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Biomaterials

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Biomaterials

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Biomaterials

Introduction

Biomaterials are metals, ceramics, polymers, glasses, carbons, and composite materials intended to interface with biological systems. They are often used to treat, augment, or replace bodily tissues, organs, or functions. Such materials are used in various forms, including molded or machined parts, coatings, fibers, films, foams, and fabrics. Biomaterials are usually nonliving, but recent definitions also include living skin and tissues produced in culture.

A biocompatible material is different from a biological material produced by a biological system, such as bone. Artificial hips, vascular stents, artificial pacemakers, and catheters are all made of biocompatible materials that typically have a synthetic origin. An extraordinarily wide range of medical devices are made from biomaterials. Figure 1 shows some representative examples of medical devices that use biomaterials.

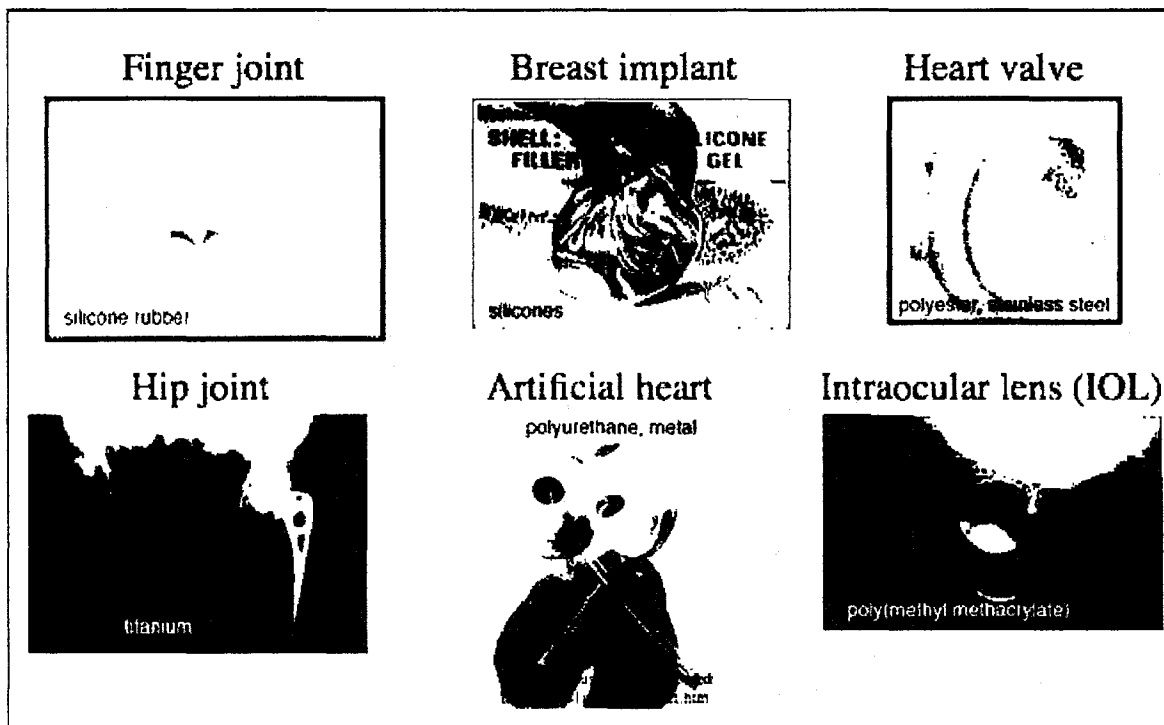


Figure 1. Biomaterial Applications in Medical Devices

Encompassing elements of medicine, biology, chemistry, and materials science, biomaterials science has experienced steady and strong growth over its approximately half-century history.

Although biomaterials are used primarily for medical applications, they are also used to grow cells in culture, to assay for blood proteins in the clinical

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laboratory, in processing biomolecules in biotechnology, for fertility regulation implants in cattle, in diagnostic gene arrays, in the aquaculture of oysters, and for investigational cell-silicon "biochips." The common thread in these applications is the interaction between biological systems and synthetic or modified natural materials.

Biomimetic materials, in contrast, are not made by living organisms but have compositions and properties similar to materials made by living organisms. For example, the calcium hydroxyapatite coating found on many artificial hips—used as metal-bone interface cement to make it easier to attach implants to bone—is similar to the coating found in mollusk shells.

IMPORTANCE OF BIOCOMPATIBILITY

Biocompatibility is an important issue in biomedical implants and sensors. A material-tissue interaction that results from implanting a foreign object in the body is a major obstacle to developing stable and long-term implantable devices and sensors.

The processes that occur when sensors are placed in the complex living environment of the human body are sometimes known as biofouling. In biofouling, the physical or chemically sensitive portion of the sensor interface becomes coated with proteins, blood-formed elements, adherent immunological cells, and sometimes forms of scar tissue that tend to isolate the sensor from the rest of the body environment. This response of tissue is a foreign body reaction to any object introduced in tissue that does not express surface characteristics that identify it as part of the host tissues.

Experiences of many investigators (more than 600 reported studies since 1996) with the biocompatibility of biomaterials related to the function of implanted biosensors have been poor such that many companies have abandoned implantable sensor devices altogether. Rather, the recent trend in medical biosensors is toward placing them outside the body. Newer sensors are often based on optical principles in an effort to obviate the biocompatibility and biomaterial issues of placing sensors inside the human body.

SCIENCE OF BIOMATERIALS

The study and use of biomaterials bring together researchers from diverse academic backgrounds who must communicate clearly. Professions that intersect in the development, study, and application of biomaterials include bioengineer, chemist, chemical engineer, electrical engineer, mechanical engineer, materials scientist, biologist, microbiologist, physician, veterinarian, ethicist, nurse, lawyer, regulatory specialist, and venture capitalist.

The number of medical devices used each year in humans is very large. Figure 2 estimates usage for common devices, all of which employ biomaterials.

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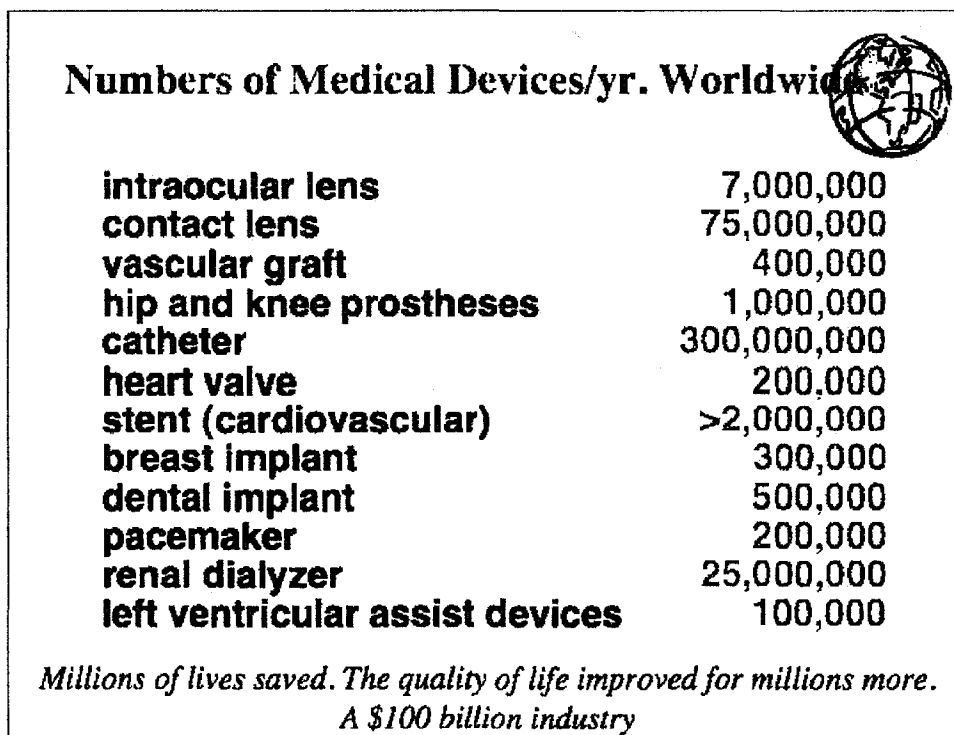
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Figure 2. Common Medical Devices That Use Biomaterials

The development of biomaterials is the junction of materials science and chemistry. Medical devices may be composed of a single biomaterial or a combination of several materials. A heart valve might be fabricated from polymers, metals, and carbons. A hip joint might be fabricated from metals and polymers (and sometimes ceramics) and will be interfaced to the body through a polymeric bone cement.

Biomaterials by themselves do not make a useful clinical therapy but rather have to be fabricated into devices. This is typically an engineer's role, but the engineer might work closely with synthetic chemists to optimize material properties and with physicians to ensure the device is useful in clinical applications.

Biomaterials must be compatible with the body, and there are often issues that must be resolved before a product can be placed on the market and used in a clinical setting. Because of this, biomaterials are usually subjected to the same very stringent safety requirements as those of new drug therapies.

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Biomaterials for Biosensors

Implantable biosensors for the human body place some of the greatest functional demands on biomaterials. Biosensors monitor the physiologic state of tissues for medical therapeutics or for assessing human performance. Sensors for glucose, oxygen, blood pH, adrenal hormones, nervous activity, heart performance, and blood pressure monitors are all of interest.

Blood biochemistry sensors are the most difficult sensors to keep functioning over time primarily because the sensor interface materials provoke low-level foreign-body reactions in tissues. These types of responses are not specifically important to implantable devices that have structural rather than sensing functions, such as heart valves, but they can completely render a biosensor for blood glucose, for example, useless after a few days.

Chemically sensitive biosensor interfaces to tissue and body environments employ membranes in an effort to protect the biosensor active-sensing surface from possible body reactions. The membrane allows small molecules of interest to pass through its pores while excluding larger proteins, blood-formed elements, and cells like macrophages that would engulf the sensor.

The membrane's biomaterial composition, pore size, and long-term physical integrity are critical components in the functioning of the sensor. If the biomaterial chosen retards the adhesion of proteins and does not provoke a biological response, then this improves sensor longevity. Figure 3 shows some representative biomembranes.

No one biomaterial is best for all sensor applications, primarily because different biomaterials behave differently relative to the substance being sensed. Membranes that pass glucose, for example, may not pass oxygen that is needed for a sensor to function. Membrane biofouling starts immediately upon contact of the sensor with the body cells. Proteins and other biological components adhere to the sensor surface, and in some cases, impregnate the pores of the material. This process retards diffusion of the molecules of interest to the sensor surface and either slows the sensor's response to changes in concentration or reduces the overall response to the point where the sensor falls out of calibration.



Figure 3. Biomaterials Such as Polycarbonates, Cellulose, and Silicones Used in Membranes for Sensors, Dialyzers, and Oxygenators

The design of sensor membrane materials has been found to be critically dependent on subtle features of the membrane's chemistry, material thickness, and porosity, as well as, more generally, where in the human body the sensor is located. The blood stream is

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the most hostile location both for sensor performance and in terms of the potential for danger to the patient through the provocation of blood clotting.

The most successful biomembrane materials have been porous forms of Teflon, polyurethanes, and cellulose-based materials such as cellulose acetate. As important as the material composition is for sensors, so are aspects of a membrane's structure and mechanical properties, such as its ability resist abrasion and adhere to sensor surfaces.

Biomaterials for Biomedicine

In this review, we look at representative biomaterials as well as representative applications. These biomaterials are among the most popular of those used in medicine today, and the applications in some cases represent multibillion-dollar-a-year markets.

Some of the best known of the biomaterials are:

- Silicone
- Teflon
- Biodegradable polymers
- Hydrogels
- Titanium alloys
- Ceramics
- Tissue constructs

Some of the largest applications are:

- Cardiovascular – stents, synthetic blood vessels, heart valves
- Hip and knee joints
- Contact lenses
- Drug delivery devices
- Kidney dialysis

BIOMEDICAL SILICONES- POLYDIMETHYLSILOXANES

Perhaps the most well known of all biomaterials are the silicones—soft, pliable, and semitransparent materials that are used in many different applications in modern society, ranging from water sealants to fibrous insulations.

Silicone is often mistakenly called "silicon." Although silicones contain silicon atoms, they are an organic material of greater complexity and are not made up exclusively of silicon. Silicone is used in an exceptionally large number of biomedical applications. It is blood compatible, sterilizable, rugged, and strong but flexible. Its mechanical properties

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can be tailored to varying degrees of hardness and strength for stiffness in catheter applications.

Biomedical silicones attracted notoriety in 1995 when a class-action lawsuit against Dow Corning, Inc., brought a huge settlement resulting from the supposed dangers of silicone breast implants.

After reviewing years of evidence and research concerning silicone gel-filled breast implants, the national Institute of Medicine found that "evidence suggests diseases or conditions such as connective tissue diseases, cancer, neurological diseases or other systemic complaints or conditions are no more common in women with breast implants than in women without implants." Dow moved out of the medical silicone business and has since been replaced by an array of smaller companies offering specialized silicone products.

Figure 4 shows the present form of silicone used for reconstructive surgery following a mastectomy, particularly after breast cancer in women.

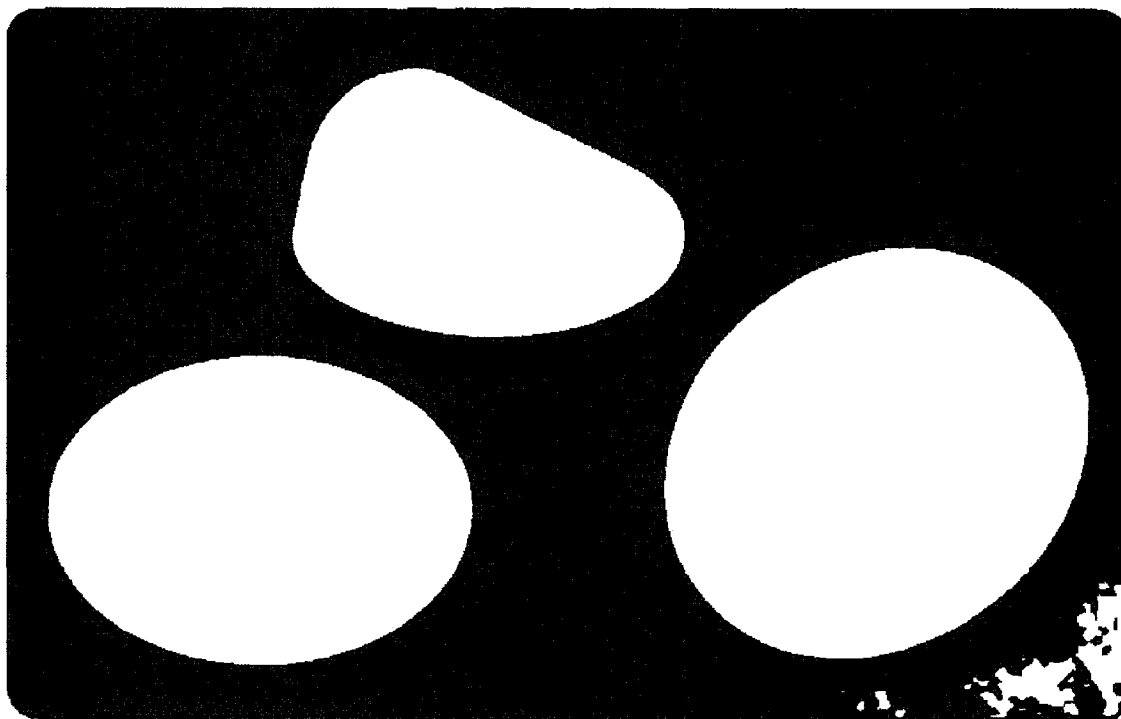


Figure 4. Photograph of Silicone (polydimethylsiloxane) Biomedical Implants Used in Breast Reconstructive Surgery

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SILICONE CHEMISTRY

Silicone is actually a common name for the chemical compound polydimethylsiloxane (PDMS), a class of synthetic polymers with repeating units of silicon and oxygen. Figure 5 shows the polymeric repeating structure of medical silicones. Various functional groups—often methyl—can be attached to that backbone to change the material properties. Silicone polymers can easily be transformed into linear or cross-linking materials without using any toxic plasticizers. The resulting materials are elastic at body temperature.

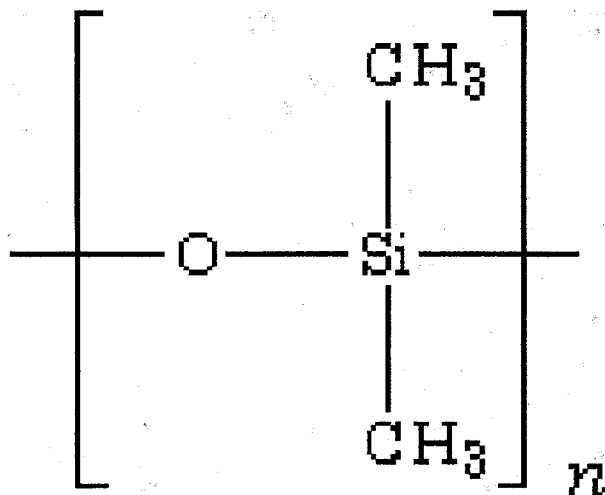


Figure 5. Silicone Chemical Groups

The simultaneous presence of different groups attached to the silicon-oxygen backbone gives silicones a range of viscous and mechanical properties that allow their use as fluids, emulsions, compounds, resins, and elastomers in numerous applications. Thus, silicone is a versatile polymer, although its use is often limited by its relatively poor mechanical strength. However, this limitation can be overcome by reinforcing silicone with a silica filler or by chemically modifying the backbone.

The stability, lack of toxicity, and excellent biocompatibility of PDMS make these materials well suited for use in personal care, pharmaceutical, and medical device applications. Silicone is easily molded and cast using room temperature curing (known as RTV) or through the use of an organic catalyst.

SILICONE IN BIOMEDICAL PRODUCTS

Silicone membranes are made by casting the silicone liquid precursor into thin sheets. Such membranes are often used in oxygen and carbon dioxide blood biosensors because membranes made of this material are highly transmissive to these gases while they block most other chemical substances present in the blood stream. In addition, silicone's resistance to protein adhesion and its excellent overall biocompatibility make it one of the most commonly used materials for encapsulating biosensors for tissue or blood contact.

Recent formulations of silicone can be patterned with ultraviolet light and, thus, lend themselves to manufacture with biosensors made by photolithography.

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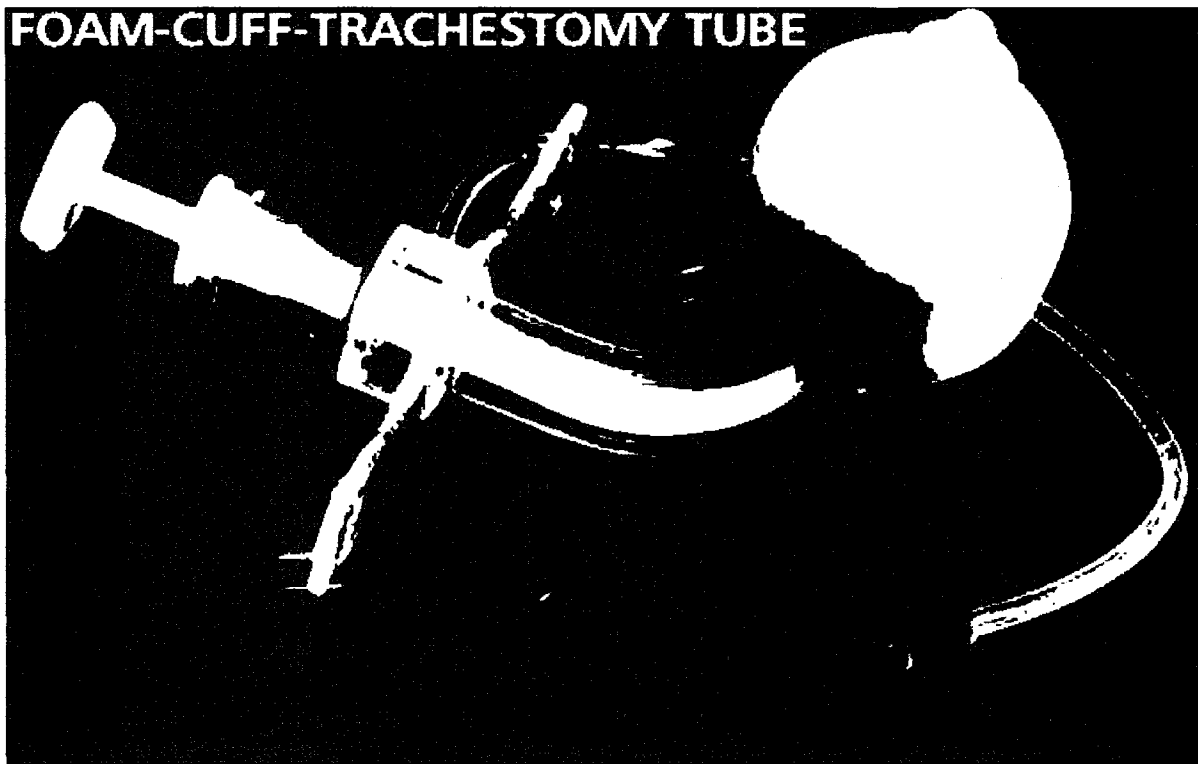


Figure 6. Silicone Tracheostomy Tube

Figure 6 is a representative example of silicone-based medical products involving tubes or catheters. A tracheostomy tube, or "trach tube," is a 2- to 3-inch-long curved metal or plastic tube placed in a surgically created opening (tracheostomy) in the windpipe to keep it open. Versions of these products are used in cases where patients have difficulty breathing on their own, such as in a spinal cord injury.

A product known as Mepiform™ is an example of silicone use in a sheet form for the management of scars, particularly keloid scars. Figure 7 shows this product.



Figure 7. Silicone Sheets Used Under the Skin as a Physical Supporting Layer for Repair of Scar Tissue

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TEFLON

Biomedical materials must be inert to the complex chemistry of biological fluids so they neither suffer nor instigate change in tissue. Teflon™ admirably fulfills these requirements. Teflon is a trade name for polytetrafluoroethylene (PTFE), a fluorocarbon-based polymer. It is made by free radical polymerization of tetrafluoroethylene and has a carbon backbone chain in which each carbon has two fluorine atoms attached to it.

This polymer is hydrophobic (water hating), biologically inert, and nonbiodegradable and also has low friction characteristics and excellent "slipperiness." The chemical inertness (stability) of PTFE is related to the strength of the fluorine-carbon bond that makes it resistant to adhesion. Figure 8 shows the structure of this material. It is a long chain of repeating chemical units, as shown in the right of the figure.

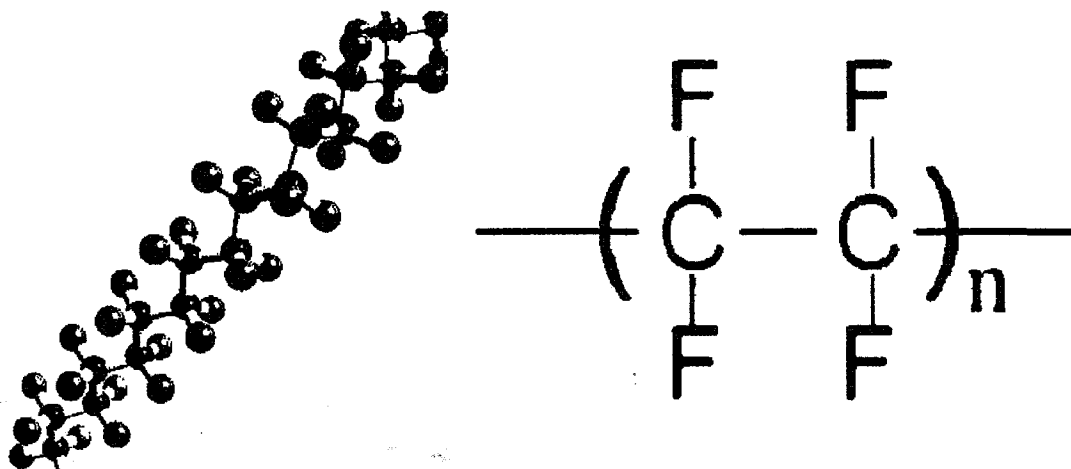


Figure 8. Teflon Structure

Goretex® is a medical form of Teflon (PTFE) that, when stretched and extruded, entraps air cells in its microstructure much like foam does and, thus, is relatively soft and repellant to most liquids. This material is known as e-PTFE (expanded PTFE).

PTFE can be fabricated in many forms, including pastes, tubes, strands, and sheets, while ePTFE can be woven into a porous, fabric-like mesh. When implanted in the body, this strong mesh allows tissue to grow into its pores, making it ideal for medical devices such as vascular grafts.

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Preformed ePTFE subcutaneous implant materials have been used to improve facial reconstruction and cosmetic surgery outcomes. Figure 9 is a manufacturer's product information showing the utility of using ePTFE in cosmetic surgery.

PTFE has relatively low wear resistance, but under compression or in situations where rubbing or abrasion can occur, it can produce wear particles. These can result in a chronic inflammatory reaction, an undesirable outcome. For a given application, the biomaterials engineer must consider many aspects of the physical and biological properties of the materials. Thus, although PTFE is highly inert in the body, applying it in the wrong circumstances (for example, to a device that is under compression or exposed to wear) may lead to a reaction that no longer qualifies as "biocompatible."

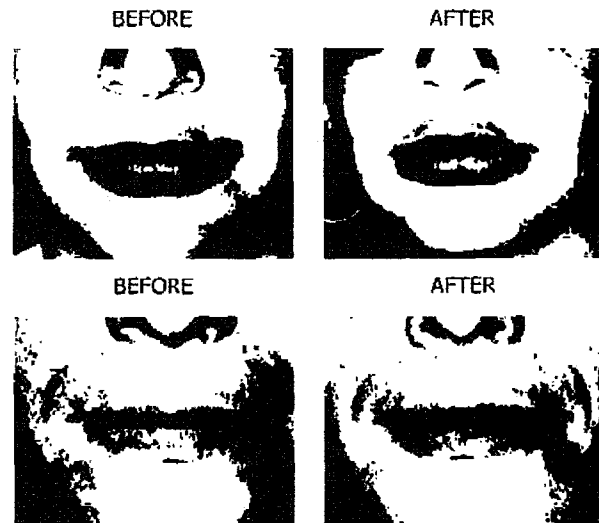


Figure 9. Expanded PTFE (Gore-Tex or ePTFE) Used in Lip Implants. This is a synthetic implant that has been used in the face and body for many years. The main advantage is that it is not absorbed over time and the results are permanent.

BIODEGRADABLE POLYMERS

Biodegradable polymers are an important and relatively large category of biomaterials that are used extensively in the medical and food industries. In the latter, they are used as food wrappings and other packaging derived from natural food substances that slowly degrade—by evaporation into water vapor and carbon dioxide—when exposed to the sun and outdoor environments, thus minimizing waste disposal. Figure 10 shows a complex shape made from polylactide (PLA), a biodegradable polymer.

Biodegradable polymers can be either natural or synthetic. In general, synthetic polymers offer greater advantages than do natural materials in that they can be tailored to give a wider range of properties and more predictable lot-to-lot uniformity than can materials from natural sources. Synthetic polymers also represent a more reliable source of raw materials—

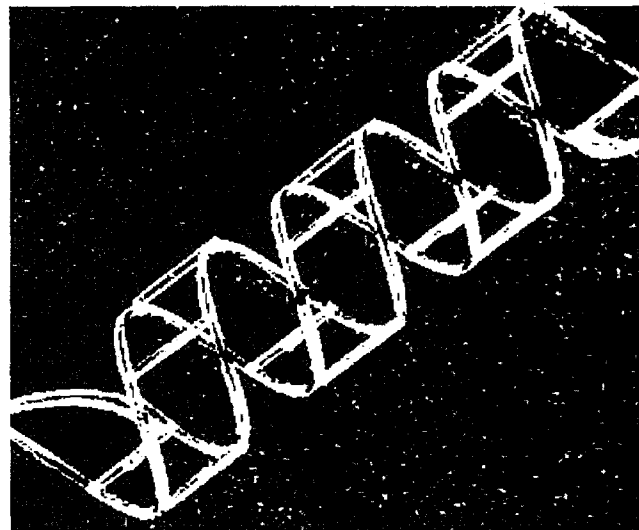


Figure 10. Biodegradable Polymers. Polymers such as PLA are much like conventional plastics and, as such, have qualities of clarity, flexibility, and strength.

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one free from concerns of immunogenicity. These polymers can be optically clear, exhibit good flexibility, and have strength comparable to that of many plastics.

BIODEGRADATION ADVANTAGES

In the human body, biodegradable polymers have good compatibility but also decompose to harmless materials and over time dissolve altogether. Biodegradable polymers undergo a chemical hydrolysis in the salty and wet environment of tissues by way of a labile chemical backbone of the polymer. The degradation starts immediately upon water exposure and occurs in two steps.

In the first step, the material thoroughly hydrates, and the water attacks the polymer chains, converting long chains into shorter, water-soluble fragments. The desirable aspect of this process is a reduction in molecular weight without a loss in physical properties, since the device matrix is still held together, even with the shorter chains.

In the second step, the shorter polymer chains are attacked by enzymes that are naturally present in tissues. Basically, a metabolization of the fragments by the body tissues results in a rapid loss of polymer mass, what is referred to as bulk erosion. All the commercially available synthetic devices and sutures degrade by bulk erosion.

DEGRADABLE BIOMATERIALS

Different biodegradable polymers have different lifetimes in tissues, ranging from a few days to years. Combining two different biopolymers—for example, short-lived (days) PLA (polylactide) and longer lived (months) PGA (polyglycolide)—reveals that polymers can be produced with intermediate decomposition times. Thus, their decay times can be custom determined through their formulation.

Biodegradable polymers fulfill a physician's desire to have an implanted device that will not require a second surgical intervention for removal, which is desirable in many applications. In orthopedic applications, for example, a fractured bone that has been fixated with a rigid, nonbiodegradable stainless implant has a tendency for refracture upon removal of the implant, making removal undesirable. This refracturing results from the offloading of the stress on the bone by the stainless steel support because the bone has not carried a sufficient load during the healing process. However, a fixation system prepared from a biodegradable polymer can be engineered to degrade at a rate that will slowly transfer the load to the healing bone, thereby avoiding the risk of refracture and eliminating the need to remove the implant.

POLYLACTIC ACID AND POLYGLYCOLIC ACID

Polylactic acid (PLA), polyglycolic acid (PGA), and their copolymers are the most widely used of the biodegradable polymers. These materials, when exposed to the sun and weather, will degrade into water and carbon dioxide and essentially vanish, given sufficient time.

In the human body, combinations of PLA and PGA are used to control the longevity of a material by controlling its degradation rate when exposed to tissues. The degradation products in the human body are also water and carbon dioxide.

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PLA, or polylactide, is a thermoplastic, long-chained organic material derived from renewable resources, such as corn starch (in the United States) or sugarcane (in the rest of the world). PLA has been recognized for more than a century and is of commercial interest primarily because of its biomedical applications. Figure 11 shows the chemical structure of PLA.

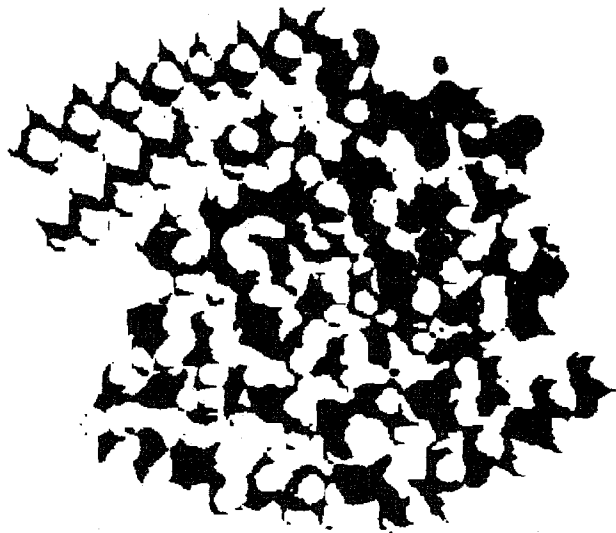


Figure 11. Structure of Polylactic Acid (a Biodegradable Polymer)

These materials are popular because they have already been used in many approved medical implant devices and have been shown to be safe, nontoxic, and biocompatible. They have been used in the development of several commercially available medical products, including sutures, tissue screws and tacks, guided tissue-regeneration membranes for dentistry, internal bone-fixation devices, microspheres for implantable drug delivery systems, and meniscus and cartilage repair systems.

These polymers can potentially be used in the design of vascular and urological stents and skin substitutes. This is possible through the manipulation of the polymer characteristics of these materials, such as their three-dimensional architecture, their mechanical and structural integrity, and their biodegradability. The materials can also be used as scaffolds for tissue engineering and for tissue reconstruction.

A medical application of these materials in thin-sheet form is their placement as a thin barrier layer that prevents entry of debris into wounds and as an underlayer to the skin and body tissue. Figure 12 is an artist's conception of a layer of PLA polymer being placed over the heart after open-heart surgery.

The Clear Choice



Protection in case there is a re-operation...

Figure 12. Biodegradable PLA as an Antiadhesion Barrier after Open-Heart Surgery

The PLA sheet acts as a barrier and spacer to prevent the healing heart wall from growing an attachment to the chest wall and from forming adhesions onto the overlying

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tissues. The barrier remains in place only for a week or so during the healing process before biodegrading so no foreign body is left inside of the body.

POLYETHYLENE GLYCOL OR POLYETHYLENE OXIDE

Polyethylene glycol (PEG) is a widely used material in biomedicine, pharmaceuticals, cosmetics, and agriculture. Its chemical compatibility, water solubility, nontoxicity, biocompatibility, and multiple physical states allow it be used as coatings and in solid form to create surfaces that are very acceptable to biology. Figure 13 shows the marketing of PEG to broad markets that include biodegradable polymers.

One of PEG's major applications is in the creation of "nonfouling" surfaces when exposed to blood or biological environments. The nonfouling, or cell- and protein-resistant, properties of surfaces containing PEG are due to the material's highly hydrated state.

PEG is used in drug delivery systems to improve the solubility of drugs and to help stabilize immunogenic or unstable protein drugs. This can enhance the circulation times and stabilities of drugs in the body.

HYDROGELS

Hydrogels are liquid or semisolid materials that have a strong affinity for water. Poly(hydroxyethyl methacrylic acid), or poly(HEMA), is one of the most important hydrogels in the biomaterials world because it has many advantages over other hydrogels. These include a water content similar to living tissue, inertness to biological processes, resistance to degradation, permeability to metabolites, and resistance to absorption by the body.

Poly(HEMA) can easily be manufactured into many shapes and forms and be easily sterilized. This is due to its structure, which is



Figure 13. Biodegradable Polymers Based on Copolymers of Polylactic Acid and Polyethylene Glycol



Figure 14. Dots of Hydrogel

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composed of long-chain molecules crosslinked to one another to create many small empty spaces that can absorb water or other liquids like a sponge. Hydrogels can be extruded into nearly any shape. Figure 14 shows them as small dots.

If the spaces are filled with a drug, the hydrogel can dispense the drug gradually as the structure biodegrades. Hydrogels are also used for tissue engineering and tissue repair, where the spaces in the gel might be filled with stem cells, tissue-growth factors, or a combination of the two.

Hydrogels are cross-linked polymer networks that are insoluble in body fluids but are able to swell and often have a water content of up to 90 percent. These can be formed by crosslinking one or several types of monomer units into a network, forming a homopolymer, copolymer, or multipolymer. With the incorporation of different monomers, gels with wide-ranging chemical and physical properties can be formed. The gels can be neutral or charged, soft or stiff, strong or brittle. Hydrogels are routinely used for biomedical and pharmaceutical applications such as drug release, artificial tendons, wound-healing bioadhesives, artificial kidney membranes, artificial skin, and contact lenses.

TITANIUM – HIP AND KNEE JOINTS

Titanium-based hip and knee implants are quite successful and are among the most common orthopedic procedures. When a hip replacement is performed, the arthritic, damaged hip joint is removed. The ball-and-socket hip joint is then replaced with an artificial implant.

Hip implants often show no visible sign of their existence in either walking gait or functionality. In adults, they can last a lifetime. Knee implants are also known to be successful. Figure 15 shows an assortment of titanium hip joint assemblies. The long shaft part of the device fills a drilled hole in the long bone of the femur.

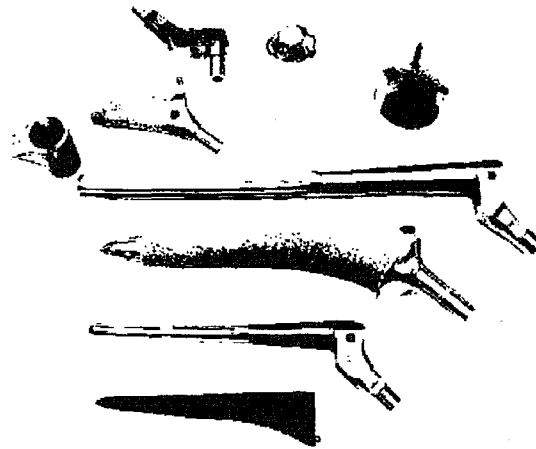


Figure 15. Various Titanium Components Used in Hip Joint Replacement

BIOCERAMICS

Ceramic materials are sometimes used directly or modified for use in applications in the human body and, so, become known as bioceramics.

The most common applications are in bone repair, dentistry, and the use of ceramics in hip and knee joint replacements, where their exceptional hardness can be put to advantage in wear joints.

Bioceramics range in biocompatibility from the ceramic oxides, which are inert in the body, to the other extreme of resorbable materials, which are eventually replaced by the materials they were used to repair.

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Two common ceramics used in dentistry and hip prostheses are alumina and hydroxyapatite (HA). HA is a major component of the inorganic compartment of bone. Commercially prepared HA is processed using a technique of phosphoric acid and hydrothermal exchange that produces a porous, "bone-like" morphology in the resulting structure. Figure 16 shows this result. When implanted into bone defects, HA supports bone growth through the pores and, thus, becomes an intermediate scaffold, as well as an eventual support matrix.

Hydroxyapatite composites have been successfully used to repair, reconstruct, and replace diseased or damaged body parts, especially bone. They have been used in vertebral prostheses, intervertebral spacers, bone grafting, middle-ear bone replacements, and jawbone repair.



Figure 16. Hydroxyapatite Porous Bone-Like Structure After Commercial Processing

Aluminum oxide, or alumina (Al_2O_3), has been used in orthopedic surgery for more than 20 years as the joint surface in total hip prostheses because of its exceptionally low coefficient of friction and minimal wear rates. Alumina has excellent corrosion resistance, good biocompatibility, high strength, and high wear resistance, making it ideal for orthopedic applications.

Other bioceramics include coral skeletons, which can be transformed into hydroxyapatite by high temperatures. Their porous structure allows relatively rapid ingrowth of living cells at the expense of initial mechanical strength. The high temperature also burns away any organic molecules, such as proteins, preventing graft-versus-host disease and rejection.

Bioceramics made from a calcium phosphate material containing tiny pores have been used to coat metal joint implants or as unloaded space fillers for bone ingrowth. Tissue ingrowth into the pores occurs, with



Figure 17. Bioceramic Used in Artificial Hip Replacement Component

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an increase in the interfacial area between the implant and the tissues. This tissue ingrowth results in an increased resistance to device movement within the tissue. As in natural bone, proteins adsorb to the calcium phosphate surface to provide the critical intervening layer through which the bone cells interact with the implanted biomaterial. Figure 17 shows an example of this.

DENTAL CERAMICS

Dental ceramics are a major subclass of biomaterials. Porcelains are hard ceramic materials that are based on a glass of silica and alumina, with fluxes used to lower their fusion temperature. Dental porcelains can have a hardness that exceeds that of the enamel of natural teeth, but they are often more brittle and more likely to fracture. They also do not have the same optical properties, thermal conductivity, or natural fluorescence as biological materials.

Full-porcelain (ceramic) dental materials include porcelain, ceramic, or glasslike fillings and crowns (a metal-free option known as a jacket crown). They are used as inlays, onlays, crowns, and aesthetic veneers. A veneer is a very thin shell of porcelain that can replace or partially cover tooth enamel. Full-porcelain (ceramic) restorations are particularly desirable because their color and translucency mimic natural tooth enamel.

Zirconium oxide is a very strong and refractory material that has recently appeared as a dental material. With a three-point bending strength exceeding 900 megapascals, zirconium oxide is expected to be applicable to many new applications in dentistry, including bridges, implant suprastructures, and root dowel pins.

Casting the shape of a broken tooth into a natural shape or one that resembles the fragment of the broken tooth is greatly facilitated by the use of computerized CAD/CAM technologies. These technologies are used to make molds for the casting of dental ceramics. Figure 18 illustrates natural-looking teeth made from dental porcelains defined by a computer-generated mold.

TISSUE CONSTRUCTS AS BIOMATERIALS

Figure 18. Computer-Based Sculpted Ceramic Teeth

Living tissues are sometimes considered biomaterials if they have been cultured prior to application to the human body or utilized much the same way as a synthetic material would be utilized. The formation of living tissues into constructs is sometimes called tissue engineering. This is a bit of a misnomer in that it is an advanced form of cell culture and cellular biology and has little in common with engineering in the classical sense of application of mathematics and physics to problems.

Rather, tissue engineering is the application of biological and cell culturing techniques to encourage the growth of tissues in certain ways and in the development of viable substitutes that restore and maintain the function of human tissues. This is a form of

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medical therapeutics and differs from standard drug therapy or permanent implants in that the culture becomes integrated within the patient, affording a potentially permanent and specific cure of the disease state.

There are many approaches to tissue engineering, but all involve one or more of the following key ingredients: harvested cells, introduction of specialized signaling molecules, and three-dimensional matrices.

The approach involves seeding highly porous biodegradable matrices (or scaffolds) in the shape of the desired bone or tissue, with cells and signaling molecules (for example, protein growth factors), then culturing and implanting the scaffolds into the defect to induce and direct the growth of new bone or tissue. The goal is for the cells to attach to the scaffold, multiply, differentiate (that is, transform from a nonspecific or primitive state into cells exhibiting the specific functions), and organize into normal, healthy tissue as the scaffold degrades. The signaling molecules can be adhered to the scaffold or incorporated directly into the scaffold material. Figure 19 illustrates the sequence of steps in this process.

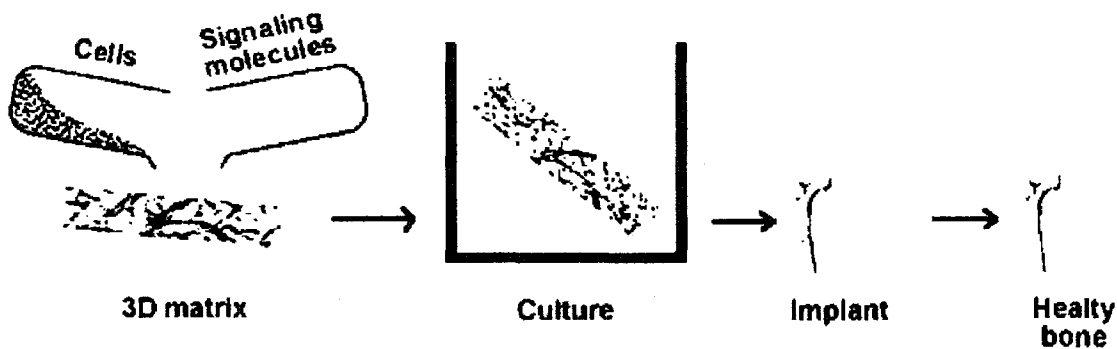


Figure 19. Scaffold-Guided Tissue Regeneration

Perhaps the biggest challenge for tissue engineering is how to ensure angiogenesis in a timely fashion within the scaffold construct; without a blood supply, cells will die, and mass infection will occur.

In biology, "autologous" refers to cells, tissues, or even proteins that are reimplanted into the same individual they were taken from. Bone marrow, skin biopsy, cartilage, and bone can be used as autografts. In contrast, cells or tissues transplanted from a different individual are referred to as allogeneic, homologous, or an allograft.

TISSUE SCAFFOLD BIOMATERIALS

An intriguing idea in tissue engineering is the use of biodegradable polymers as a scaffold for growing tissues of a certain defined shape—for example, the cartilage of an ear pinna lost in an accident.

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Biodegradable polymers have been used with computer-based rapid prototyping machines to form porous shapes where tissue cells can ingrow. The result after many weeks of submersion in tissue culture is that the polymer slowly degrades, leaving the cultured tissue in the shape of the predefined scaffold. Although this approach cannot grow complex organs, like a heart or kidney, that have many different tissues, it can be used to create simple structures of cell products—for example, of cartilage excreted by fibroblast cells. These structures do not create their own networks of blood vessels, a problem whose solution lies in the future.

Figure 20 shows CSLA (Crosslinkable Star Lactide-co-Glycolide), a biodegradable polymer deposited into a honeycomb structure by a process not unlike ink-jet printing. The ink-jet pen is supplied with a hot liquid form of the CSLA polymer, which then hardens when it cools and is exposed to the air. Using a computer to rewrite successive layers on top of one another, a three-dimensional structure is built.

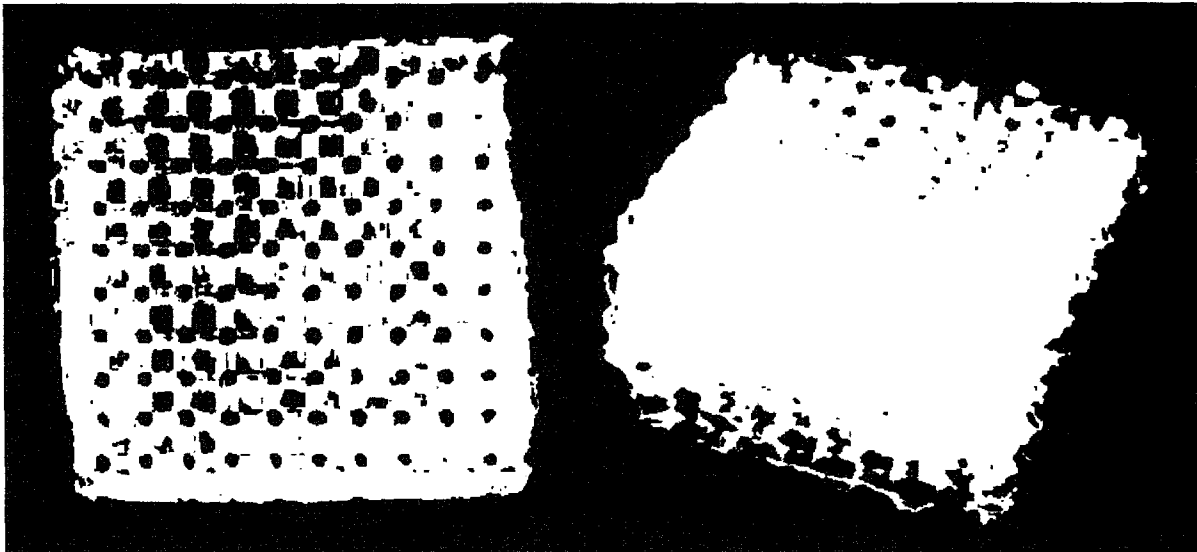


Figure 20. Biodegradable Material CSLG Deposited in a Honeycomb Structure to Allow Infiltration by Living Cells While in a Submerged Cell Culture

CARDIOVASCULAR BIOMATERIALS

Biomaterials are often made into medical devices rather than being sold in raw form. Among the largest and most demanding of all biomaterial applications are devices that come into direct contact with blood. In general, various derivatives of Teflon and silicone are the most widely used for blood contact, while metals and ceramics are more often used in tissues.

Cardiovascular (heart and blood vessel) applications are one of the most important categories of implant biomaterials. Biomaterials for cardiovascular applications are usually prepared using polymers, because polymers are available in a wide variety of compositions with adequate physical and mechanical properties and can easily be manufactured into products with the desired shape. In addition, some metals and ceramics are used in the blood stream. Figure 21 lists some of the common cardiovascular devices and how long they are in contact with blood.

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| |
|--|
| Medical Devices Used in the Bloodstream |
|--|

| | <u>Blood contact time</u> |
|--|---------------------------|
| Catheters | Min-days |
| Guidewires | Min-hrs |
| Sensors | Min-months |
| Pacemaker | 10 yrs |
| Vascular Graft | lifetime |
| Heart Valve | lifetime |
| Stent | lifetime |
| Extracorporeal Oxygenation | hrs |
| Artificial Kidney (hemodialyzer) | hrs |
| Total Artificial Heart | 10 yrs |
| Left Ventricular Assist Device (LVAD) | Days-yrs |

Figure 21. Some of the More Popular Biomedical Devices and Duration of Their Blood Contact

Biomaterials are used as vascular grafts for artery replacements in which they are connected (grafted) onto natural blood vessels at both ends. When arteries, particularly the coronary arteries and the vessels of the lower limbs, become blocked by fatty deposits (atherosclerosis), segments in some cases can be replaced with grafts. Figure 22 shows commercial vascular grafts made by Gore Medical (Flagstaff, Arizona, USA).

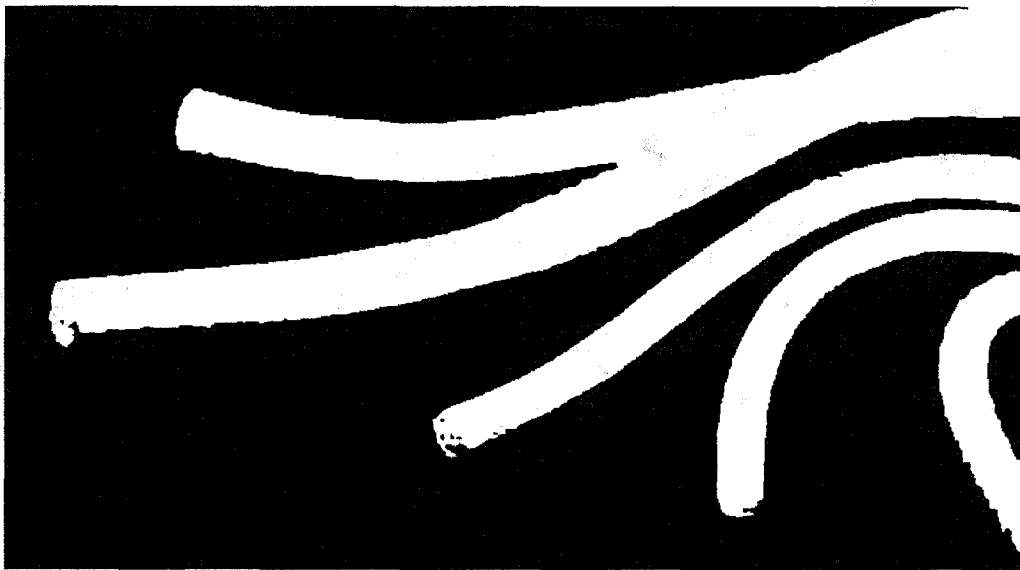


Figure 22. Gore Medical Teflon Foam Used in Vascular Grafts. These are artificial blood vessels used to replace blood vessels in the human body damaged by accident, atherosclerosis, or diabetic vascular disease.

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A problem most materials cause when in blood contact is that they trigger the rapid formation of thrombus (an aggregation of blood cells). The formation of a thrombus is dangerous, as the thrombus could either adhere to the surface of the biomaterial or be detached. If a thrombus is detached, it can travel in the blood stream and occlude smaller vessels in the brain (called a stroke) or lungs (called an embolism). Some small-diameter vascular grafts (< 5-millimeter internal diameter) and prostheses for reconstruction of diseased veins are "safe" only when anticoagulant drugs are used.

In addition to thrombus formation, biomaterials can become colonized with infection-causing bacteria. Some microorganisms found in hospitals are extremely resistant to antibiotic therapy, and infections cannot be fully resolved until the biomaterial is removed. This is particularly a problem with hip and knee implants, where there is poor blood flow near the joint and the body's immune system has limited access. Methicillin-resistant staphylococcus aureus infections are dangerous in these situations.

The high tolerance of the body for woven and formed Teflon allows it to be used as a flexible patch material for other blood-contacting surfaces, in addition to blood vessels. For example, Gore, Inc., makes a Teflon-based material that is used to patch holes in the heart of infants born with atrial septal defects. Figure 23 is an artist's conception of how the patch is inserted into the hole in the atrial wall using a catheter.

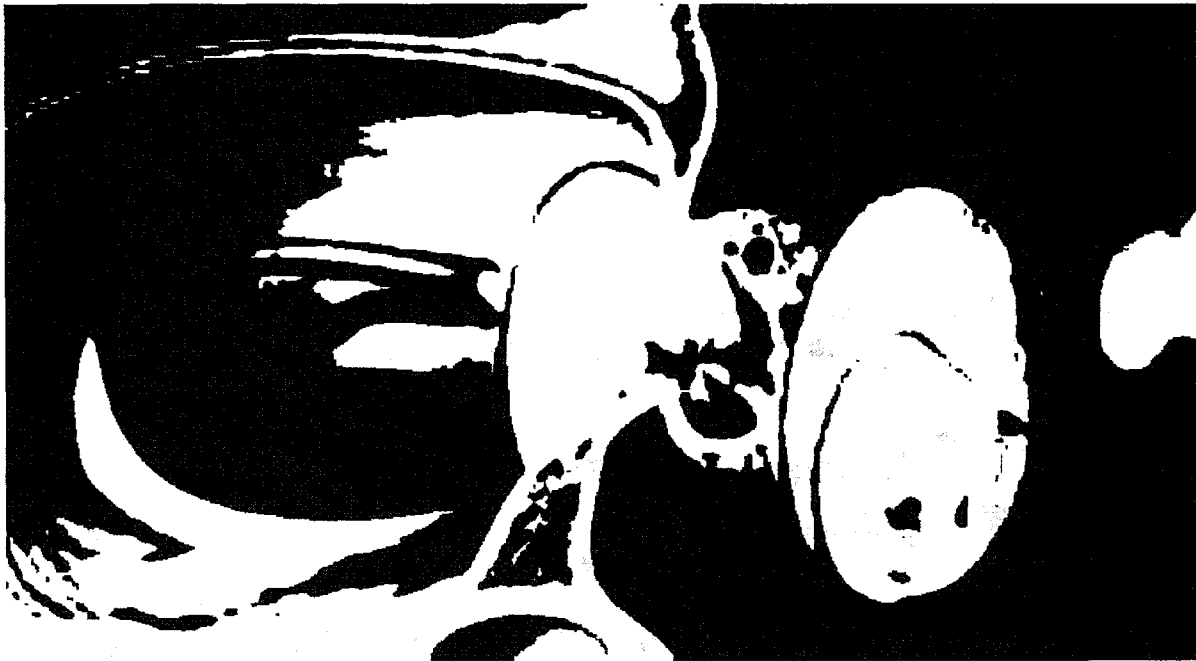


Figure 23. Illustration of Treatment of an Atrial Septal Defect Using a Teflon-Based Product Manufactured by Gore, Inc.

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Heart valves are another application of biomaterials in which the materials are in direct contact with blood. They are typically constructed using a form of stainless steel and woven Teflon (or Dacron) as a suture ring to anchor the device. Figure 24 shows one of these devices.

STENT BIOMATERIALS

A stent is a metal mesh tube that looks something like a Chinese finger puzzle and is used to prop open a clogged artery. These are delivered to the heart in a catheter on the end of a wire usually inserted into an artery in the groin.

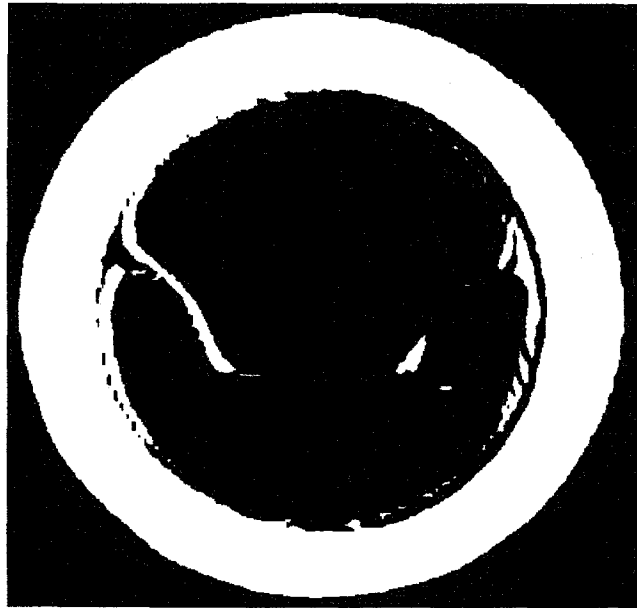


Figure 24. Stainless Steel and Teflon Bjork Shiley Heart Valve

The stent is collapsed to a small diameter and placed over a balloon catheter. It is then surgically moved into the area of the blockage. When the balloon is inflated, the stent expands, locks into place, and forms a scaffold that holds the artery open. Figure 25 shows an artist's conception of this process.

The stent stays in the artery permanently, holds it open, improves blood flow to the heart muscle, and relieves symptoms (usually chest pain). Within a few weeks after the stent was placed, the inside lining of the artery (the endothelium) grows over the metal surface of the stent.

Stents are often made from a form of stainless steel that is ductile enough to be expanded by a balloon and then resist closure forces of the vessel wall after the balloon is removed.

The insertion and use of the balloon to expand the stent involves some hazards that can be overcome if the stent is made from a self-expanding metal called Nitinol™. With a nitinol stent, the stent is placed into the body collapsed while it is held cold by a flow of refrigerated saline through the catheter. When allowed to heat up to body temperature by shutting off the cold water to the catheter, the stent expands and more reproducibly applies a calibrated amount of pressure to the blood vessel walls.

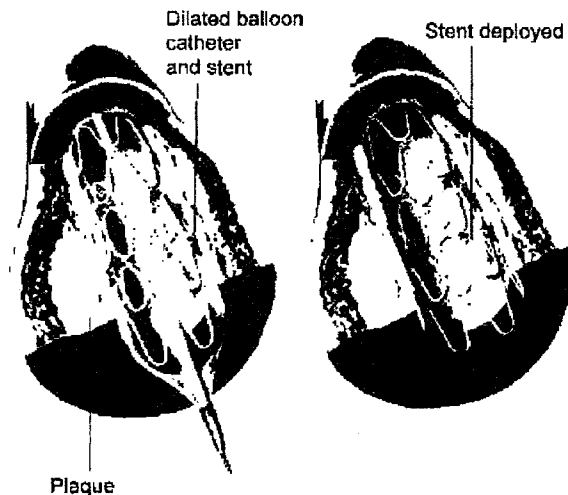


Figure 25. Illustration of Stent Placement. The stent is used to expand the luminal opening of a clogged blood vessel.

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NITINOL AS A BIOMATERIAL

The use of nitinol metal in stents is a clever application of the properties of a class of materials called shape memory alloys (SMAs). SMAs are mixtures of metals that, after being stress treated, can be deformed significantly but then triggered to return to their original shape.

SMAs have a rather remarkable property: they remember their shape. This "smart" property is the result of the substance's ability to undergo a phase change. This occurs at the atomic level, where atoms in the solid subtly shift their positions in response to a stimulus, such as a change in temperature or the application of mechanical stress.

Once the metal is formed at a high temperature it remembers this shape. Subsequent distortions of the material when it is cold remain locked in place while the material remains at a low temperature. However, warming the material to a specific temperature that is relatively closer to its formation temperature will trigger a return to its original formed shape.

In stents, the web is collapsed while it is cold for easy insertion into a blood vessel and held cold by a flow of cold saline out of the catheter. When the stent warms up as the catheter is removed, it expands itself and the surrounding blood vessel. Figure 26 shows a Nitinol stent.

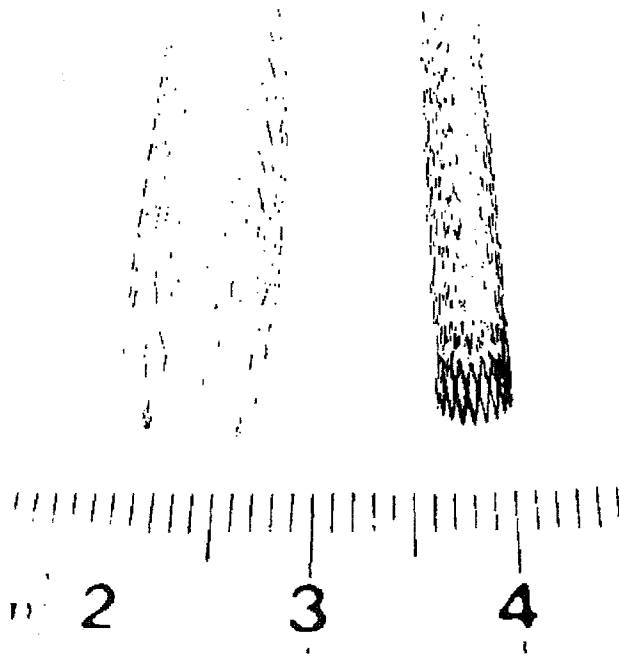


Figure 26. Nitinol Stent. Nitinol is an alloy of titanium. It is biocompatible and also a shape memory material.

CONTACT LENSES

Contact lenses are used to correct vision in the same way as worn glasses but are lightweight and virtually invisible. Their practicality and popularity ultimately depend on the biomaterials of which they are made.

Modern soft contact lenses were invented by Czech chemist Otto Wichterle and his assistant, Drahoslav Lím who also invented the first gel used for their production. However, it was not until the employment of poly-methyl-methacrylate, known as PMMA (a cousin of acrylic plastics, such as Plexiglas™), that they began to enjoy mass appeal. Figure 27 shows a gas-permeable contact lens.

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PMMA, however, is not an ideal contact lens material since no oxygen is transmitted through the lens to the conjunctiva and cornea. This can cause a number of adverse clinical effects. To solve this problem, a range of oxygen-permeable but rigid materials were developed. These materials, referred to as "rigid gas-permeable" or "RGP" materials or lenses, were made by synthetically adding dimethylsiloxane (a form of silicone) to acrylate plastics. Silicones have a very high level of oxygen transport, and amalgamating them with plastics adds this quality, while the acrylics provide strength and hardness. The easy diffusion of oxygen across silicones is thought to be a result of an intermediate solubility of oxygen in the gas phase with the gel phase of silicone.

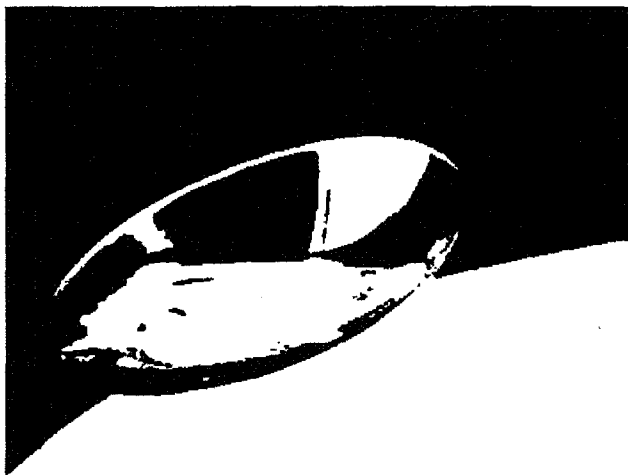


Figure 25. Contact Lens. Modern contact lenses are made of a mixture of acrylics and silicones that readily pass oxygen to the cornea.

Occasionally, the term "gas permeable" is used to describe RGP lenses, but this is potentially misleading, as soft lenses are also gas permeable in that they allow oxygen to move through the lens to the ocular surface.

In 1999, first silicone hydrogels were launched on the contact lens market. These new materials had the advantage of high oxygen permeability, with the comfort and clinical performance of the conventional hydrogels that had been used for the previous 30 years. These lenses were initially advocated primarily for extended (overnight) wear, although more recently, daily (no overnight) wear silicone hydrogel contact lenses have been launched.

DRUG DELIVERY POLYMERS

One area of biomaterials research is the use of biodegradable materials in the design of systems for controlled drug delivery. Much of this work is driven by the need for the slow release of insulin for the control of brittle diabetes. Mechanical insulin delivery pumps are moderately successful but usually are worn on the outside of the body and are cumbersome.

The ability to introduce insulin and other drugs in a controlled-release manner using biopolymers has clear advantages in terms of user convenience. Similarly, the slow release of other drugs, such as chemotherapeutic agents, is necessary to maintain the drug in the desired therapeutic range with just a single dose.

The basic strategy with some of these systems is to encapsulate drugs in membranes, capsules, microcapsules, liposomes, and hollow fibers. Another approach is to disperse

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the active agent in a biodegradable polymer, as shown in Figure 28. The polymer host to the drug dissolves, releasing the drug in a controlled manner over time.

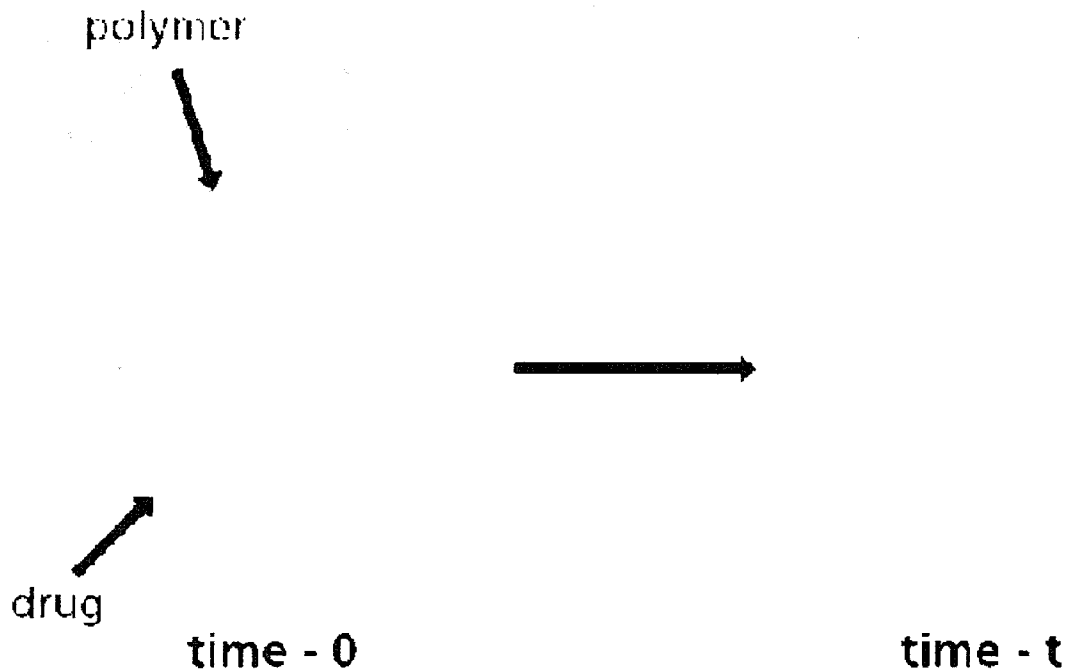


Figure 26. Schematic Representation of Biodegradable (Bioerodible) Drug Delivery Device

The use of biodegradable materials allows the drug to be introduced without much concern for the build-up of the polymer carrier. The carrier is eventually absorbed by the body and, thus, need not be removed surgically.

Drug diffusion through the polymer matrix can also determine the drug dosage rate without actual loss of the polymer. This rate is determined by the choice of polymer, the size of its pores, and the rate at which the drug diffuses from the pores.

The three key advantages polymeric drug delivery products can offer are:

- **Localized Delivery of Drugs:** The polymer-drug combination can be implanted directly at the site where drug action is needed and, hence, whole-body exposure of the drug can be reduced. This becomes especially important for toxic drugs, such as the chemotherapeutic drugs.
- **Sustained Delivery of Drugs:** Once injected, the encapsulated drug is released over extended periods, thereby eliminating the need for multiple injections. This feature can improve patient compliance, especially with drugs for chronic indications that require frequent injections (such as for deficiency of certain proteins).
- **Stabilization of the Drug:** The polymer can protect the drug from the physiological environment and hence improve its stability in vivo. This particular feature makes this technology attractive for the delivery of labile drugs, such as proteins.

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An appropriate selection of the polymer matrix is necessary in order to develop a successful drug delivery system. The most commonly used polymers for this application, polylactide (PLA) and poly(lactide-co-glycolide) (PLGA), have been used in biomedical applications for more than 20 years and are known to be biodegradable, biocompatible, and nontoxic. A vast amount of literature is available on the characterization of these polymers and their biodegradation and drug-release properties.

MEDICAL TITANIUM AS A BIOMATERIAL

Titanium metal has qualities of strength, inertness, and a biological compatibility that make it desirable as a biomaterial. Essentially all pacemakers, neurostimulators, and various other implanted medical devices use titanium as a packaging case material.

Titanium metal exposed briefly to the atmosphere oxidizes to form a microscopically thin layer of titania (titanium oxide). Titania is a hard, adherent, and inert ceramic-like compound and is thought to be largely responsible for titanium's acceptability in biomedical applications where metal corrosion in warm, salty body fluids ordinarily would be a problem.

Titanium is used for its high strength in replacement hip and knee joints. In these cases, it is important how the metal integrates with living tissue and bone because load must be transferred from the metal to the bone. Titanium generally does exceedingly well and is used as the metal of choice in nearly all biomedical applications where high strength and impact resistance is important.

Titanium has a particular ability among the various metals that might otherwise be chosen in that it can integrate itself well with living bone. The recognition of this dates back to 1952, when Swedish Professor Per-Ingvar Brånemark conducted an experiment in which he studied blood flow in living rabbit bone. The bone was fixed in a roughly machined titanium holder. At the conclusion of the experiment, after many days, he found that the bone had integrated so completely with the titanium that removing it was impossible. He called this osseointegration and saw the possibilities for human use.

Figure 29 shows a photomicrograph of a titanium-bone interface. The close approximation of the titanium (black) to the tissue is an indicator of a close-metal-tissue integration. Osseointegration was first implemented in dentistry to fixate teeth. It is now also used for head and jaw reconstruction.

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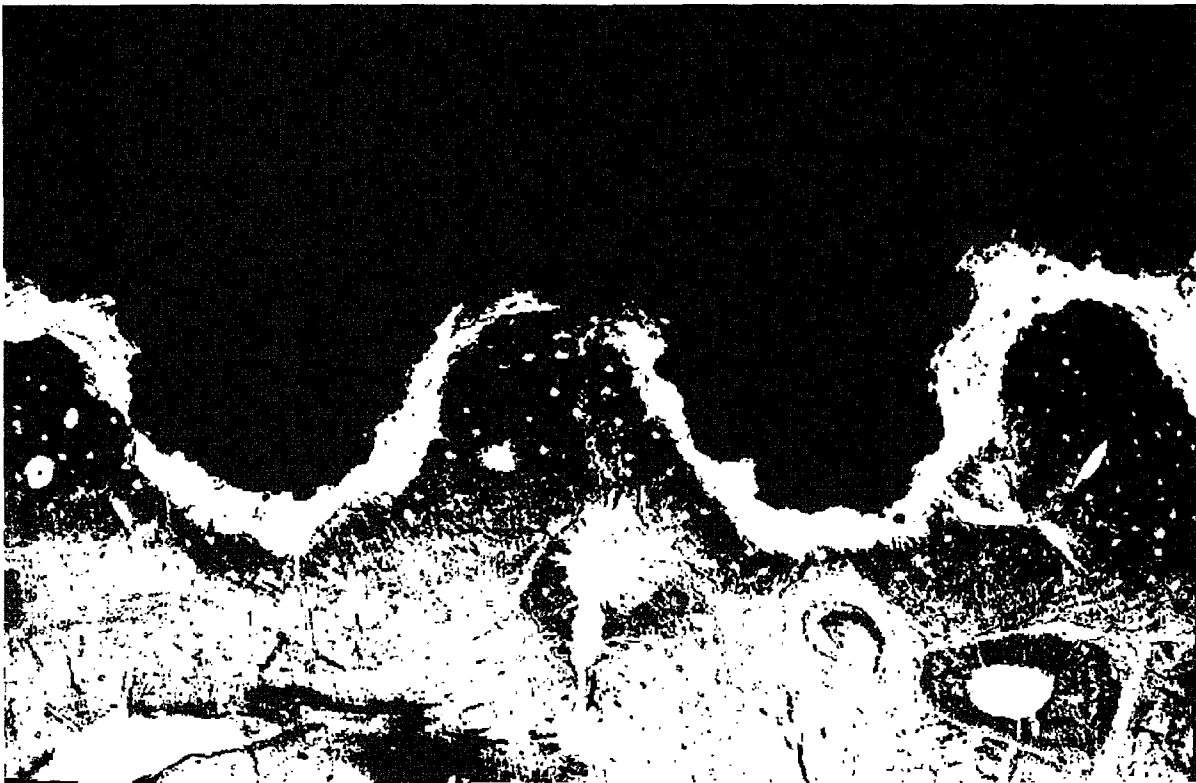


Figure 27. Photomicrograph of Titanium Metal (Appears Black in This Photo) in an Intimate Integration With Living Bone. The intersection of the two materials shows a thin barrier layer and then healthy tissue very close to the metal. It does not show inflammation or scar tissue formation.

Optimization of the bone integration with titanium has been much studied over the years. It has been found that if single cells can nestle into pores on the metal surface and then can reach out and attach to their neighbors, this forms a particularly good adhesive interface. This observation has led to new types of surface treatments for titanium to improve its ability to attach to bone. The need for a particular porosity size scale for optimal bone integration has only recently been recognized.

Sand blasting of the titanium surface has long been done, but, recently, plasma etching and pitting with the use of acids have been found effective. Some of the more recent (2008) innovations have been the use of lasers to create a surface modification by melting pits.

Another good approach is to coat metal implants with bioactive materials, such as hydroxyapatite (HA). HA has excellent biocompatibility, bioactivity, and bone-binding properties. It forms a bond with titania thin films on the surface of titanium implants and so prepares the surface for adhesion. Researchers recently determined that making this layer thick (about 1 micron) encourages cell proliferation and bonding.

Recent improvements in HA have included manufacturing it in the form of a spherical nanopowder that is more acceptable to tissues than are spicule forms of its natural occurrence. Using HA in the form of a nanopowder stimulates bone formation leading to a natural, as well as chemical, adhesion, much like glue.

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Another recent discovery is that treating the titanium surface with a silane compound will create a surface chemistry that attracts certain biomaterials known as proteoglycans. From this point, it is possible to lay down layers of collagen on the surface from which connective tissues will form.

Titanium metal used for implants is usually a biomedical alloy, Ti-6Al-4V, since biomedical alloys provide good corrosion resistance and reasonable fatigue life and are much stiffer than cortical bone. The Ti-6Al-4V alloy is more suitable than is the Co-Cr alloy for coating with HA because it has less potential proximal stress shielding and bone resorption.

BIOMATERIALS IN DIALYSIS

Medical therapeutic dialysis, often called hemodialysis, is a method of removing uric acid and other waste products from blood, a necessity when the kidneys fail. It is also useful in removing exogenous poisons like ethanol, aspirin, barbiturates, and boric acid from the blood in cases of poisoning.

Hemodialysis accesses the blood stream through the use of two large needles—one in an artery and one in a vein—in order to flow a patient's blood through a series of hair-thin, hollow-membrane, tube-like fibers.

A dialyzer is composed of thousands of tube-like hollow fiber strands encased in a clear plastic cylinder several inches in diameter. Blood flows on the inside of the membrane fiber, and a dialysate (extraction stream) flows across the outside. Low-molecular-weight waste products pass out through the membrane, while blood cells and other large molecules in the blood are retained. Figure 30 shows an illustration (left) and photograph (right) of dialyzers used to treat kidney failure.

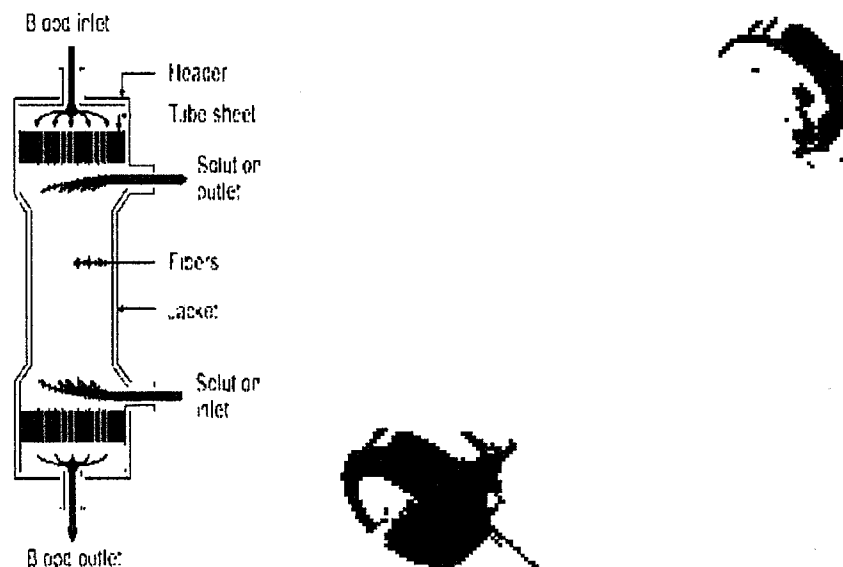


Figure 28. Illustration (Left) and Photograph (Right) of a Blood Dialyzer as Used in Medicine

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Dialysis works on the principles of natural diffusion of metabolic waste products in the blood across a semipermeable membrane. Waste products in high concentration in the blood will diffuse across the membrane. The membrane allows the passage of certain-sized molecules across it but prevents the passage of other, larger molecules of the blood, thus helping to get rid of waste products. Figure 31 illustrates this idea. The blood cells are kept on the outside of the membrane (orange) while waste product solutes (violet and yellow dots) pass through.



Figure 29. Cuprophane Membrane Passes Blood Waste Products (Violet and Orange Dots) Through Pores and Blocks Passage of Red Blood Cells

Advances in bioengineering and in the technical aspects of dialysis machines have made hemodialysis a safe and effective procedure.

The design of dialyzers is primarily an exercise in biomaterial selection. Biomembrane materials play the critical role in cleansing the blood, but they must not damage the blood or provoke thrombus. The most common biomaterial used in dialyzers is a semipermeable membrane made of cellulose acetate trade-named Cuprophane™.

Dialyzer membranes come with different pore sizes. Nanotechnology is being used in some of the most recent high-flux membranes to create a uniform pore size. The goal of high-flux membranes is to pass relatively large molecules, such as beta-2-microglobulin (MW 11,600 daltons), but not albumin (MW ~ 66,400 daltons). Dialysis membrane materials are crucial to the practical performance of medical hemodialysis systems. These systems/materials support the survival of millions of people in kidney failure that undergo routine dialysis, usually for several hours during the day and three to four times a week.

Summary and Recommendations

The performance of biomaterials underlies the success of many medical devices that must be acceptable to body tissues. These materials often serve critical—perhaps life-and-death—functions and, so, require large amounts of money and time to rigorously test. This appears to be the reason the biomedical industry is slow to produce and accept new materials.

Existing materials for implants are generally based on materials that have been available for more than 20 years. Biodegradable materials, particularly the polylactide and glycolide, have a long history of safe and effective use. Building on this solid foundation, most of the innovation is occurring in devising new ways to embody the materials and apply them to new applications. Thus, the markets are expanding for biomaterials, and physicians can look forward to new products that will help speed patient recovery.

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