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New Challenges in Biomaterials

Nicholas A. Peppas and Robert Langer

Significant opportunities and challenges exist in the creation and characterization of biomaterials. Materials have been designed for contact with blood, as replacements for soft and hard tissues, as adhesives, and as dental materials. Current methods of synthesis and characterization of these materials are outlined. Approaches for controlling the interface between tissue and biomaterials and ways in which the engineered materials may contribute to medicine are considered.

In general, biomaterials are substances other than food or drugs contained in therapeutic or diagnostic systems that are in contact with tissue or biological fluids. They are used in many pharmaceutical preparations—for example, as coatings for tablets or capsules or as components of transdermal patches. They play a central role in extracorporeal devices, from contact lenses to kidney dialyzers, and are essential components of implants, from vascular grafts to cardiac pacemakers (*1*). There are many current biomaterials applications (Table 1), found in about 2700 different kinds of medical devices, 2500 separate diagnostic products, and 39,000 different pharmaceutical preparations. Estimated annual sales of medical devices and diagnostic products in the United States is about $24 billion, and that of pharmaceutical products exceeds $80 billion (*2*, *3*). Although biomaterials have already made an enormous health impact, the need exists for better polymer, ceramic, and metal systems and improved methods of characterizing and testing them.

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Synthetic Approaches to New Biomaterials

The development of biomaterials has been an evolving process. Many biomaterials in clinical use were not originally designed as such but were off-the-shelf materials that clinicians found useful in solving a problem. Thus, dialysis tubing was originally made of cellulose acetate, a commodity plastic. The polymers initially used in vascular grafts, such as Dacron, were derived from textiles. The materials used for artificial hearts were originally based on commercial-grade polyurethanes. These materials allowed serious medical problems to be addressed. Yet, they also introduced complications. Dialysis tubing may activate platelets and the complement system; Dacron-based vascular grafts can only be used if their diameter exceeds about 6 mm, otherwise occlusion can occur because of biological reactions at the blood-material and tissue-material interfaces; and blood-materials interactions can also lead to clot formation in an artificial heart, with the subsequent possibility of stroke and other complications.

A number of polymer manufacturers have also recently withdrawn certain polymer grades used as biomaterials. This has created a shortage, making it urgent to find or synthesize polymers that can replace those no longer available.

In the last few years, imaginative synthetic techniques have been used to impart desirable chemical, physical, and biological properties to biomaterials (*4*). Materials have either been synthesized directly, so that desirable chain segments or functional groups are built into the material, or indirectly, by chemical modification of existing materials to add desirable segments or functional groups.

Polymeric biomaterials can be produced by copolymerizations or terpolymerizations of conventional monomers (*5*) to achieve nearly monodisperse polymers. It is possible to produce polymers containing specific hydrophilic or hydrophobic entities, biodegradable repeating units, or multifunctional structures that can become points for three-dimensional expansion of networks. Advanced computer techniques allow researchers to follow the kinetics of formation of three-dimensional structures of these biomaterials (*6*).

The properties of various star polymers and dendrimers have led to different synthetic techniques for their preparation (*7*). Star polymers and dendrimers are hyperbranched structures that emanate from a central core and consist of large numbers of terminal groups with a definite geometrical pattern (Fig. 1). Biomaterials based on star polymers may prove useful as a means of increasing the density of desired ligands. For example, increased densities of poly(ethylene oxide) (PEO) compared with linear PEO polymers have been achieved with a divinyl benzene core from which 10 to 50 PEO arms extend (*8*). This approach potentially enhances biocompatibility because the high PEO density is more effective in sterically repelling proteins or cells, making it difficult for them to "see" a non-PEO surface. From a biomaterials standpoint, crucial issues to be addressed for star polymers are toxicology, ability to increase production, and, in some cases, cost.

Another synthetic approach involves genetic engineering for the preparation of artificial proteins of uniform structure (*9*). This enables the synthesis of periodic polypeptides that form well-defined lamellar crystals, polypeptides containing nonnatural amino acids, and monodisperse helical rods. Important issues to be addressed include immunogenicity and purification from contaminants during large-scale production. If techniques are developed to produce polymers with the use of nonamide backbones, the versatility of this approach would be extended.

Synthesis of polymers such as polyphosphazenes with particularly stable backbones may make it possible to tailor structures for different applications. For example, with polyphosphazenes, a high molecular weight polymer may be synthesized and a simple chemical reaction can be used to exchange an original set of functional groups for groups with a desired functionality without having to synthesize the entire polymer from monomers (*10*).

Efforts have also been made toward chemical modification of polymer surface or bulk properties, by treatments such as plasma modification (*11*). One surface treatment of biomaterials involves grafting inert substances such as PEO segments onto or within existing polymers such as polyurethanes to enhance biocompatibility or reduce protein adsorption (*12*). In addition, polymers have been synthesized that promote a desirable interaction between themselves and surrounding cells. Thus, peptide sequences, such as Arg-Glu-Asp-Val, that promote endothelial cell seeding have been synthesized into polymers for potential use as artificial blood vessels (vascular grafts) (*13*) and copolymers of lactic acid and lysine have been synthesized, to which specific amino acid sequences that promote adhesion of hepatocytes or other cells can be attached for potential use in tissue engineering (*14*).

Other desirable characteristics of biomaterials include controllable (fast or slow) degradation (*15*). For example, drug delivery often requires carriers that display surface erosion (*16*). This property provides a more predictable approach to polymer dissolution, in contrast to bulk erosion, the way most degradable materials dissolve. To address this issue, researchers synthesized polymers, such as polyanhydrides (Fig. 2) or polyorthoesters (*17*), that contain hydrophobic repeating units with water-labile linkages. Such polymers can protect labile drugs from water-induced aggregation because of the polymer's hydrophobicity, as well as prevent large amounts of drug from being released all at once (dose dumping). In another development, amino acids have been coupled through nonamide bonds to yield a family of polymers, "pseudo-poly(amino acids)," which combine the desirable safety and other characteristics of amino acids but permit the construction of

Table 1. Examples of biomaterials applications.

Cardiovascular implants	Hearts and valves Vascular grafts Pacemakers Stents
Plastic and reconstructive implants	Breast augmentation or reconstruction Maxillofacial reconstruction Penile implant
Orthopedic prostheses	Knee joint Hip joint Fracture fixation
Opthalmic systems	Contact lenses Intraocular lenses
Dental implants	
Neural implants	Hydrocephalus shunt Cochlear implant
Extracorporeal	Oxygenators Dialyzers Plasmapheresis
Catheters	
Devices for controlled drug delivery	Coatings for tablets or capsules Transdermal systems Microcapsules Implants
General surgery	Sutures Staples Adhesives Blood substitutes
Diagnostics	

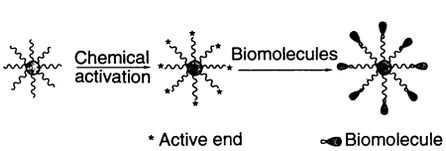

Fig. 1. Schematic diagram of a star polymer. It is possible to chemically activate the ends of the arms of star polymers to immobilize biomolecules.

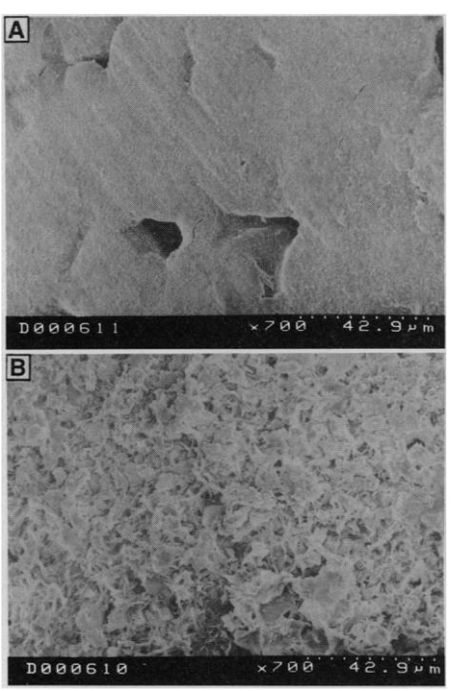

Fig. 2. Scanning electron micrographs showing the surface texture of (**A**) a poly(fumaric-*co*-sebacic) anhydride microsphere (20% fumaric, 80% sebacic) and (**B**) the same type of microsphere after incubation in phosphate-buffered saline (pH 7.5, 23°C) for 20 hours. Extensive erosion occurred across the microsphere surface.

polymers with properties, for example, mechanical strength, superior to conventional polyamides (*18*). Certain tyrosine monomers possessing immunological adjuvant activity have been synthesized into such polymers through degradable iminocarbonate linkages to prepare vaccine delivery devices, thus increasing the vaccine-promoting effects of antigens being released from these polymers (*19*).

Other synthetic approaches have been used to develop environmentally responsive biomaterials (to surrounding pH, ionic strength, or temperature) (*20*). For example, poly(acrylic acid) with ionizable side groups responds to changes in pH or ionic strength by altering its physical structure or permeability (*21*). Such systems are being studied as substrates for cell growth, linings for artificial organs, carriers for drug delivery, and candidates for biomedical adhesives (*21*).

Issues in Biomaterials Characterization

Advanced characterization techniques have been used to understand the behavior of biomaterials. Carbon-13 nuclear magnetic resonance (NMR) is routinely used to identify the cross-linked structure of biomaterials, whereas solid-state NMR spectroscopy is used for analysis of the relaxational behavior of polymer carriers used in controlled drug delivery during their dynamic swelling and release of their contents (*22*). Attenuated total-reflectance Fourier transform infrared (FTIR) spectroscopy and dynamic photoellipsometry are techniques that can be used to study protein adsorption on biomaterial surfaces, whereas near-field FTIR spectroscopy has provided information about bioadhesion mechanisms of biomaterials such as poly(acrylic acid) (*23*). Optical methods that use second-harmonic generation may be useful in characterizing the interfaces between gels and liquids (*24*).

Classical surface analysis techniques such as x-ray photoelectron spectroscopy (XPS), static secondary ion mass spectroscopy (SIMS), and scanning tunneling microscopy (STM) continue to provide information on surface structure (*25*). However, important challenges remain. For example, the use of the ultrahigh vacuum conditions needed for these approaches while attempting to maintain a surface structure that is representative of the biomaterial in a hydrated environment is a major issue. In addition, in complex chemical structures, deconvolution programs of XPS spectroscopy lead to relatively large errors and, therefore, significant uncertainty of surface-structure chemical analysis.

Similarly, the bulk properties of biomaterials can be better tested with recent advances in mechanical properties determination. For example, dynamic mechanical testing allows measurement of the dynamic mechanical behavior of biomaterials under different testing conditions, such as penetrant content and temperature (*26*).

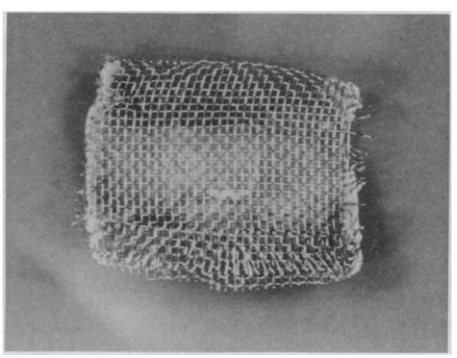

Fig. 3. Stainless steel mesh cage implant. The cage implant contains a specimen for evaluation. Implantation of the cage permits investigators to temporally evaluate inflammatory cells and exudate components without killing the animal. This system has been used to evaluate the biocompatibility of numerous polymers, the release kinetics of drug-polymer systems, and the biodegradation and biostability of polyurethanes. Macrophage adhesion and foreign body giant cell development in vivo have also been investigated with this system.

Testing of Biomaterials

Toxicological testing of biomaterials generally includes examination of local tissue response, systemic toxicological response, and allergic, pyrogenic, carcinogenic, and teratogenic responses. Three levels of testing are recommended for eventual regulatory approval: (i) toxicological tests in animals and in vitro systems, (ii) tests in animals at sites where the biomaterial is to be used, and (iii) clinical trials in humans. Both the material itself and extracts in fluids simulating components of physiological fluids [for example, saline, poly(ethylene glycol), and cottonseed oil] are usually tested (*27*). In vitro testing under proper simulating conditions is very important. For example, in vitro studies attempting to duplicate in vivo environmental stress cracking of polyurethane pacemaker leads are very dependent on in vitro test conditions (*28*). Development of appropriate reference materials standards is also becoming increasingly important for the evaluation of biomaterials (*29*).

Other in vivo tests may also be useful in an examination of biocompatibility. One test involves implanting a biomaterial in the rabbit corneal pocket. Because of the eye's sensitivity to inflammation, as well as the rabbit's docility and large eye size, this is a straightforward and sensitive approach that allows investigators to noninvasively follow (using an ophthalmologic microscope) the time course of material biocompatibility. Signs of inflammation such as neovascularization, edema, and white cell infiltration can be directly visualized and, if needed, confirmed histologically (*30*). A useful method of quantitating the in vivo cellular reaction to a biomaterial is the "cage method" (*31*). By surrounding an implant with an artificial cage, samples of fluid can be removed and specific inflammatory cells can be quantitatively determined (Fig. 3).

An example of the tests needed to be performed on biomaterials before they are used in humans can be seen in the development of polyanhydrides as a family of polymers for local delivery of drugs to treat brain cancer. Initial studies focused on mutagenicity, cytotoxicity, and teratogenicity in in vitro tests and on rabbit eye studies (*32*). This was followed by five in vivo studies: (i) polymer biocompatibility in the rat brain, (ii) biocompatibility of high levels (up to 100 times the anticipated dose) of polymer implanted subcutaneously in rats, (iii) polymer biocompatibility in the monkey brain, (iv) autoradiography of drug released from the polymer in the rabbit brain, and (v) efficacy of the treatment in rats. Once these studies were completed, safety and efficacy studies in humans were conducted with U.S. Food and Drug Administration (FDA) approval (*33*).

It would be valuable if more rapid and less expensive methods for biocompatibility testing were developed and approaches were created that substitute for extensive animal or human tests. Technologies that use tissue culture and other noninvasive methods may eventually reduce in vivo testing. In this regard, engineered tissues, such as artificial skin grown from human embryonic fibroblasts on synthetic polymers (*34*), have proven useful for screening compounds for potential cosmetic or dermatologic applications.

Opportunities in Biomaterials Development

Soft tissue replacement. Biomaterials implanted into vascularized tissue exhibit foreign body reactions, inflammation, and a

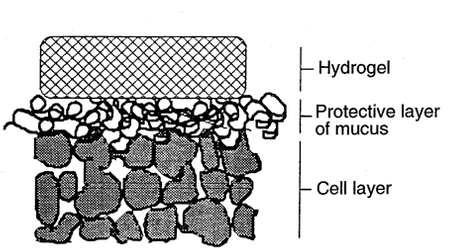

Fig. 4. Schematic diagram of a mucoadhesive system.

healing response. New areas of research include the role of macrophages and monocytes in inflammation, cytokine induction by monocyte-biomaterial interactions, and adhesion mechanisms in monocyte or macrophage activation on biomaterials surfaces.

Elastomers are predominantly used in applications that require compliance with soft or cardiovascular tissue. The materials may be needed for permanent implantation (artificial hearts, mammary prostheses, pacemaker lead insulators, and vascular grafts) or temporary use (semiocclusive dressings). The combination of biocompatibility, performance, and ease of manufacture make polyurethane elastomers the polymer of choice in many medical devices (*35*).

To avoid problems of leachable unreacted compounds, new biomaterials for soft tissue replacement are being developed that use benign processing methods. For example, uncross-linked, physically reinforced gels of poly(vinyl alcohol) have been tested as biomaterials (*36*). There is a trend toward such biomaterials, as in the manufacture of artificial tendons from blends of poly(vinyl alcohol) and poly(acrylic acid).

Blood-contacting materials. Improving the biocompatibility of blood-contacting surfaces continues to be a challenge. Although such materials are important in the development of improved extracorporeal devices (for example, hemodialyzers and blood oxygenators) and implantable devices (for example, vascular grafts), they sometimes cause damage to the blood's cellular components and cause thrombosis. Current pharmacological solutions to these problems may prove harmful. For example, relatively large quantities of the anticoagulant heparin must often be added to extracorporeal devices to prevent thrombosis. However, these quantities of heparin can cause bleeding, such as brain hemorrhage (*37*).

Early attempts to improve blood compatibility involved ionically binding heparin to the material surface. Although improved performance was sometimes observed, it was often attributed to heparin leaching from the material. Subsequent attempts involved other methods of coupling heparin to surfaces, generally using covalent bonds (*38*). The performance of heparin in preventing thrombosis depends on the method by which it is bound to a biomaterial and the type and length of spacers used in the coupling procedure (*39*). Physically or chemically incorporating other agents—such as phospholipids (*40*), fibrinolytic enzymes (streptokinase or urokinase) (*41*), or prostaglandins (*42*)—or altering polymer hydrophilicity (*43*) also reduces thrombogenicity. An additional approach involves biological modification of a polymer by protein adsorption or seeding with endothelial cells (*44*) (including genetically altered cells producing tissue plasminogen activator).

Calcification of biomaterials may also occur, particularly if the materials undergo repeated flexing (*45*). Approaches to the prevention of calcification, such as localized sustained release of calcium chelating agents, are being studied (*46*).

Medical adhesives. Medical adhesives are generally polymers that adhere to natural tissues and mucosa (Fig. 4). They have found widespread application as topical and surgical adhesives and are being studied for drug delivery. Potential adhesives have been evaluated for adhesive properties, durability, and biological inertness (*47*). Medical adhesives based on cyanoacrylates provide challenges because of their unpredictable degradation characteristics. In addition, pressure-sensitive adhesives based on silicones and acrylates are being developed. Mucoadhesive materials are usually based on poly(acrylic acid), carboxymethyl cellulose, and other polymers that induce hydrogen bonding (*48*). An alternative method of design is based on replication of the amino acid sequences found in naturally occurring adhesives, such as marine bioadhesives (in mussels and barnacles).

Development of better bioadhesives depends on a judicious choice of surface wettability, ionic interactions, and the adhesive's natural tendency to penetrate the polymer-tissue interface. Yet, there are numerous unanswered questions, such as the importance of chain penetration across the adhesive interface, the role of anionic or cationic groups in adhesion, and the influence of the bioadhesive's molecular weight and structure.

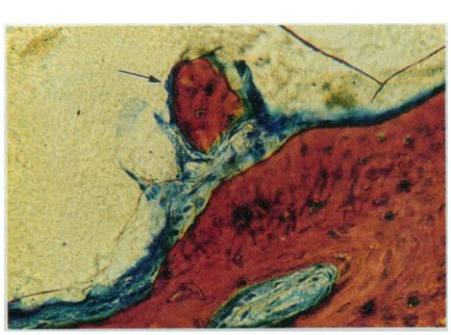

Fig. 5. Histological section (magnification, ×40; staining by van Gieson picrofuchsin and Stevenel's blue; 6 months after implantation; rabbit femur) of a transcortically implanted pin of poly(DTH carbonate), a pseudo-poly(amino acid) derived from the natural amino acid L-tyrosine. The white area in the upper part of the figure is implant material, bone tissue is stained red, and cellular tissue appears blue. Contrary to commonly used orthopedic implant materials such as poly(glycolic acid), the tyrosine-derived polymer is invaded by growing bone (arrow) during polymer degradation. This represents an example of an interactive, degradable implant material.

Orthopedic applications. Biomaterials are used in many forms of orthopedic surgery. In some cases, such as joint replacement, the materials—iron, cobalt, and titanium—are designed to be permanent. However, because these substances are subject to corrosion and wear and because of the difference in mechanical properties between metal and bone, the bone around the implant may become weak (*49*). Furthermore, implanted metals frequently do not adhere well to bone and often induce a fibrous capsule around the implant, leading to impaired function of the repaired site (*50*).

Degradable polymers may be useful in orthopedic applications because they circumvent the problems of a persistent foreign body and the need for implant retrieval. The materials should be sufficiently strong to withstand the stresses to which bones are normally subjected, provide good tissue biocompatibility, and allow operative ease to obtain osseous union with minimal bone morbidity. However, most degradable polymers are too weak to be used in load-bearing implants.

One approach to address this issue has been the design of self-reinforced composites in which cylindrical fibers of polyglycolic acid (PGA) are embedded within a PGA matrix (*51*). Such materials have been tested on over 20,000 patients and are sometimes considered superior to metal fixation devices. However, drawbacks include poor visibility during x-ray imaging, too rapid a loss of stiffness to ensure bone healing, and a noninfectious inflammatory response that occurs in a small but significant percentage (8%) of patients and requires drainage. This response may be caused by acidic polymer breakdown products (*50, 52*).

An alternative approach involves the synthesis of stronger polymers. One such material is polydioxanone, which has received FDA approval for applications such as sutures (*53*). Although this material is useful for fixation of osteochondral fractures, it has insufficient mechanical properties for treatment of long bone fractures. Other strategies include the synthesis of polymers containing aromatic monomers (*54*) such as tyrosine with degradable backbones (Fig. 5).

Ceramic materials, especially bioactive materials, that is, those that form a bond with living tissue, may be useful in bone repair. Hydroxyapatite and certain glasses are examples. The rates of biomineralization and bioactive fixation as well as knowledge of their time dependence are critical to the molecular design of such ceramics. For non–load-bearing prostheses, such as might be used in the middle ear or maxillofacial repair, bonding to both hard and soft tissues is required and highly bioactive implants

are needed (55). However, for load-bearing tissues such as those needed for vertebral repair, implants with higher interfacial shear strength and lower bioactivity are preferable.

Medical devices composed of orthopedic biomaterials may also benefit from computer-aided design and manufacture. This may allow on-site (in hospital) and on-demand (overnight) production of even complex implants from preshaped parts (56).

Dental materials. Important challenges are faced in developing dental biomaterials, including the use of inert polymers that can be prepared by relatively inexpensive and highly reproducible methods and that exhibit high mechanical stability. For these reasons, highly cross-linked polymers are extensively used. These materials are typically made by free radical polymerization of polyfunctional acrylates and methacrylates initiated by ultraviolet irradiation (57).

Cross-linked polymers (for example, polydimethacrylates) have been widely used as denture bases, crowns and bridges, orthodontic appliances, and artificial teeth (58). Restoration of teeth is one of the more challenging applications of cross-linked materials not only because monomers must be nontoxic and polymerize rapidly, but primarily because they must be capable of polymerization in the presence of oxygen and water. Additionally, such polymers must be comparable in properties to tooth enamel, adhere to the tooth enamel or tissue to which they are being attached, and not degrade or exhibit yellowing upon aging.

Biomaterials are also used in controlled-release devices for the treatment of periodontal diseases. Such devices are usually thin rods composed of ethylene-vinyl acetate or other polymers wrapped around the tooth, which can release tetracycline or other drugs (59). However, it would be useful if degradable, and in some cases adhesive, systems could be developed.

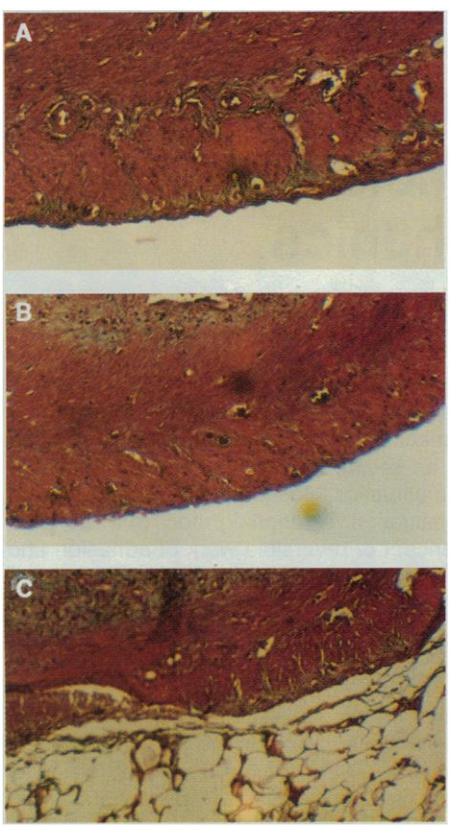

Fig. 6. Histological cross section of rat uterine horns (a model for adhesions) showing the tissue near the horn surface: (**A**) healed horn, injured and treated with polymer, (**B**) normal horn, neither injured nor treated, and (**C**) adhered horn, injured and not treated (control), showing intimate adhesion to the mesentery. Staining by Masson's trichrome; collagen is indicated by blue-green staining. Horns were examined 7 days after injury. [Reprinted from (66) with permission.]

New Directions

Many materials have been developed that have the potential to become useful biomaterials. For example, electrically conducting materials or polymers have been studied for applications in biosensors (60), for electrochemically controlled drug release (61), and as surfaces that can noninvasively control mammalian cell shape and function (62). This latter property may be useful in controlling cellular function in tissue engineering. The most widely used electrically conducting polymer is polypyrrole because of its chemical stability, ease of preparation, and electroactivity. However, it will be necessary to better understand polypyrrole's behavior under biological conditions and to synthesize biocompatible electrically conducting polymers.

Piezoelectric biomaterials may find interesting applications in medicine. For example, copolymers of vinylidene fluoride and trifluorethylene stimulated axonal regeneration after nerve injury in rats (63). Bioelastic polymers may also have applications and are being studied as muscle substitutes and preprogrammable drug delivery systems in which chemical triggers induce mechanical effects, leading to enhanced drug release (64).

Several families of materials may be useful in surgical procedures. Metal stents keep blood vessels open after angioplasty. However, the stent may cause proliferation of vascular smooth muscle cells, resulting in restenosis. Approaches to modification of the local physiologic environment, such as localized delivery of gene therapy agents or antisense oligonucleotides, have proven useful in preventing restenosis in animal models (65). Memory metals such as nickel-titanium alloys are being used as components of laparoscopic instruments and provide a means of inserting a thin, wirelike device, contained in a needlelike casing, through a small incision; the device, when composed of the memory metal, can regain a more complex shape (such as a hook) once the casing is removed. The shaped device can then be easily manipulated by its user. It would be desirable to have available biocompatible polymers with memory properties that could be administered through small incisions, subsequently regain their original shape in vivo, and then stay there to perform a desired function. Biocompatibility and, in some cases, degradability would be essential material attributes. Polymers that can be triggered to undergo a phase change may also be useful in such applications. Materials that are initially liquid might be administered through a minimally invasive surgical device and then triggered to solidify or gel in the presence of ultraviolet light, visible light, or ionic change in vivo. This type of approach has proven useful in preventing gynecologic adhesions in animal models (66) (Fig. 6).

Polymers that can be gelled under mild methods, such as under aqueous conditions triggered by light or ions, may also provide ways of encapsulating sensitive entities such as mammalian cells. Encapsulation prevents the cells from being destroyed by immune cells in vivo (67).

Finally, we are reaching a point where the understanding of cell biology and biochemistry is permitting the design of specific biologic activities into biomaterials (13, 14, 19). As more discoveries are made about particular amino acid, lipid, or carbohydrate sequences that control cell differentiation, immunologic responses, or other biologic phenomena, they can be built directly into a biomaterial. Thus, a significant future activity will involve merging knowledge of cell biology with materials science to design a new generation of materials that can actually promote desired medical outcomes.

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68. We thank J. M. Anderson, L. Brannon-Peppas, L. Cima, P. Didisheim, A. Hoffman, J. A. Hubbell, J. Kohn, E. Mathiowitz, and L. W. Schroeder for assistance. Supported by grants to N.A.P. from NIH (GM43337 and GM45027), NSF (CTS92-12482 and CTS 93-11563), Trask Fund, and Showalter Foundation and to R.L. from NIH (GM25810, GM26998, and AR41972), NSF (BCS-9202311), Advanced Tissue Sciences, and W. R. Grace.

Adhesion: Molecules and Mechanics

Kevin Kendall

There is a difference between adhesion at the molecular level and adhesion in engineering. There is no doubt that molecules of solid materials stick together and can be separated mechanically. The problem is explaining the connection between molecular attractions and mechanical measurements. False ideas such as keying and gluing require critical assessment because they confuse molecules and mechanics. Mechanisms such as adhesive hysteresis, stringing, and clustering deserve evaluation. A rational theory of these phenomena should be based on the theoretical concept of reversible work of adhesion and on the measured quantity of adhesive energy, which includes the extra energy required to restructure the interface as surfaces move.

A critical observation can define a concept in a spectacular way. Brownian motion is one such observation: It defines kinetic theory by showing that micrometer-sized particles in a fluid are in eternal haphazard motion as if bombarded by invisible moving atoms (*1*). This behavior contrasts strongly with the static behavior of engineered objects.

In the study of adhesion, the equivalent observation is the spontaneous jumping of smooth surfaces into contact (*2*, *3*). Two ultrasmooth pieces of mica, gold, polymer, or solid gelatin solution cannot be held apart when their separation becomes small enough, typically 1 to 10 nm. Such attraction is impossible to explain by electrostatic, magnetic, or gravitational forces, which act from the center of bodies and obey the inverse square law. These forces can be detected at much greater separations. The attractive force that pulls the surfaces into contact is more akin to surface tension, a short-range surface force that can be changed by a single layer of molecules laid at an interface. Engineered objects are not usually much affected by these short-range surface forces.

After the surfaces have abruptly pulled

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