tissue response and production of tumors in laboratory animals, cyanoacrylates are not approved for routine clinical use in the United States although a commercial material based on *n*-butyl cyanoacrylate (Histoacryl blue) is approved by several other countries.

The current uses are as a surface wound dressing in dental surgery, especially in periodontics, and in life-threatening applications such as brain arteriovenous malformations. Reports of sarcomas in laboratory animals (Reiter, 1987) late complications after dura surgery (Chilla, 1987), and evidence of *in vitro* cytotoxicity (Ciapetti *et al.*, 1994) appear likely to restrict their further use in spite of work on synthesis of new types of cyanoacrylate.

Fibrin Sealants

Fibrin sealants involve the production of a synthetic fibrin clot as an adhesive and wound-covering agent. The concept of using fibrin dates back to 1909 but was placed on a specific basis by Matras *et al.* in 1972 (Schlag and Redl, 1987). The commercial materials first available (Tisseel, Tissucol, Fibrin-Kleber) consisted of two solutions that are mixed immediately before application to provide a controlled fibrin deposition. More recently a "ready to use" formulation (Tisseel Duo) has been introduced.

The essential components of these solutions are as follows:

Solution A	Solution B
Fibrinogen	Thrombin
Aprotinin	$CaCl_2$

The fibrinogen is at a much higher concentration than that in human plasma. On mixing the two solutions, a reaction similar to that of the final stages of blood clotting occurs in that polymerization of the fibrinogen to fibrin monomers and a white fibrin clot are initiated under the action of thrombin and $CaCl_2$.

Fibrinogen for commercial material is manufactured from the pooled plasma of selected donors. The material is subjected to in-process virus inactivation and routinely screened for hepatitis virus and HIV (Schlag and Redl, 1987). To minimize these risks, recent processes produce the fibrinogen in a "closed" blood bank or from the patient's own blood (Silberstein *et al.*, 1988; Lerner and Binar, 1990). Autologous fibrin glue now appears to be the approach of choice (Tawes *et al.*, 1994).

Fibrin sealant has four main advantages: (1) it is hemostatic, (2) it adheres to connective tissue, (3) it promotes wound healing, and (4) it is biodegradable, with excellent tissue tolerance (Schlag and Redl, 1987). The adhesive strength is not as high as cyanoacrylates but is adequate for many clinical situations. Possible complications include formation of antibodies and thrombin inhibitors. The material has been used in a wide variety of surgical techniques that are reviewed in a seven-volume report by Schlag and Redl (1987) and in numerous papers in the recent literature (Lerner and Binar, 1990; Tawes *et al.*, 1994). The composition may be adjusted to promote hemostasis, for example, or to minimize persistence of the clot to avoid fibrosis. The use of fibrin sealant alone or in admixture with bone chips, tricalcium phosphate, and antibiotics in orthopedic surgery has been reviewed (Schlag and Redl, 1987). More recently, the material has been used as a drug release vehicle for local sites.

Gelatin–Resorcinol–Formaldehyde Glue

This glue was developed in the 1960s by Falb and coworkers (Falb and Cooper, 1966; Cooper *et al.*, 1972) as a less toxic material than methyl cyanoacrylate. The material is fabricated by warming a 3 : 1 mixture of gelatin and resorcinol and adding an 18% formaldehyde solution. Cross-linking takes place in about 30 sec.

This glue was used in a variety of soft tissue applications but technical problems and toxicity have limited its application in recent years to aortic dissection (Nakayama *et al.*, 1994). In attempts to overcome the toxicity and potential mutagenicity/carcinogenicity of the formaldehyde component, modified formulations have been developed in which other aldehydes such as glutaraldehyde and glyoxal (Ennker *et al.*, 1994a,b) are substituted for the formaldehyde. Favorable results with this material (GR-DIAL) have been reported (Ennker *et al.*, 1994a,b).

Bioadhesives

Bioadhesives are involved in cell-to-cell adhesion, adhesion between living and nonliving parts of an organism, and adhesion between an organism and foreign surfaces. Adhesives produced by marine organisms such as the barnacle and the mussel have been extensively investigated over the past 20 years be-

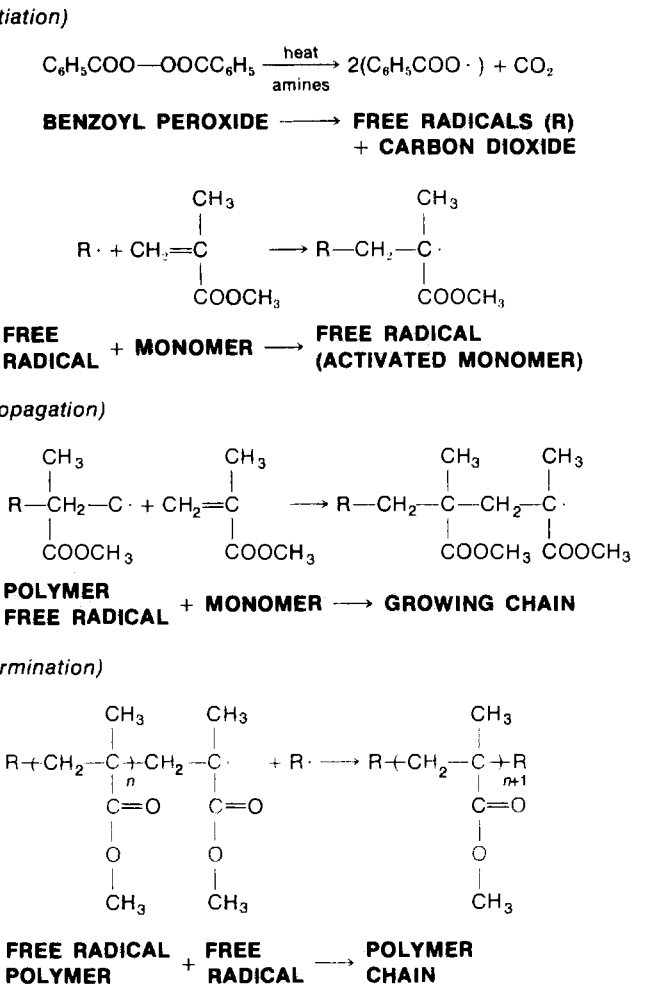

FIG. 7. Auto-polymerizing methyl methacrylate systems as used in dental resins and acrylic bone cement. (From R. Roydhouse (1989), in *Dental Materials Properties and Selection*, W. J. O'Brien, ed., p. 129. Quintessence Books, Chicago, with permission.)

cause of their apparent stable adhesion to a variety of surfaces under adverse aqueous conditions. These studies have shown that these organisms secrete a liquid acidic protein adhesive that is cross-linked by a simultaneously secreted enzyme system. The bonding probably involves hydrogen and ionic bonding from the acidic groups (Waite *et al.*, 1989).

The adhesive from the mussel has been identified as a polyphenolic protein, molecular weight about 130,000 Da, which is cross-linked by a catechol oxidase system in about 3 min. A limiting factor in the practical use of this material is the difficulty of extracting it from the natural source. The basic unit of the polyphenolic protein has been identified as a specific decapeptide. Recombinant DNA technology and peptide synthesis have been used in attempts to produce an affordable adhesive with superior properties. Little information has been reported on the performance of these materials.

Hard Tissue Adhesives

As previously noted, prostheses can be attached to calcified tissues (bone, tooth enamel, dentin) by gross mechanical interlocking to machined surfaces. Thus, room temperature-polymerizing methyl methacrylate (Fig. 7) systems are used to fix orthopedic implants (e.g., acrylic bone cement, see Chapter 7.7) and for dental restorations. The former, in a closed system, has been relatively successful. However, conditions are much more stringent in the mouth because of the changing environment, thermomechanical stresses on the bond, and the presence of oral bacteria that result in renewed tooth decay. Thus, considerable development of new dental cements and adhesive systems has occurred in recent years in attempts to provide a leakproof bond to attach fillings, crowns, and veneers to the tooth (Fig. 8).

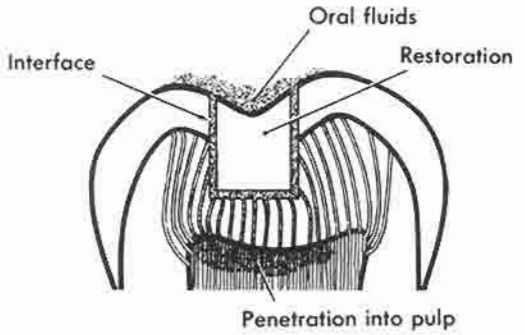

FIG. 8. Leakage of oral fluids and bacteria around dental filling material in tooth crown. (From R. W. Phillips (1991). *Science of Dental Materials*, 9th Ed., p. 62. W. B. Saunders, Philadelphia, with permission.)

Dental cements are traditionally fast-setting pastes obtained by mixing solid–liquid components. Most of these materials set by an acid–base reaction and more recent resin cements set by polymerization (Smith, 1988, 1991).

Zinc phosphate cement is the traditional standard. This material is composed primarily of zinc oxide powder and a 50% phosphoric acid solution containing Al and Zn. The mixed material sets to a hard, rigid cement (Table 1) by forming an amorphous zinc phosphate binder. Although the cement is gradually soluble in oral fluids and can irritate pulp, it is clinically effective over 10–20-year periods. The bonding arises entirely from penetration into mechanically produced irregularities on the surface of the prepared tooth and the fabricated restorative material. Some interfacial leakage occurs because of cement porosity and imperfect adaptation (Fig. 1), but this is usually acceptable since the film thickness is generally below 100 μm.

Polycarboxylic acid cements were developed in 1968 (Smith 1988, 1994) to provide materials with properties comparable to phosphate cements but that would adhere to calcified tissues. Zinc polyacrylate (polycarboxylate) cements are formed from zinc oxide and a polyacrylic acid solution. The metal ion cross links the polymer structure via carboxyl groups, and other carboxyl groups form a complex to Ca ions in the surface of the tissue (Fig. 5). The zinc polycarboxylate cements have adequate physical properties, excellent biocompatibility in the tooth, and proven adhesion to enamel and dentin (Smith, 1988).

The glass ionomer cements are also based on polyacrylic acid or its copolymers with itaconic or maleic acids, but utilize a calcium aluminosilicate glass powder instead of zinc oxide (Smith, 1988, 1994). In this case, the cements set by cross-linking of the polyacid with Ca and Al ions from the glass. The set structure and the residual glass particles yield a stronger, more rigid cement (Table 1) but with adhesive properties similar to the zinc polyacrylate cements. In recent materials the polyacid molecule contains both ionic carboxylate and polymerizable methacrylate groups and is induced to set both by an acid–base reaction and visible light polymerization. These cements are widely used clinically. Adhesive bonding but not complete sealing is obtained because of imperfect adaptation to the bonded surfaces under practical conditions.

Resin cements are fluid or pastelike monomer systems based on aromatic or urethane dimethacrylates (Fig. 9). Silanated ceramic fillers may be present to yield a composite composition. The two-component materials polymerize on mixing through a two-part organic peroxide–tertiary amine initiator–activator system in about 3 min. More recent are one-component materials containing diketone polymerization initiators that achieve polymerization in about 30 sec by exposure to visible (blue) light energy. These set materials are strong, hard, rigid, insoluble, cross-linked polymers (Table 1). Bonding is achieved by mechanical interlocking to surface roughness. In recent materials, reactive adhesive monomers may also be present (see the following discussion), conferring also a presumed chemisorption mechanism.

Enamel and dentin bonding systems are composite polymer–ceramic formulations similar to resin cements but are more complex systems containing reactive monomers. Their use usually involves an acidic pretreatment of the tooth surface, an unfilled monomer bonding (primer resin) composition to achieve good wetting of the tooth surface, and a filled bonding agent for the bulk of the bond. These materials are used to

TABLE 1 Properties of Dental Cements and Sealants

Material	Strength (MPa)		Modulus of elasticity (GPa)	Fracture toughness K_1C $MN^{-3/2}$
	Compressive	Tensile		
Zinc phosphate	80–100	5–7	13	~0.2
Zinc polycarboxylate	55–85	8–12	5–6	0.4–0.5
Glass ionomer	70–200	6–7	7–8	0.3–0.4
Resin sealant unfilled	90–100	20–25	2	0.5
Resin sealant filled	150	30	5	
Resin cement	100–200	30–40	4–6	
Composite resin filling material	350–400	45–70	15–20	1.6

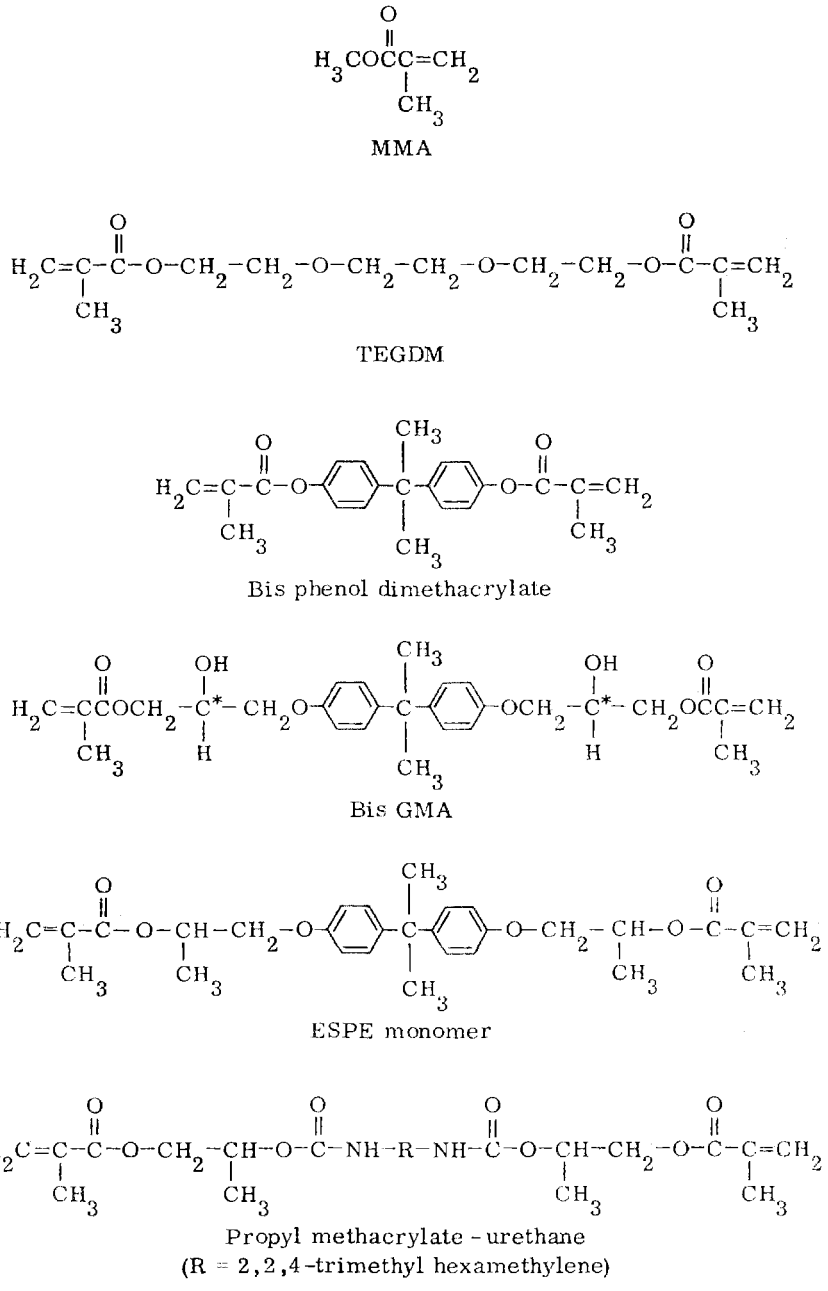

FIG. 9. Structures of some dimethacrylate monomers used in dental composite filling and bonding systems.

attach composite resin restorative materials, ceramic veneers, and orthodontic metal and ceramic brackets to enamel and dentin surfaces. Because of the different composition and physical properties of enamel and dentin (see Chapter 3.4), more complex and greater demands are placed on multipurpose adhesive systems intended for both tissues.

Bonding to enamel is achieved by pretreating the surface with 35–50% phosphoric acid for 30–60 sec as described earlier (Fig. 3). This resulting washed and dried surface is readily wettable and penetratable by resin cements and bonding agents. The resulting resin tags (5–50 μm long) in the surface of the tissue result in efficient micromechanical interlocking with a potential tensile bond strength of about 20 MPa, which is equivalent to cohesive failure in the resin or in the enamel.

Bonding to dentin currently involves pretreatment of the prepared (machined) surface with acidic solutions (phosphoric, nitric, maleic acids) or ethylenediaminetetracetic acid (EDTA) to remove cutting debris (the smear layer). This procedure opens the orifices of the cut dentinal tubules and creates micro-

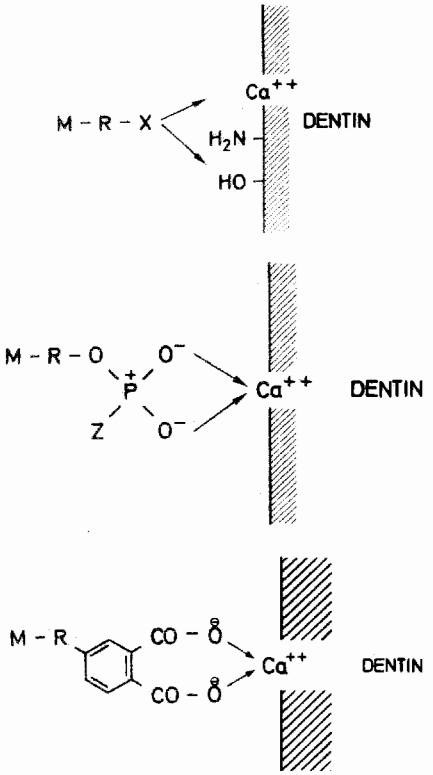

FIG. 10. Reactive monomer structures for bonding to calcific tissues. M-R, monomer portion of molecule. (After Asmussen, E., Aranjo, P. A., and Pentsfeld, A. 1989, *Trans. Acad. Dent. Mater.* 2: 59.)

porosity in the surface (Fig. 4). A primer treatment is then applied that comprises a reactive monomer system (Fig. 10) containing a carboxylate or a polyphosphate function, depending on the type of product. These primers also contain hydrophilic monomers, such as hydroxyethyl methacrylate (HEMA), and may also contain water.

The function of the primer is to penetrate the demineralized dentin surface and facilitate wetting by an unfilled dimethacrylate bonding resin which is subsequently applied. Polymerization of this treatment layer by visible light activation results in the formation of micromechanical bonds by penetration into the dentin and surface tubules, forming the so-called hybrid layer (Nakabayashi *et al.*, 1991) or resin-interdiffusion zone (Van Meerbeck *et al.*, 1992). Chemical interaction with the hydroxyapatite and/or proteinaceous phases of the dentin surface may also occur (Asmussen and Hansen, 1993). However, direct chemical evidence has not been provided yet for the postulated interactions (Eliades, 1993). Under the best conditions, initial tensile bond strengths of 15–25 MPa can be obtained depending on test conditions. The long-term durability of these bonds under oral conditions is being investigated.

NEW RESEARCH DIRECTIONS

As a result of the experience of the past two decades, the problems involved in developing an adhesive system for both soft and hard tissues have been addressed. Nevertheless, it is difficult to reconcile short- and long-term biocompatibility needs with chemical adhesion mechanisms that use reactive monomer systems.

Where relatively temporary adhesion is required, as in wound healing, systems based on natural models that allow biodegradation of the adhesive and interface and subsequent normal tissue remodeling appear to merit further development. For longer term durability in both soft and hard tissues, hydrophilic monomers and polymers of low toxicity which can both diffuse into the tissue surface and form ionic bonds across the interface seem to be the most promising approaches. Evidence has been obtained of the need for hydrophobic–hydrophilic balance in adhesive monomer systems (Nakabayashi *et al.*, 1991). The use of hydrophilic monomers such as hydroxyethyl methacrylate in commercial materials has facilitated surface penetration.

On calcified surfaces, the use of hydrophilic electrolytes such as the polycarboxylates has demonstrated that proven ionic bonding *in vitro* can also be achieved *in vivo*. An advantage of such systems is that surface molecular reorientations can improve bonding with time. Encouraging preliminary results have been obtained with such glass ionomer cements in orthopedics and there is considerable scope for the future development of such polyelectrolyte cements.

A practical limitation in many systems is ease of manipulation and application. For example, the effectiveness of the fibrin sealant is critically dependent on proper mixing of the ingredients and uniform application. Further technology transfer could improve this often-neglected area of adhesive development. For example, the visible-light polymerization technology developed in dentistry that allows extended working time and curing "on demand" in a few seconds could usefully be applied to medical applications. Laser activation of fibrin sealants has received an initial trial.

The development of more efficient adhesives and sealants that, in addition to enhancing the durability of current applications, would permit new applications such as osteogenic bone space fillers, percutaneous and permucosal seals, and functional attachment of prostheses is a challenging problem for the future.

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7.6 OPHTHALMOLOGIC APPLICATIONS

Miguel F. Refojo

Light that penetrates into the eye is partially refracted in the cornea, passes through the aqueous humor and the pupil (the opening in the center of the iris), is further refracted in the crystalline lens, passes through the vitreous humor, and converges on the retina (Fig. 1). Diverse polymeric devices, such as spectacles, contact lenses, and intraocular implants, are used to correct the optical function of the eye. The materials used in spectacle lenses are outside the scope of this chapter. Contact lenses, however, being in intimate contact with the tissues of the eye, are subject to the same regulations that govern the use of implant materials, and they are included in this chapter with other biomaterials used to preserve and to restore vision, such as intraocular implants.

CONTACT LENSES

General Properties

Contact lenses are optical devices that must have good transmission of visible light. Pigments and dyes are added to some contact lenses for cosmetic effect. Contact lenses also may have ultraviolet (UV) light-absorbing additives, usually copolymerized in the contact lens material, to protect the eye from the harmful effects of UV light. UV light absorbed by the normal crystalline lens is harmful to the retina and also may contribute to the clouding of the lens (cataract) (Miller, 1987).

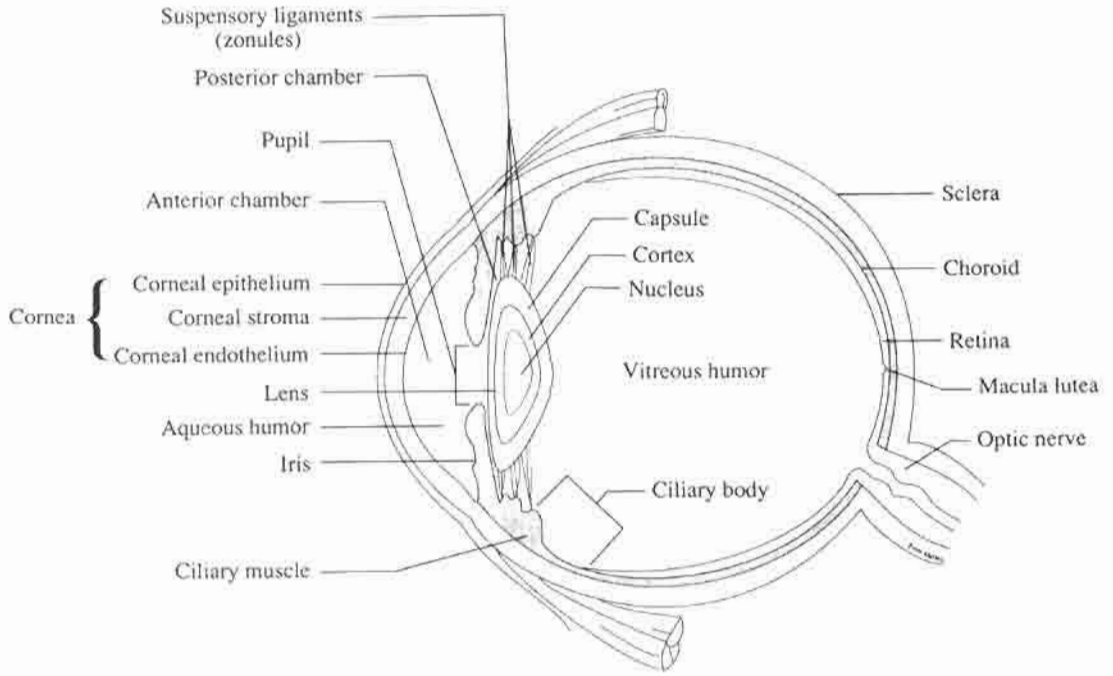

FIG. 1. Schematic representation of the eye.

The principal properties sought in contact lens materials, in addition to the required optical properties, chemical stability, and amenability to manufacture at reasonable cost, are high oxygen transmissibility (to meet the metabolic requirements of the cornea), tear film wettability (for comfort), and resistance to accumulation on the lens surfaces of mucus/protein/lipid deposits from the tear film and other external sources. Contact lenses also must be easy to clean and disinfect (Kastl, 1995).

Most of the available contact lenses were developed with the important property of oxygen permeability in mind. The oxygen permeability coefficient, P, is a property characteristic of a material. [$P = Dk$, where D is the diffusivity, in cm^2/sec, and k is the Henry's law solubility coefficient, in cm^3 (STP)/cm^3 mm Hg.] For a given contact lens, its oxygen transmissibility (Dk/L) is more important than its permeability; oxygen transmissibility is defined as the oxygen permeability coefficient of the material divided by the average thickness of the lens (L, in cm) (Holden *et al.*, 1990).

For oxygen permeability, the ideal contact lens would be made of poly(dimethyl siloxane). For better mechanical properties and manufacture, most silicone elastomeric lenses have been made of diverse poly(methyl phenyl vinyl siloxanes). Because of its hydrophobic character, to be useful, a silicone rubber lens must be treated in an RF-plasma reactor or other suitable procedure to make its surface hydrophilic and tolerated on the eye. Nevertheless, the silicone rubber lenses have not been very successful for general cosmetic use, not only because of surface problems and comfort, but principally because they have a strong tendency to adhere to the cornea.

There are currently a wide variety of contact lens materials with diverse physical properties that determine the fitting characteristics of the lens on the eye (Kastl, 1995).

Soft Hydrogel Contact Lenses

The soft hydrogel contact lenses (SCL) are supple and fit snugly on the corneal surface. Because there is little tear exchange under these lenses, most of the oxygen that reaches the cornea must permeate through the lens. The oxygen permeability coefficient of hydrogel materials increases exponentially with the water content.

The hydrogel lenses are made of slightly cross-linked hydrophilic polymers and copolymers. The original hydrogel contact lens material was poly(2-hydroxyethyl methacrylate) (PHEMA) (Wichterle and Lim, 1960); at equilibrium swelling in physiological saline solution, it contains about 40% water of hydration. (Hydration of hydrogel contact lenses is customarily given as a percentage of water by weight, on a wet basis.) The oxygen transmissibility of the original rather thick PHEMA hydrogel contact lenses was found to be insufficient for normal corneal metabolism. New hydrogel contact lenses were soon developed with higher water content or with a water content similar to that of PHEMA but more amenable to fabrication in an ultrathin modality. New fabrication techniques were also developed to make ultrathin PHEMA lenses. This takes advantage of the law of diffusion which, applied to contact lenses, will guarantee that for any lens type under the same conditions of wear, the oxygen flux through the lens will double when the thickness is halved.

Other hydrogel contact lens materials include HEMA copolymers with other monomers such as methacrylic acid, acetone acrylamide, and vinyl pyrrolidone. Commonly used also are copolymers of vinyl pyrrolidone and methyl methacrylate, and of glyceryl methacrylate and methyl methacrylate. A variety of other monomers as well as a variety of cross-linking agents

TABLE 1 Chemical Composition of Some Hydrogel Contact Lenses

Polymer	USAN[a]	% H_2O
2-hydroxyethyl methacrylate (HEMA) with ethyleneglycol dimethacrylate (EGDM)	Polymacon	38
HEMA with methacrylic acid (MAA) and EGDM	Ocufilcon A	44
	Ocufilcon C	55
HEMA with sodium methacrylate and 2-ethyl-2-(hydroxymethyl)-1,3-propanediol trimethacrylate	Etafilcon A	58
HEMA with divinyl benzene, methyl methacrylate (MMA) and 1-vinyl-2-pyrrolidone (VP)	Tetrafilcon A	43
HEMA with VP and MAA	Perfilcon A	71
HEMA with N-(1,1-dimethyl-3-oxobutyl) acrylamide and 2-ethyl-2-(hydroxymethyl)-1,3-propanediol trimethacrylate	Bufilcon A	45
	Bufilcon B	55
2,3-Dihydroxypropyl methacrylate with MMA	Crofilcon A	39
VP with MMA, allyl methacrylate and EGDM	Lidofilcon A	70
	Lidofilcon B	79
MAA with HEMA, VP and EGDM	Vifilcon A	55

[a]U.S. adopted name.

are used as minor ingredients in hydrogel contact lenses (Refojo, 1979) (Table 1).

Hydrogel lenses have been classified by the U.S. Food and Drug Administration (FDA) into four general groups: low water (<50% H_2O), nonionic; high water (>50% H_2O), nonionic; low water, ionic; and high water, ionic. The ionic character is usually due to the presence of methacrylic acid, which is responsible for higher surface protein binding to the contact lenses. High water of hydration is a desirable property for good oxygen permeability, but it carries some disadvantages, such as friability and protein penetration into the polymer network. Physiologically and optically, ultrathin low-water-content contact lenses can perform very well as daily-wear lenses.

As a result of temperature changes and water evaporation, all hydrogel contact lenses dehydrate to some degree on the eye. Higher-water-content lenses dehydrate more than low-water-content lenses, and thin lenses dehydrate more easily than thick lenses (Refojo, 1991). A drawback of high-water-content, thin hydrogel contact lenses is that as they dehydrate on the eye, they induce corneal epithelium injuries by a mechanism still unclear. Therefore, the ideal hydrogel contact lens would be ultrathin, resistant to mechanical damage, made of a nonionic polymer, and retain a high water content (i.e., >70% H_2O) on the eye.

Flexible Fluoropolymer Lenses

The flexible fluoropolymer (FFP) lens was made from a copolymer of a telechelic perfluoropolyether (which imparts high oxygen permeability) with vinyl pyrrolidone (which imparts wettability) and methyl methacrylate (which imparts rigidity). This flexible, nonhydrated contact lens, made by the molding procedure, had a high oxygen permeability and, owing to its high fluorine content, was claimed to be more resistant to coating by tear proteins than other contact lens materials. At this time, the FFP lenses are no longer commercially available.

Rigid Contact Lenses

The rigid contact lenses, as well as the FFP lenses, fit loosely on the cornea and move with the blink more or less freely over the tear film that separates the lens from the corneal surface. The mechanical properties of rigid and FFP contact lenses must be such that any flex on the lens provoked by the blink must recover instantaneously at the end of the blink.

The first widely available contact lenses were made of poly(methyl methacrylate), which is an excellent optical biomaterial in almost all respects except for its virtual impermeability to oxygen. Several materials that were specially developed for the manufacture of rigid gas-permeable (RGP) contact lenses are copolymers of methyl methacrylate with siloxanylalkyl methacrylates (Refojo and Dabezies, 1984). To compensate for the hydrophobic character imparted to the polymer by the high siloxane content of these copolymers (required for oxygen permeability), the copolymer also contains some hydrophilic comonomers. The most commonly used hydrophilic comonomer in rigid lenses is methacrylic acid. There are also minor ingredients and cross-linking agents. A diversity of RGP contact lenses, consisting of different but closely related comonomers used in a variety of proportions to obtain the most desirable properties, are commercially available (Table 2). However, any subtle change in the chemistry of a contact lens material might strongly affect its clinical performance. As a general rule, the oxygen permeability coefficient of the siloxanylalkyl methacrylate contact lens materials is inversely proportional to the density.

The development of the fluorine-containing contact lenses and the realization that the fluoroderivatives may improve oxygen permeability and resistance to deposit formation caused contact lens chemists to include a fluoroalkyl methacrylate or a similar fluorine-content monomer as an additional ingredient in the siloxanylalkyl methacrylate-comethyl methacrylate RGP contact lens materials. These perfluoroalkyl-siloxanylalkyl-methyl methacrylate contact lenses have high oxygen permeability and, supposedly, better surface properties than the non-fluorine-containing rigid contact lenses.

Cellulose acetate butyrate (CAB) is also used as a rigid oxygen-permeable contact lens material. However, CAB not only has relatively low oxygen permeability compared with the siloxanylalkyl methacrylate copolymers but also has low scratch resistance and tends to warp with humidity changes.

Other copolymers useful as contact lens materials are isobutyl and isopropyl styrene, with hydrophilic comonomers of the HEMA or vinyl pyrrolidone type.

TABLE 2 Composition of Some Rigid Gas-Permeable Contact Lenses

Polymer	USAN[a]
Cellulose acetate dibutyrate	Porofocon Cabufocon
3-[3,3,5,5,5-pentamethyl-1,1-bis[pentamethyldisiloxanyl)oxy] trisiloxanyl]propyl methacrylate, with methyl methacrylate (MMA), methacrylic acid (MAA) and tetraethyleneglycol dimethacrylate (TEGDMA)	Silafocon
MMA with MAA, EGDMA, 3-[3,3,3,-trimethyl-1,1-bis(trimethylsiloxy)disiloxanyl] propyl methacrylate (TRIS) and N-(1,1-dimethyl-3-oxybutyl)acrylamide.	Nefocon
VP with HEMA, TRIS, allyl methacrylate and α-methacryloyl-ω-(methacryloxy) poly(oxyethylene-co-oxy(dimethylsilylene)-co-oxyethylene.	Mesifilcon
TRIS with MMA, dimethyl itaconate, MAA and TEGDMA.	Itafocon
TRIS with 2,2,2,-trifluoro-1-(trifluoromethyl) ethyl methacrylate, 1-vinyl-2-pyrrolidone (VP), MAA and ethyleneglycol dimethacrylate (EGDMA).	Melafocon
TRIS with 2,2,2-trifluoroethyl methacrylate, MAA, MMA, VP with EGDMA.	Paflufocon

[a]U.S. adopted name.

CORNEAL IMPLANTS

The cornea is an avascular tissue that consists of three principal layers (Fig. 1). The outermost layer, which itself consists of about five cellular layers, is the epithelium. The central and main portion of the cornea is the stroma, a collagenous connective tissue that is 78% hydrated in its normal state. Normal corneal hydration is disrupted by injury to the limiting epithelial and endothelial membranes. The endothelium is the innermost monocellular layer, which by means of a "pump-leak" mechanism, is mostly responsible for maintaining normal corneal hydration. Swelling, tissue proliferation, and vascularization may compromise the transparency of the cornea. There are several types of corneal implants (Refojo, 1986a; Abel, 1988) that replace all or part of the cornea.

Epikeratophakia and Artificial Epithelium

To correct the optics of the eye after cataract extraction, the surgeon may perform an epikeratophakia procedure which consists of transplanting a slice of donor cornea. The transplanted tissue heals into a groove carved into the recipient corneal surface and is reepithelialized with the recipient corneal epithelium (Werblin *et al.*, 1987). A modification of this technique attempts to obtain similar results with an artificial material that would heal into the donor cornea and be able to grow the epithelium of the donor cornea on its surface (Fig. 2).

An epithelium that has become irregular through swelling and proliferation has been replaced by an artificial epithelium made of a hard plastic contact lens glued with a cyanoacrylate adhesive to the corneal stroma (Fig. 2). This procedure has not been successful mainly because of failure of the glue to maintain a tight attachment of the prosthesis to the corneal stroma and also because of epithelial penetration between the prosthesis and the cornea.

Artificial Corneas

Corneal transplants from donor eyes are usually highly successful. In the rare instance of transplant failure, an opaque cornea can be replaced with an artificial cornea (keratoprosthesis) (Barber, 1988). These are usually through-and-through corneal implants, consisting of a central optical portion and some modality of skirt that fixes the prosthesis to the recipient cornea (Fig. 3). The main problem with through-and-through keratoprostheses is common to all kinds of implants that are not fully buried in the recipient tissue: faulty tissue–prosthesis interface, epithelium downgrowth, and tissue ulceration and infection around the prosthesis. The most feasible solution to these problems would be the development of a material for the optical portion of the keratoprosthesis that would accept growth and attachment of transparent epithelium on its surface. Also needed are biomaterials that would heal into the recipient corneal tissue.

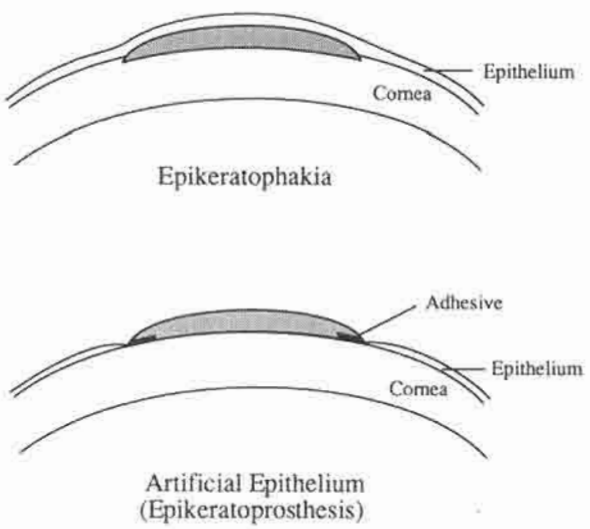

FIG. 2. Schematic representation of superficial corneal implants. (Top) In the epikeratophakia procedure, the corneal epithelium is removed before the implant is placed on the stromal surface and epithelium grows over the implant. (Bottom) The artificial epithelium or epikeratoprosthesis is a contact lens glued to a deepithelialized cornea. Ideally, the epithelium should not grow over or under the glued-on lens.

Artificial Endothelium

The corneal endothelium has been replaced, but not very successfully in the long term, by a silicone rubber membrane that passively controls corneal hydration (Fig. 3). Unfortunately, the membrane serves as a barrier not only to water but also to the nutrients that the cornea normally receives from the aqueous humor.

Intracorneal Implants

Ophthalmic surgeons may use diverse polymeric devices to correct the optical function of the eye. Thus, intracorneal implants can be used instead of spectacles or contact lenses to correct nearsightedness and farsightedness (Fig. 4). The intracorneal implants most likely to succeed are made of hydrogel materials tailored to have high permeability to metabolites and able to correct severe myopia (McCarey *et al.*, 1989). The stromal cells (keratocytes) and the epithelium receive their nutrients from the aqueous humor and also release waste products in the same direction. Therefore, some previously used intrastromal implants, such as poly(methyl methacrylate) and polysulfone, which are impermeable to metabolites, will result in the ulceration and vascularization of the overlying stroma. A more recent development is the intrastromal ring made of poly(methyl methacrylate) or silicone rubber, which may change the corneal curvature and, hence, the eye's optical power. These rings can make the corneal curvature steeper, increasing the refractive power, or flatter, decreasing the refractive power.

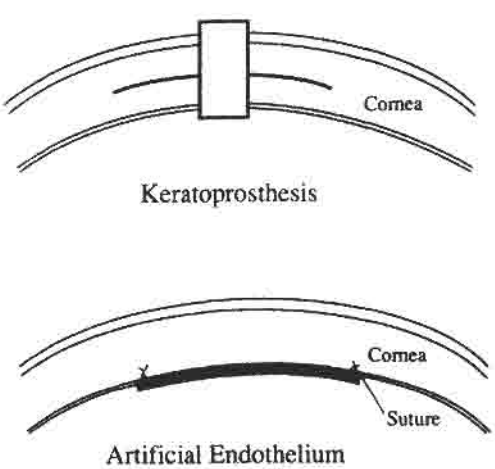

FIG. 3. (Top) Schematic representation of a through-and-through artificial cornea (kerastoprosthesis) that consists of an optical cylinder that penetrates the opaque tissue. The prosthesis has an intrastromal rim that holds the prosthesis in the cornea. (Bottom) Schematic representation of the artificial corneal endothelium that consists of a transparent membrane sutured to the posterior part of the cornea denuded of its endothelium. This membrane acts as a barrier to the inflow of aqueous fluid into the corneal stroma.

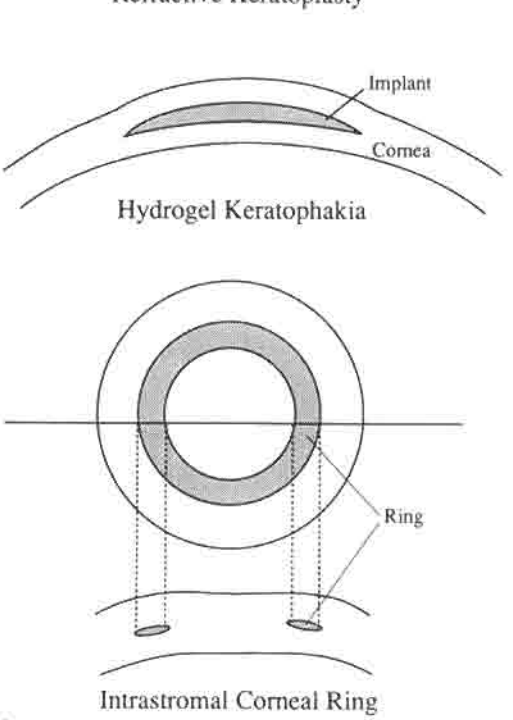

FIG. 4. Schematic representation of intracorneal implants used to change the curvature of the cornea in refractive keratoplasty. (Top) An intrastromal hydrogel intracorneal implant. (Bottom) An intrastromal corneal ring.

IMPLANTS FOR GLAUCOMA

Polymeric devices are used to control abnormally high intraocular pressure in otherwise intractable glaucoma (Krupin *et al.*, 1988). These devices consist essentially of tiny tubes that transport the aqueous humor—which normally maintains the physiological intraocular pressure and flows in and out of the eye in a well-regulated manner—from the anterior chamber to some artificially created space between the sclera and the other tissues that surround the eyeball; then the aqueous humor is absorbed into the blood circulation. The main problem with glaucoma implants is tissue proliferation around the outlet of the plastic device. Tissue proliferation, or capsule formation, takes place in and around all implanted biomaterials and may retard or even stop the outflow of aqueous humor from the eye.

INTRAOCULAR LENS IMPLANTS

Intraocular lenses (IOLs) are used after cataract extraction to replace the opaque crystalline lens of the eye (Apple *et al.*, 1984). IOLs consist of an optical portion and haptics that support the optical portion in its proper place in the eye (Fig. 5). IOLs may be placed in the anterior chamber, in the pupil, and in the posterior chamber. The last type are most commonly used at this time; they are usually placed within the posterior capsule of the crystalline lens, which remains in the eye after the lens contents have been removed surgically (Fig. 5). A large variety of IOL designs and shapes are available; the choice does not necessarily depend on need but rather on the preferences of surgeons and manufacturers.

The requirements of IOL materials are good optical properties and biocompatibility with the surrounding tissues. Although oxygen or metabolite permeability is irrelevant for IOLs, one may have to be concerned with the potential absorption in the IOL material of aqueous humor proteins or a topical or systemic drug given to a patient wearing an IOL, particularly if the IOL material is a hydrogel or silicone rubber.

Most IOLs are made of poly(methyl methacrylate), and the haptics are often made of the same material or polypropylene fiber (Apple *et al.*, 1984). Filtration of UV light by UV-absorbing moieties polymerized into the IOL is desirable to protect the retina (Miller, 1987).

Corneal astigmatism may result from tissue distortions occurring as a consequence of the uneven healing of the wound made when the IOL was implanted. There is currently a strong interest in developing soft IOLs, which can be inserted in the eye through smaller surgical incisions that are required for implanting rigid lenses. A smaller incision may result in a lower incidence of astigmatism. Soft IOLs have been made of HEMA or other hydrogels, which can be inserted into the eye fully hydrated or in the dehydrated state; in the latter case they will swell *in situ* to their equilibrium hydration (Barrett *et al.*, 1986). Flexible IOLs are made also of silicone rubber and of alkyl acrylate copolymers.

Biopolymers in the form of a viscoelastic solution are also used in IOL implantation. The corneal endothelium is an extremely delicate cell layer and can be irreversibly damaged upon contact with an IOL, during or after insertion. The surgeon must be extremely careful not to touch the corneal endothelium with the IOL or with any instrument used during surgery. Highly viscous, and preferably viscoelastic, solutions of biopolymers such as sodium hyaluronate, chondroitin sulfate, or hydroxypropyl methylcelluose are useful adjuncts in IOL implant surgery for maintaining anterior chamber depth during introduction of the implant and for preserving the corneal endothelium (Fernandez-Vigo *et al.*, 1989). Other important developments may be the surface modification of IOLs with permanent hydrophilic or hydrophobic coatings.

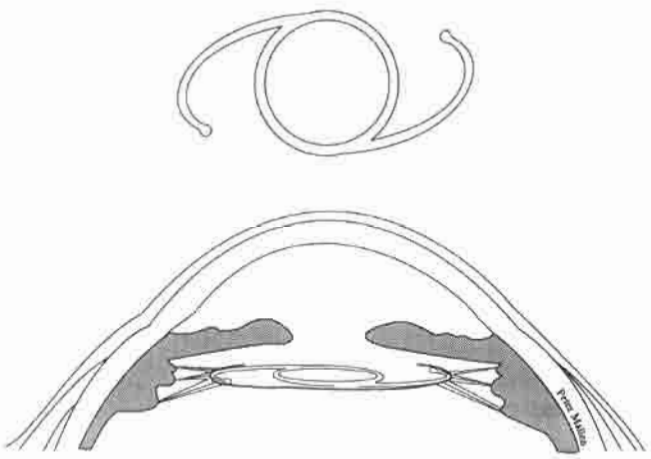

FIG. 5. (Top) Schematic representation of a typical intraocular lens implant with a central optical portion and the haptics or side-arms that hold the lens in the eye. (Bottom) A schematic representation of the anterior segment of the eye with an intraocular lens placed into the empty crystalline lens bag.

IMPLANTS FOR RETINAL DETACHMENT SURGERY

A retina detached from its source of nutrition in the choroidal circulation ceases to be sensitive to light. The choroid is the vascular layer between the retina and the sclera (Fig. 1). In cases of retinal detachment, the surgeon must reattach the retina to restore vision. Retinal detachment could result from traction of a retracting vitreous humor or from seepage of liquefied vitreous through a retinal hole between the retina and the choroid. Retina surgeons can often restore vision to these eyes with vitreous implants and scleral buckling materials (Refojo, 1986b) (Fig. 6).

Vitreous Implants

Vitreous implants are desirable in certain difficult cases of retinal detachment surgery (Refojo, 1986b). Physiological saline solution, air and other gases, as well as a sodium hyaluronate solution frequently are injected into the vitreous cavity during virtreoretinal surgery. These fluids may perform well as a short-term vitreous substitute. For long-term vitreous replacement, however, the only substance used at this time, and with variable results, is silicone oil of high viscosity (1,000 to 12,500 centistokes) and for short-term vitreous replacement, perfluorocarbon compounds of low viscosity. The main problem with long-lasting intravitreous implants is tolerance. Retinal toxicity, oil emulsification, glaucoma, and corneal clouding are some of the complications of permanent vitreous implants. These complications may be avoided by removing the implant after choroidal-retinal adhesion has been achieved, but implant removal involves further surgery, is difficult to achieve completely, and carries the risk of recurrence of the retinal detachment.

Scleral Buckling Materials

Scleral buckling materials for retinal detachment surgery must be soft and elastic. Solid silicone rubber and silicone sponge have been used successfully. More recently an acrylic hydrogel made of a copolymer of 2-hydroxyethyl acrylate with methyl acrylate has become available. It may improve the already relatively small rate of infection resulting from the use of the sponge and the potential for long-term pressure necrosis of the more rigid solid silicone rubber implants (Refojo, 1986b).

SURGICAL ADHESIVES

As in most applications of polymers as biomedical implants, in ophthalmology any polymeric device must be as free as

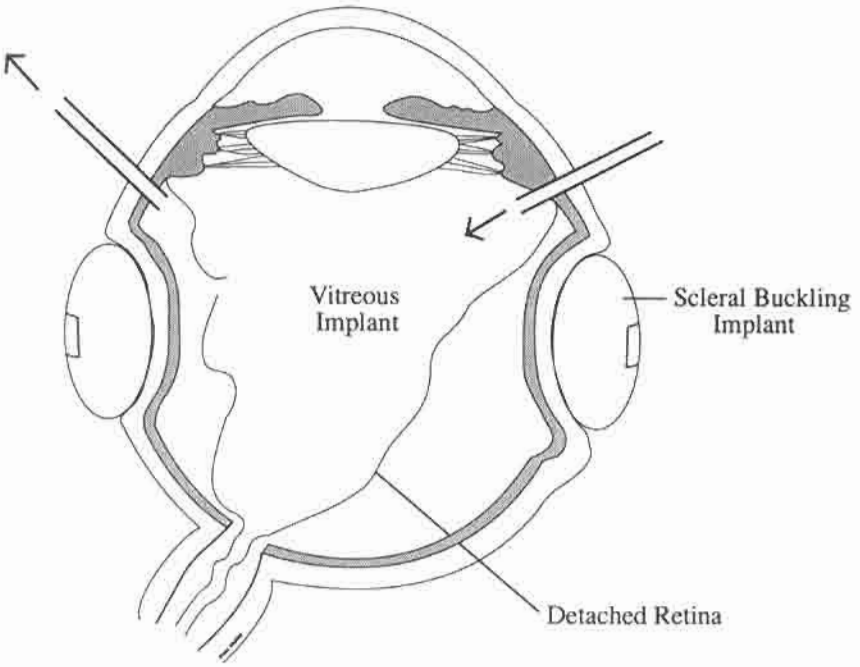

FIG. 6. Schematic representation of an eye with a detached retina. The retina can be pushed back into its normal place by injecting a fluid in the vitreous cavity (inside arrow) while the subretinal fluid is drained (outside arrow). A scleral buckling implant (the drawing represents an encircling implant) is placed over retinal tears to counteract the traction on the retina of a shrinking vitreous and to reapproximate the retina to the underlying tissues.

possible of residual monomer. However, in the unique case of the cyanoacrylate surgical adhesives, the monomers are applied directly to the tissues and almost instantaneously polymerize and adhere tenaciously to the tissues. The cyanoacrylate adhesives have been used in many diverse applications in the eye but have been particularly useful in corneal perforation and ulcers as well as in gluing artificial epithelium to the corneal surface and repairing retinal detachments (Refojo *et al.*, 1971).

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7.9 SUTURES

Dennis Goupil

Approximately 250 million sutures are used in the United States annually for a variety of surgical procedures ranging from routine skin lacerations to delicate organ transplants. Under the assumption that an equal number of sutures are used outside the United States, this total of nearly 500 million surgical devices represents the largest volume and most commonly used surgical device in the world.

A suture is a complicated medical product that must be designed and manufactured consistently to meet a range of physical and clinical demands. Its major functions are to bring and hold tissue together following separation by surgery or trauma. When one considers how sutures benefit the facial reconstruction of an accident victim, or the fatal consequences of suture breakage following a heart transplant, one begins to understand their complexity and function.

CATEGORIES AND CHARACTERISTICS

Sutures are broadly categorized according to the type of material (natural, synthetic) from which they are made, the

TABLE 1 Major Commercially Available Polymeric Sutures

Suture type	Generic chemical structure	Construction[a]	Sterilization method[b]	Representative commercial product (manufacturer)	Major clinical use
Natural materials					
Catgut	Protein	Tw	ETO/Rad.	Catgut (D+G, Ethicon)	Ob/Gyn, urology
Silk	Protein	B	ETO/Rad.	Silk (D+G) Surgical silk (D+G)	Cardiovascular Vascular
Synthetic absorbable					
Poly(glycolic acid)	$[-OCH_2CO_2CH_2CO-]$	B	ETO	Dexon II (D+G)[c]	General, Ob/Gyn
Poly(glycolide-co-lactide)	$[-OCH_2CO_2CH_2CO-]_{90}$ $[OCH(CH_3)CO_2CH(CH_3)-CO-]_{10}$	B	ETO	Coated vicryl (Ethicon)[d] Polysorb (USSC)[e]	General, Ob/Gyn
Poly(*p*-dioxanone)	$[-O(CH_2)_2OCH_2CO-]$	M	ETO	PDS (Ethicon)[f]	General, Ob/Gyn
Poly(glycolide-co-trimethylene carbonate)	$[-OCH_2CO-]_{67}$ $[-OCH_2CH_2CH_2OCO-]_{33}$	M	ETO	Maxon (D+G)[g]	General, Ob/Gyn
Synthetic nonabsorbable					
Poly(butylene terephthalate)	$[-O(CH_2)_4OCOC_6H_4CO-]$	B, M	ETO/Rad.	Miraline (Braun)	Cardiovascular Orthopaedics
Poly(ethylene terephthalate)	$[-O(CH_2)_2OCOC_6H_4CO-]$	B, M	ETO/Rad.	Ti.Cron (D+G) Surgidac (USSC)	Cardiovascular Orthopaedics
Poly[p(tetramethylene ether) terephthalate-co-tetramethylene]	$[-(CH_2)_4OCOC_6H_4CO]_{84}$ $[-O(CH_2CH_2CH_2CH_2O-]n$ $COC_6H_4CO-]_{16}$	M	ETO/Rad.	Novafil (D+G)	Plastic/cuticular
Polypropylene	$[-CH_2CH(CH_3)-]$	M	ETO	Surgilene (D+G) Prolene (Ethicon) Deklene (Deknatel) Surgipro (USSC)	Cardiovascular Vascular
Nylon 66	$[-NH(CH_2)_6NHCO(CH_2)_4CO-]$	B, M	ETO/Rad.	Dermalon (D+G) Ethilon (Ethicon) Monosof (USSC)	Plastic/cuticular Ophthalmic

Note. Sources listed under Bibliography.
[a]Construction: Twisted (Tw); braid (B); monofilament (M).
[b]Sterilization method: Ethylene oxide (ETO); Gamma radiation (Rad.).
[c]Dexon II package claims, Davis+Geck.
[d]Vicryl package claims, Ethicon.
[e]Polysorb package claims, United States Surgical.
[f]PDS package claims, Ethicon.
[g]Maxon package claims, Davis+Geck.

permanence of the material (absorbable or nonabsorbable), and the construction process (braided, monofilament) used. As shown in Table 1, the most popular natural materials used for sutures are silk and catgut (animal intestine). A fair amount of art and effort is required in both cases to reduce the raw material to the finished product. The synthetic materials are exclusively polymeric, except for fine-sized stainless steel sutures. All sutures, regardless of material or construction, require special surgical needles for delivery through tissue.

Approximately half of today's sutures are nonabsorbable and remain indefinitely intact when placed in the body. Common engineering polymers like polypropylene, nylon, poly(ethylene terephthalate), and polyethylene are used as sutures. Copolymers of these materials have also been used clinically. Absorbable sutures were commercially introduced by Davis + Geck in 1970 with poly(glycolic acid) (PGA) sutures and were followed by copolymers of glycolide and lactide from Ethicon and U.S. Surgical. More recently, novel absorbable polymers of polydioxanone and poly(glycolide-co-trimethylene carbonate) have been developed for surgical use (see Chapter 2.5 for additional information on resorbable materials).

Regardless of whether a suture is made from a natural or a synthetic material, or if it is absorbable or permanent, it must meet the strength requirements necessary to close a wound under a given clinical circumstance. Almost all suture products will be efficacious for minor wounds or for

TABLE 2 Representative Mechanical Properties of Commercial Sutures

Suture type	St. pull (MPa)	Kt. pull (MPa)	Elongation to break (%)	Subjective flexibility
Natural materials				
Catgut	370	160	25	Stiff
Silk	470	265	21	Very supple
Synthetic absorbable				
Poly(glycolic acid)	840	480	22	Supple
Poly(glycolide-co-lactide)	740	350	22	Supple
Poly(*p*-dioxanone)	505	290	34	Mod. stiff
Poly(glycolide-co-trimethylene carbonate)	575	380	32	Mod. stiff
Synthetic nonabsorbable				
Poly(butylene terephthalate)	520	340	20	Supple
Poly(ethylene terephthalate	735	345	25	Supple
Poly[p(tetramethylene ether) terephthalate-co-tetramethylene terephthalate]	515	330	34	Supple
Polypropylene	435	300	43	Stiff
Nylon 66	585	315	41	Stiff
Steel	660	565	45	Rigid

Note. Sources listed under Bibliography.

normally healing wounds. Hence, a poly(glycolic acid) suture, which loses strength over a 28-day period, will be just as adequate as a permanent polypropylene suture. If a patient, however, suffers from a disease or conditions that retard healing (e.g., diabetic patients), a nonabsorbable or slower degrading suture may be more appropriate. Representative mechanical properties of some commercial sutures are listed in Table 2.

The construction of a surgical suture (i.e., braid or monofilament) is important to both the surgeon and the patient for objective and subjective reasons. In addition to out-of-package tensile strength and *in vivo* tensile strength, the surgeon considers a variety of other parameters before making a choice of sutures for the patient. As shown in Table 3, the parameters range from objective issues of knot security or the number of knots required to secure a suture, to the subjective issue of "feel" in the surgeons' hands. Braided sutures are generally more supple products compared with monofilaments and hence have an advantage in regard to out-of-package memory, ease of tying, and knot security if the same knot is used for both the braid and the monofilament. Monofilament sutures tend to be more wiry out of the package and can become tangled up with surgical instruments if the surgical team is not careful. The knot security issue is simply addressed by using different knots or more "throws" of a given knot to achieve security. The major advantage of a monofilament suture is its relatively low tissue drag compared with a braided suture. This low drag or friction between the tissue and the suture allows the surgeon to use different techniques in closing wounds (e.g., continuous or running closures). The low tissue drag is also less "abrasive" when the suture is being pulled through the tissue. This aspect is especially important for fragile cardiovascular, ophthalmic, and neurological tissue, where monofilament sutures are the products of choice.

TABLE 3 Suture Characteristics

Objective	Subjective
Tensile strength	Suppleness
Knot security	Ease of tying
Diameter	Ease on hands
Strength retention	
Flexibility	
Memory out of the package	
Tissue drag	
Infection potentiation (wicking)	

PRODUCT DEVELOPMENT

It can take years to generate information to support clinical use of a new suture product, and usually 4–6 years for a completely new polymer suture. The steps required to develop a suture are outlined in Table 4. Starting with the concept or product design, several polymers are screened prior to choosing the optimum candidate. In the preclinical stage, extensive safety and animal efficacy testing is conducted to answer the questions of safety and effectiveness. This testing stage can take 2–3 years to complete. In addition to the basic requirement that the polymer must be able to be extruded and processed consistently to provide the fiber strength necessary to hold tissue together, the polymer must be able to withstand sterilization.

Extensive toxicology testing is usually required, including

acute and chronic toxicity, pyrogenicity, antigenicity, *in vitro* and *in vivo* infection potentiation, hemolytic potentiation, mutagenicity, and possibly carcinogenicity. In addition, suture strength and knot security are also evaluated in animal surgical procedures. If the suture is absorbable, the *in vivo* tensile strength over time and the absorption and metabolic fate of the polymer need to be established.

Following this testing, clinical evaluations are usually required to confirm the safety and efficacy of the product. The subjective issues of suture handling and knotting techniques need to be evaluated in the hands of many surgeons in scores of patients for each major clinical suture use. Again, this step can be lengthy, taking approximately 1–2 years to complete.

While the clinical studies are being conducted, manufacturing scale-up studies are completed and product and package stability data are assembled. The animal safety and efficacy data are combined with the clinical data and manufacturing documentation to prepare for registration or approval by a government agency (e.g., the U.S. Food and Drug Administration). The review process itself can be time consuming, often taking more than a year.

TRENDS

Several factors have influenced the suture industry in the past 5 years, including the changing regulatory environment in the United States and in Europe, the focus on cost containment in health care, the patent status of proprietary materials and processing methods, changing surgical practice toward minimally invasive techniques, and the advances in alternative wound-closure technologies (staplers, glues, etc.).

In the United States, most suture types have been reclassified from the stringent Class III (Pre-Market Approval) regulatory category to Class II (510.k) medical devices. This change will lead to more rapid commercialization of products and to the introduction of more generic sutures. The commercialization of sutures in Europe will become more difficult overall as the countries of the European Economic Community progress toward a more unified approach toward registration of medical devices. Previously, sutures could be commercialized in several countries without registration, but future use will necessitate that products meet the requirements of the CE process.

The majority of the proprietary technology that is germane to sutures is held by Ethicon, Davis + Geck, and more recently by U.S. Surgical. As the more traditional patents expire over the next 5–10 years, more manufacturers will enter an industry that is already highly competitive and cost constrained.

Sutures, which once constituted 100% of the wound closure market, are now receiving stiff competition from surgical staplers as these mechanical devices have become well accepted by surgeons. Mechanical devices have been especially useful in minimally invasive surgery and have allowed the surgeon to shift to laparoscopic surgery wherever possible. The removal of the gallbladder (cholecystectomy), which is the most frequently performed general surgical procedure, is now performed laparoscopically in approximately 90% of the cases in the United States. The promise of surgical glues and growth factors has been disappointing to date, but there are several research efforts ongoing that may find the appropriate chemistry to be both safe and efficacious.

Despite these changes, one major influence remains unchanged. By training, surgeons are conservative and must keep the well-being of their patient in mind at all times. As a result, despite commercial or technological changes that may emerge over the next decade, the surgeon will need a substantial body of clinical data before abandoning sutures. Therefore, the science and technology that support the development of sutures will remain viable for many years to come.

TABLE 4 Steps to Develop a Suture Product

Steps	Key activities
1. Concept	
Screening studies	Evaluation of polymers for extrusion ability and broad physical properties
2. Preclinical	
Manufacturing development	Extrusion optimization, including fiber annealing, braiding
Protocol physical testing	Tensile strength, knot pull strength, diameter, sterilization
Protocol animal efficacy testing	Knot security in various animal tissues, *in vivo* strength, handling
Protocol toxicology safety testing	Acute/chronic toxicity, pyrogenicity, antigenicity, *in vitro*/*in vivo* infection potentiation, hemolytic potentiation, mutagenicity, carcinogenicity.
3. Clinical	
Safety and efficacy confirmation	Clinical evaluation in representative patients (100–1000)
4. Registration	
Data summary and submission	Composition of preclinical and clinical data
Board of health approval	Agency review of documents and panel review (optional)
5. Manufacturing scaleup	Production qualification (a few lots) and validation (many lots/sizes)
6. Commercialization	Inventory stocking and promotional campaign