

CHAPTER 1

Overview of Biomaterials and Their Use in Medical Devices

A BIOMATERIAL, as defined in this handbook, is any *synthetic* material that is used to replace or restore function to a body tissue and is continuously or intermittently in contact with body fluids (Ref 1). This definition is somewhat restrictive, because it excludes materials used for devices such as surgical or dental instruments. Although these instruments are exposed to body fluids, they do not replace or augment the function of human tissue. It should be noted, however, that materials for surgical instruments, particularly stainless steels, are reviewed briefly in Chapter 3, “Metallic Materials,” in this handbook. Similarly, stainless steels and shape memory alloys used for dental/endodontic instruments are discussed in Chapter 10, “Biomaterials for Dental Applications.”

Also excluded from the aforementioned definition are materials that are used for external prostheses, such as artificial limbs or devices such as hearing aids. These materials are not exposed to body fluids.

Exposure to body fluids usually implies that the biomaterial is placed within the interior of the body, and this places several strict restrictions on materials that can be used as a biomaterial (Ref 1). First and foremost, a biomaterial must be biocompatible—it should not elicit an adverse response from the body, and vice versa. Additionally, it should be nontoxic and noncarcinogenic. These requirements eliminate many engineering materials that are available. Next, the biomaterial should possess adequate physical and mechanical properties to serve as augmentation or replacement of body tissues. For practical use, a biomaterial should be amenable to being formed or machined into different

shapes, have relatively low cost, and be readily available.

Figure 1 lists the various material requirements that must be met for successful total joint replacement. The ideal material or material combination should exhibit the following properties:

- A biocompatible chemical composition to avoid adverse tissue reactions
- Excellent resistance to degradation (e.g., corrosion resistance for metals or resistance to biological degradation in polymers)
- Acceptable strength to sustain cyclic loading endured by the joint
- A low modulus to minimize bone resorption
- High wear resistance to minimize wear-debris generation

Uses for Biomaterials (Ref 3)

One of the primary reasons that biomaterials are used is to physically replace hard or soft tissues that have become damaged or destroyed through some pathological process (Ref 3). Although the tissues and structures of the body perform for an extended period of time in most people, they do suffer from a variety of destructive processes, including fracture, infection, and cancer that cause pain, disfigurement, or loss of function. Under these circumstances, it may be possible to remove the diseased tissue and replace it with some suitable synthetic material.

Orthopedics. One of the most prominent application areas for biomaterials is for orthopedic implant devices. Both osteoarthritis and rheumatoid arthritis affect the structure of freely

movable (synovial) joints, such as the hip, knee, shoulder, ankle, and elbow (Fig. 2). The pain in such joints, particularly weight-bearing joints such as the hip and knee, can be considerable, and the effects on ambulatory function quite devastating. It has been possible to replace these joints with prostheses since the advent of anesthesia, antiseptics, and antibiotics, and the relief of pain and restoration of mobility is well known to hundreds of thousands of patients.

The use of biomaterials for orthopedic implant devices is one of the major focal points of this handbook. In fact, Chapters 2 through 7 and Chapter 9 (refer to Table of Contents) all deal with the materials and performance associated with orthopedic implants. As shown in Table 1, a variety of metals, polymers, and ceramics are used for such applications.

Cardiovascular Applications. In the cardiovascular, or circulatory, system (the heart and blood vessels involved in circulating blood throughout the body), problems can arise with heart valves and arteries, both of which can be successfully treated with implants. The heart valves suffer from structural changes that prevent the valve from either fully opening or fully closing, and the diseased valve can be replaced with a variety of substitutes. As with orthopedic implants, ceramics (carbons, as described in Chapter 6, “Ceramic Materials,” in this handbook), metals, and polymers are used as materials of construction (Table 1).

Arteries, particularly the coronary arteries and the vessels of the lower limbs, become blocked by fatty deposits (atherosclerosis), and it is possible in some cases to replace segments

with artificial arteries. As shown in Table 1, polymers are the material of choice for vascular prostheses (see Chapter 7, “Polymeric Materials,” in this handbook for further details).

Ophthalmics. The tissues of the eye can suffer from several diseases, leading to reduced vision and eventually, blindness. Cataracts, for example, cause cloudiness of the lens. This may be replaced with a synthetic (polymer) intraocular lens (Table 1). Materials for contact lenses, because they are in intimate contact with the tissues of the eye, are also considered biomaterials. As with intraocular lenses, they too are used to preserve and restore vision (see Chapter 7, “Polymeric Materials,” in this handbook for details).

Dental Applications. Within the mouth, both the tooth and supporting gum tissues can be readily destroyed by bacterially controlled diseases. Dental caries (cavities), the demineralization and dissolution of teeth associated with the metabolic activity in plaque (a film of mucus that traps bacteria on the surface of the teeth), can cause extensive tooth loss. Teeth in their entirety and segments of teeth both can be replaced or restored by a variety of materials (Table 1). A thorough review of these materials can be found in Chapter 10, “Biomaterials for Dental Applications,” in this handbook.

Wound Healing. One of the oldest uses of implantable biomaterials can be traced back to the introduction of sutures for wound closure. The ancient Egyptians used linen as a suture as far back as 2000 B.C. Synthetic suture materials include both polymers (the most widely synthetic suture material) and some metals (e.g.,

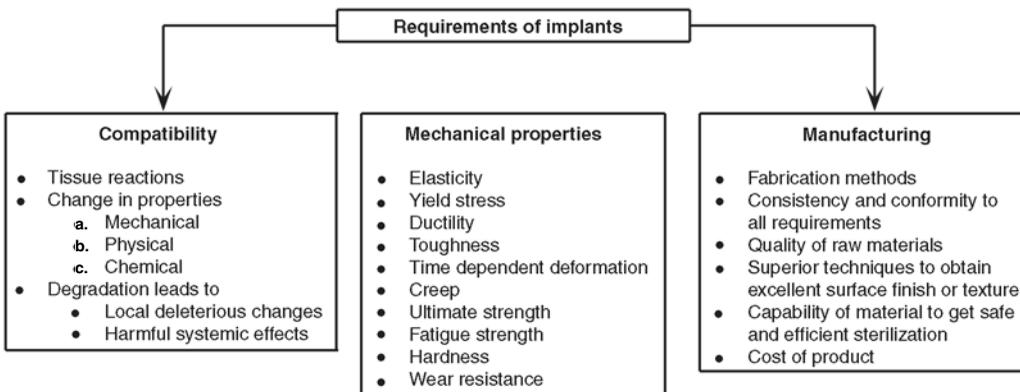


Fig. 1 Implant material requirements in orthopedic applications. Source: Ref 2

stainless steels and tantalum). Chapter 7, “Polymeric Materials,” in this handbook discusses the characteristics and properties of synthetic suture materials.

Table 1 Examples of medical and dental materials and their applications

Material	Principal applications
Metals and alloys	
316L stainless steel	Fracture fixation, stents, surgical instruments
CP-Ti, Ti-Al-V, Ti-Al-Nb, Ti-13Nb-13Zr, Ti-Mo-Zr-Fe	Bone and joint replacement, fracture fixation, dental implants, pacemaker encapsulation
Co-Cr-Mo, Cr-Ni-Cr-Mo	Bone and joint replacement, dental implants, dental restorations, heart valves
Ni-Ti	Bone plates, stents, orthodontic wires
Gold alloys	Dental restorations
Silver products	Antibacterial agents
Platinum and Pt-Ir	Electrodes
Hg-Ag-Sn amalgam	Dental restorations
Ceramics and glasses	
Alumina	Joint replacement, dental implants
Zirconia	Joint replacement
Calcium phosphates	Bone repair and augmentation, surface coatings on metals
Bioactive glasses	Bone replacement
Porcelain	Dental restorations
Carbons	Heart valves, percutaneous devices, dental implants
Polymers	
Polyethylene	Joint replacement
Polypropylene	Sutures
PET	Sutures, vascular prosthesis
Polyamides	Sutures
PTFE	Soft-tissue augmentation, vascular prostheses
Polyesters	Vascular prostheses, drug-delivery systems
Polyurethanes	Blood-contacting devices
PVC	Tubing
PMMA	Dental restorations, intraocular lenses, joint replacement (bone cements)
Silicones	Soft-tissue replacement, ophthalmology
Hydrogels	Ophthalmology, drug-delivery systems
Composites	
BIS-GMA-quartz/silica filler	Dental restorations
PMMA-glass fillers	Dental restorations (dental cements)

Abbreviations: CP-Ti, commercially pure titanium; PET, polyethylene terephthalates (Dacron, E.I. DuPont de Nemours & Co.); PTFE, polytetrafluoroethylenes (Teflon, E.I. DuPont de Nemours & Co.); PVC, polyvinyl chlorides; PMMA, polymethyl methacrylate; BIS-GMA, bisphenol A-glycidyl. Source: Adapted from Ref 3

Another important wound-healing category is that of fracture fixation devices. These include bone plates, screws, nails, rods, wires, and other devices used for fracture treatment. Although some nonmetallic materials (e.g., carbon-carbon composite bone plates) have been investigated, almost all fracture fixation devices used for orthopedic applications are made from metals, most notably stainless steels (see Chapter 3, “Metallic Materials,” in this handbook for details).

Drug-Delivery Systems. One of the fastest growing areas for implant applications is for devices for controlled and targeted delivery of drugs. Many attempts have been made to incorporate drug reservoirs into implantable devices for a sustained and preferably controlled release. Some of these technologies use new polymeric materials as vehicles for drug delivery. Chapters 7, “Polymeric Materials,” and 9, “Coatings,” in this handbook describe these materials.

Types of Biomaterials (Ref 1)

Most synthetic biomaterials used for implants are common materials familiar to the average materials engineer or scientist (Table 1). In general, these materials can be divided into the following categories: metals, polymers, ceramics, and composites.

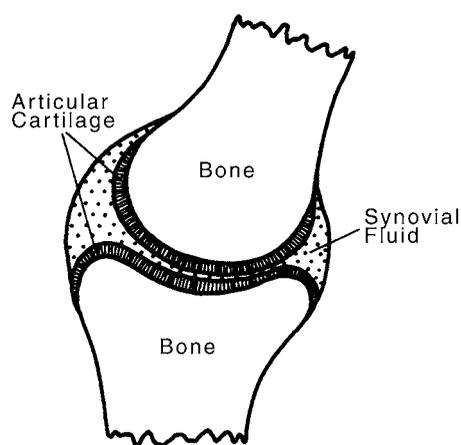


Fig. 2 Schematic showing key components of a natural synovial joint. It consists of layers of bearing material (articular cartilage) mounted on relatively hard bones forming the skeletal frame. The synovial fluid acts as a lubricant. In an artificial joint, lubrication is supplied by low-friction polymeric bearing materials. Source: Ref 4

Metals. As a class of materials, metals are the most widely used for load-bearing implants. For instance, some of the most common orthopedic surgeries involve the implantation of metallic implants. These range from simple wires and screws to fracture fixation plates and total joint prostheses (artificial joints) for hips, knees, shoulders, ankles, and so on. In addition to orthopedics, metallic implants are used in maxillofacial surgery, cardiovascular surgery, and as dental materials. Although many metals and alloys are used for medical device applications, the most commonly employed are stainless steels, commercially pure titanium and titanium alloys, and cobalt-base alloys (Table 1). The use of metals for implants is reviewed in Chapter 3, “Metallic Materials,” in this handbook. Dental alloys are discussed in Chapters 10, “Biomaterials for Dental Applications,” and 11, “Tarnish and Corrosion of Dental Alloys.”

Polymers. A wide variety of polymers are used in medicine as biomaterials. Their applications range from facial prostheses to tracheal tubes, from kidney and liver parts to heart components, and from dentures to hip and knee joints (Tables 1, 2). Chapters 7, “Polymeric Materials,” and 10, “Biomaterials for Dental Applications,” in this handbook review the use of polymers for these applications.

Polymeric materials are also used for medical adhesives and sealants and for coatings that serve a variety of functions (see Chapters 8, “Adhesives,” and 9, “Coatings,” in this handbook for details).

Ceramics. Traditionally, ceramics have seen widescale use as restorative materials in

dentistry. These include materials for crowns, cements, and dentures (see Chapter 10, “Biomaterials for Dental Applications,” in this handbook for details). However, their use in other fields of biomedicine has not been as extensive, compared to metals and polymers. For example, the poor fracture toughness of ceramics severely limits their use for load-bearing applications. As shown in Table 1, some ceramic materials are used for joint replacement and bone repair and augmentation. Chapters 6, “Ceramic Materials,” and 9, “Coatings,” in this handbook review the uses of ceramics for nondental biomedical applications.

Composites. As shown in Table 1, the most successful composite biomaterials are used in the field of dentistry as restorative materials or dental cements (see Chapter 10, “Biomaterials for Dental Applications,” in this handbook for details). Although carbon-carbon and carbon-reinforced polymer composites are of great interest for bone repair and joint replacement because of their low elastic modulus levels, these materials have not displayed a combination of mechanical and biological properties appropriate to these applications. Composite materials are, however, used extensively for prosthetic limbs, where their combination of low density/weight and high strength make them ideal materials for such applications.

Natural Biomaterials. Although the biomaterials discussed in this handbook are synthetic materials, there are several materials derived from the animal or plant world being considered for use as biomaterials that deserve brief mention. One of the advantages of using natural materials for implants is that they are similar to materials familiar to the body. In this regard, the field of biomimetics (or mimicking nature) is growing. Natural materials do not usually offer the problems of toxicity often faced by synthetic materials. Also, they may carry specific protein binding sites and other biochemical signals that may assist in tissue healing or integration. However, natural materials can be subject to problems of immunogenicity. Another problem faced by these materials, especially natural polymers, is their tendency to denature or decompose at temperatures below their melting points. This severely limits their fabrication into implants of different sizes and shapes.

An example of a natural material is collagen, which exists mostly in fibril form, has a characteristic triple-helix structure, and is the most

Table 2 Examples of polymers used as biomaterials

Application	Polymer
Knee, hip, shoulder joints	Ultrahigh molecular weight polyethylene
Finger joints	Silicone
Sutures	Polylactic and polyglycolic acid, nylon
Tracheal tubes	Silicone, acrylic, nylon
Heart pacemaker	Acetal, polyethylene, polyurethane
Blood vessels	Polyester, polytetrafluoroethylene, PVC
Gastrointestinal segments	Nylon, PVC, silicones
Facial prostheses	Polydimethyl siloxane, polyurethane, PVC
Bone cement	Polymethyl methacrylate

PVC, polyvinyl chloride. Source: Ref 1

prevalent protein in the animal world. For example, almost 50% of the protein in cowhide is collagen. It forms a significant component of connective tissue such as bone, tendons, ligaments, and skin. There are at least ten different types of collagen in the body. Among these, type I is found predominantly in skin, bone, and tendons; type II is found in articular cartilage in joints; and type III is a major constituent of blood vessels.

Collagen is being studied extensively for use as a biomaterial. It is usually implanted in a sponge form that does not have significant mechanical strength or stiffness. It has shown good promise as a scaffold for neotissue growth and is commercially available as a product for wound healing. Injectable collagen is widely used for the augmentation or buildup of dermal tissue for cosmetic reasons. Other natural materials under consideration include coral, chitin (from insects and crustaceans), keratin (from hair), and cellulose (from plants).

Examples of Biomaterials Applications

Biomedical devices range the gamut of design and materials selection considerations from relatively simple devices requiring one material, such as commercially pure titanium dental implants, to highly complex assemblies, such as the cardiac pacemaker described subsequently or the ventricular-assist device (VAD) discussed in Chapter 7, “Polymeric Materials” in this handbook (see, for example, Fig. 4 and Table 6 in Chapter 7, which illustrate the components and list the materials of construction, respectively, for a VAD).

Total Hip Replacement

Total joint replacement is widely regarded as the major achievement in orthopedic surgery in the 20th century. Arthroplasty, or the creation of a new joint, is the name given to the surgical treatment of degenerate joints aimed at the relief of pain and the restoration of movement. This has been achieved by excision, interposition, and replacement arthroplasty and by techniques that have been developed over approximately 180 years (Ref 2).

Design and Materials Selection. Hip arthroplasty generally requires that the upper femur (thigh bone) be replaced and the mating pelvis (hip bone) area be replaced or resurfaced.

As shown in Fig. 3, a typical hip prosthesis consists of the femoral stem, a femoral ball, and a polymeric (ultrahigh molecular weight polyethylene, or UHMWPE) socket (cup) with or without a metallic backing. Femoral components usually are manufactured from Co-Cr-Mo or Co-Ni-Cr-Mo alloys or titanium alloys (see Chapter 3, “Metallic Materials,” in this handbook for details). The ball (articulating portion of the femoral component) is made either of highly polished Co-Cr alloys or of a ceramic (e.g., alumina). Modular designs, where the stem and ball are of two different materials, are common. For example, hip replacement implants featuring a titanium alloy femoral stem will have a Co-Cr femoral head. Similarly, the UHMWPE socket of the common acetabulum replacement can be implanted directly in the pelvis or be part of a modular arrangement wherein the cup is placed into a metallic shell

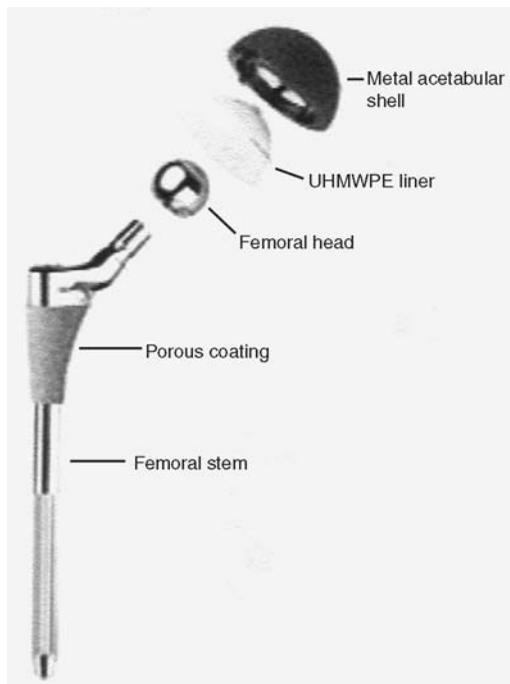


Fig. 3 Typical components found in an unassembled total hip replacement (THR) implant. It should be noted that this is one of many artificial joint designs used in THR arthroplasty. For example, implants secured by bone cements would not be porous coated. Similarly, the ultrahigh molecular weight polyethylene (UHMWPE) acetabular cup is sometimes not capped by a metal (cobalt- or titanium-base alloys or unalloyed tantalum) shell.

(Fig. 4). Design variations include the modular approach, straight stems, curved stems, platforms and no platforms, holes and holes in the femoral stem, and so on.

Table 3 lists some of the femoral head-to-socket combinations that have been used for total hip replacement arthroplasty. Cobalt-base alloys are the most commonly used metals for current metal-on-polymer implants. As indicated in Table 3 and elaborated in Chapter 3, “Metallic Materials,” in this handbook, the oxide surface layer on titanium alloy femoral heads results in excessive wear to the UHMWPE acetabular cups. Figure 5 compares the wear behavior of various femoral head/cup combinations.

Knee Implants

In a total knee arthroplasty (TKA), the diseased cartilage surfaces of the lower femur

(thighbone), the tibia (shinbone), and the patella (kneecap) are replaced by a prosthesis made of metal alloys and polymeric materials. Most of the other structures of the knee, such as the connecting ligaments, remain intact.

Design. For simplicity, the knee is considered a hinge joint because of its ability to bend and straighten like a hinged door. In reality, the knee is much more complex, because the surfaces actually roll and glide, and the knee bends. The first implant designs used the hinge concept and literally included a connecting hinge between the components. Newer implant designs, recognizing the complexity of the joint, attempt to replicate the more complicated motions and to take advantage of the posterior cruciate ligament (PCL) and collateral ligaments for support.

Up to three bone surfaces may be replaced during a TKA: the lower ends (condyles) of the thighbone, the top surface of the shinbone, and the back surface of the kneecap. Components are designed so that metal always articulates against a low-friction plastic, which provides smooth movement and results in minimal wear.

The metal femoral component curves around the end of the thighbone (Fig. 6) and has an interior groove so the knee cap can move up and down smoothly against the bone as the knee bends and straightens.

The tibial component is a flat metal platform with a polymeric cushion (Fig. 6). The cushion may be part of the platform (fixed) or separate (mobile), with either a flat surface (PCL-retaining) or a raised, sloping surface (PCL-substituting).

The patellar component is a dome-shaped piece of polyethylene that duplicates the shape of the kneecap, anchored to a flat metal plate (Fig. 6).

Materials of Construction. The metal parts of the implant are made of titanium alloys (Ti-6Al-4V) or cobalt-chromium alloys. The plastic

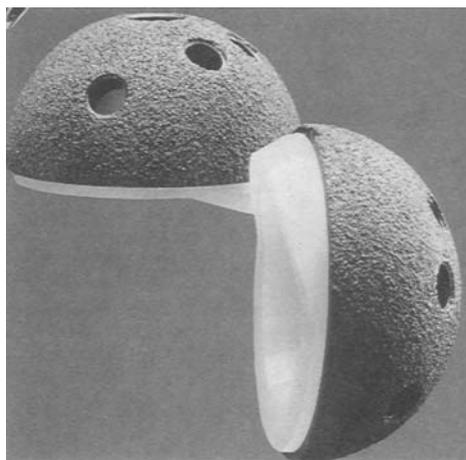


Fig. 4 Acetabular cup components, which are fitted over the femoral head, featuring plasma-sprayed shell with anatomic screw hole placement

Table 3 Materials combinations in total hip replacement (THR) prostheses

Femoral component	Socket component	Results
Co-Cr-Mo	Co-Cr-Mo	Early high loosening rate and limited use; new developments show lowest wear rate (THR only—in clinical use in Europe)
Co-Cr-Mo	UHMWPE	Widely employed; low wear
Alumina/zirconia	UHMWPE	Very low wear rate; zirconia more impact resistant
Alumina	Alumina	Minimum wear rate (components matched); pain—not in clinical use in the United States
Ti-6Al-4V	UHMWPE	Reports of high UHMWPE wear due to breakdown of titanium surface
Surface-coated Ti-6Al-4V	UHMWPE	Enhanced wear resistance to abrasion; only thin treated layer achieved

UHMWPE, ultrahigh molecular weight polyethylene. Source: Ref 2

parts are made of UHMWPE. All together, the components weigh between 425 and 565 g (15 and 20 oz), depending on the size selected.

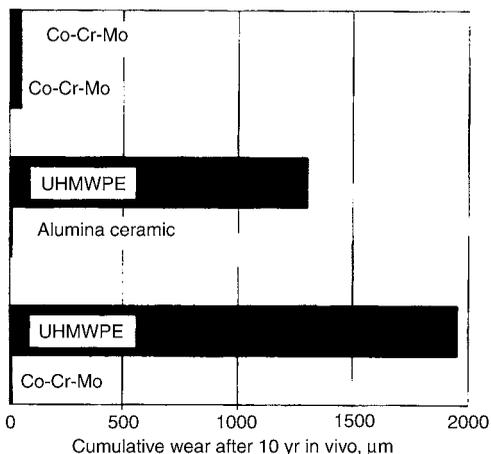


Fig. 5 Wear behavior of various femoral head/cup combinations. Even higher ultrahigh molecular weight polyethylene (UHMWPE) wear rates are encountered with titanium-base femoral heads. Source: Ref 2

Cardiac Pacemakers

Function. Cardiac pacemakers are generally used to manage a slow or irregular heart rate. The pacemaker system applies precisely timed electrical signals to induce heart muscle contraction and cause the heart to beat in a manner very similar to a naturally occurring heart rhythm. A pacemaker consists of a pulse generator, at least one electrode, and one or two pacing leads connecting the pacemaker to the heart. Figure 7 shows various types of pulse generators and pacing leads.

Components and Materials of Construction. The casing of the pulse generator functions as housing for the battery and circuits, which provide power. It is usually implanted between the skin and pectoral muscle. The sealed lithium iodine battery provides electrical energy to the pacemaker. This battery replaced the mercury-zinc battery in 1975, extending the life of some pacemaker models by over 10 yr. The circuitry converts the electrical energy to small electrical signals. The circuitry also con-

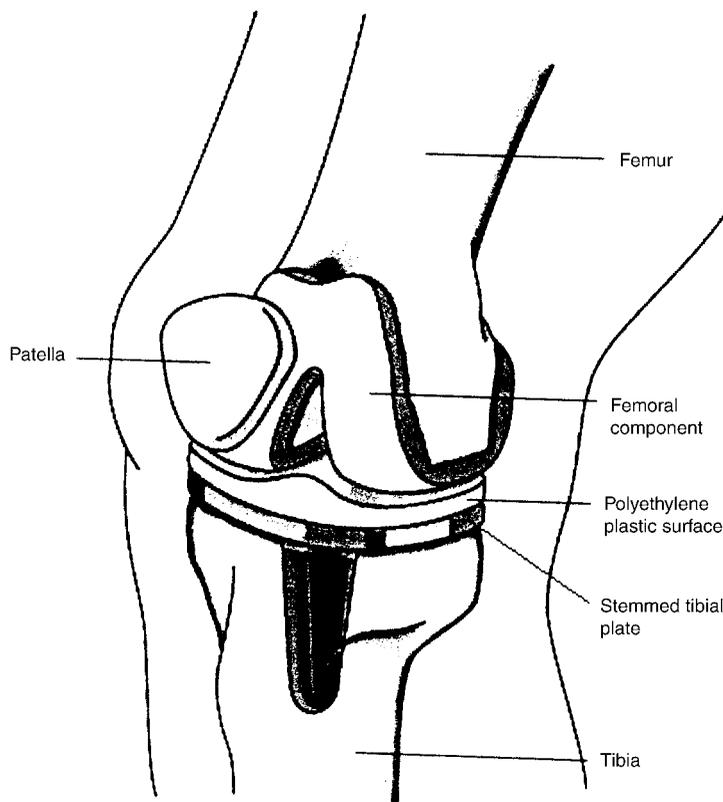


Fig. 6 Components of a total knee replacement arthroplasty. See text for details.

trols the timing of the electrical signals delivered to the heart. A connector block, made of polyurethane, is located at the top of the pacemaker (Fig. 7). It serves to attach the pacemaker to the pacemaker lead. Formerly, glass materials were used to comprise the connector block. The pulse generator is encased in ASTM grade 1 titanium. Titanium replaced ceramics and epoxy resin, which were used for encapsulation of some pacemakers in the past, with silicone

rubber. This upgrade to titanium allowed patients to safely use appliances such as microwave ovens, because titanium helps to shield the internal components and reduce the external electromagnetic interference.

A pacing lead is vital to the pacemaker system, because it transmits the electrical signal from the pacemaker to the heart and information on the heart activity back to the pacemaker. One or two leads may be used, depending on the type

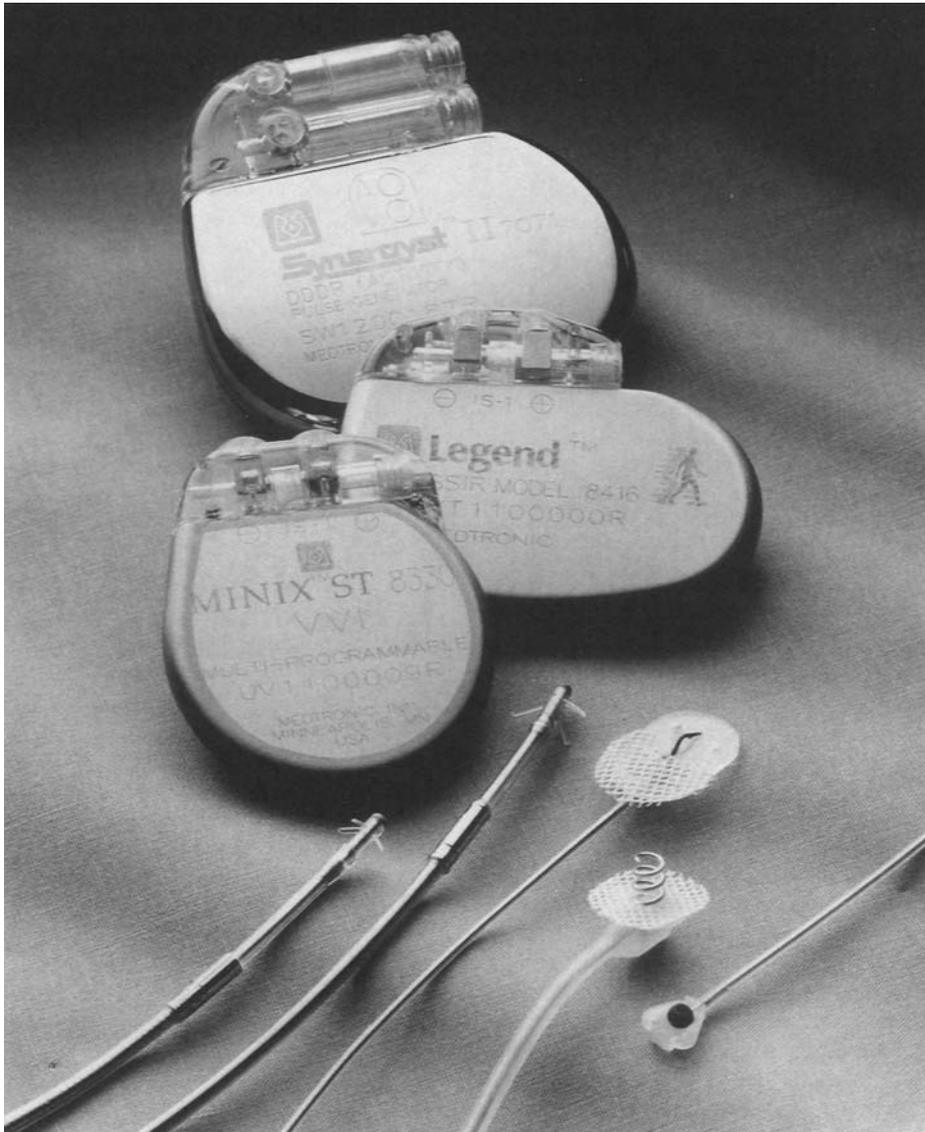


Fig. 7 Various pacemaker component designs. Top: Three examples of titanium-encased pulse generators. Connector blocks, which serve to attach the pacemaker to the pacemaker lead, are shown at the top of each pulse generator. Bottom: Various types of insulated endocardial and myocardial leads. Note that the lead shown at the center of the figure has a silicone sewing pad and Dacram mesh disk for implant fixation. Source: Ref 5

of pacemaker. One end of the lead is attached to the connector block of the pacemaker. The other end is inserted through a vein and placed in the right ventricle or right atrium of the heart. The lead is an insulated wire consisting of a connector pin, lead body, fixation mechanism (Fig. 7), and at least one electrode. The connector pin is the portion of the lead that is inserted into the connector block. The lead body is the insulated metal wire that carries electrical energy from the pacemaker to the heart.

The lead must be able to withstand the flexing induced by the cardiac contractions in the warm and corrosive environment in the body. Thus, the materials used must be inert, nontoxic, and durable. The lead body must be flexible, noncorrosive, and durable. It must also be a good electrical conductor. The early lead body was insulated with polyethylene. Currently, the lead body is insulated with a more resilient material such as silicone rubber tubing or polyurethanes. Polyurethanes are generally stronger than silicone rubbers, which are easily damaged. The strength of polyurethanes enables a thinner lead to be used in the pacemaker and offers greater lead flexibility. Another advantage of polyurethanes is their very low coefficient of friction when wet. However, metal-ion-induced oxidation may degrade polyurethanes, while silicones are not affected by this mechanism of degradation. The fixation mechanism serves to hold the tip of the lead in place in the heart. Currently, either a nickel-cobalt alloy with a silver core helix or an electrically active platinum-iridium helix may be used to anchor the electrode of the lead to the surface of the heart. The electrode is located at the tip of the lead. It serves to deliver the electrical energy from the pacemaker to the heart and information about the natural activity of the heart back to the pacemaker. Electrodes may be composed of platinum, titanium, stainless steel, silver, or cobalt alloys. Titanium has been used because it forms a nonconducting oxide layer at the surface. This surface prevents the exchange of charge carriers across the boundary. Titanium also exhibits a high modulus of elasticity, high resistance to corrosion, and high durability. Electrodes may be coated with iridium oxide to prevent nonconductive layers from forming. The coated electrodes may also provide lower acute and chronic thresholds due to the reduced local inflammation.

Drug-Eluting Leads. Leads have developed immensely since they were first introduced. The earliest leads were attached to the outer surface

of the heart. In the mid-1960s, transverse leads were introduced. They could be inserted through a vein leading to the heart, thus eliminating the need to open the chest cavity during implantation. In the 1970s, tined and active fixation leads were developed to replace smooth tip leads. The prongs on the tined leads and the titanium alloy screws in the active fixation leads provide a more secure attachment to the heart and are still used today. In the early 1980s, steroid-eluting leads were developed. These leads emit a steroid drug from the tip of the electrode on the lead to suppress inflammatory response of the heart wall, thus reducing the energy requirements of the pacemaker. The steroid also results in low chronic thresholds. Ceramic collars surrounding the electrode tip were first used to contain and emit the steroid. This technique is still used, where dexamethasone sodium phosphate is the eluted steroid. A silicone rubber matrix contains the steroid, and this matrix is contained in a platinum-iridium porous tip electrode. The combination of platinum and iridium results in a material stronger than most steels. The porous tip electrode provides an efficient pacing and sensing surface by promoting fibrotic tissue growth and physically stabilizing the tissue interface. In order to facilitate passage of the fixation mechanism to the heart, either a soluble polyethylene glycol capsule or a mannitol capsule is placed on the electrode tip. When the electrode tip is exposed to body fluids, the steroid is released. The polyethylene glycol capsule dissolves within 2 to 4 min after the electrode tip is inserted into the vein. The mannitol capsule dissolves within 3 to 5 min after the insertion.

ACKNOWLEDGMENTS

The application examples describing knee implants and cardiac pacemakers were adapted from the following web sites:

- American Academy of Orthopaedic Surgeons, www.orthoinfo.aaos.org
- T. Reilly, "Structure and Materials of Cardiac Pacemakers," University of Wisconsin-Madison, www.pharmacy.wisc.edu/courses/718-430/2000presentation/Reilly.pdf

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