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Fundamentals of Medical Implant Materials

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OVER THE LAST SEVERAL DECADES, an increase in longevity and life expectancy has raised the average age of the world's population. Among the countries currently classified by the United Nations as more developed (with a total population of 1.2 billion in 2005), the overall median age rose from 29.0 in 1950 to 37.3 in 2000 and is forecast to rise to 45.5 by 2050 (Ref 1). This worldwide increase in the average age of the population has, in turn, led to a rapidly increasing number of surgical procedures involving prosthesis implantation, because as the human body ages, the load-bearing joints become more prone to ailments. This has resulted in an urgent need for improved biomaterials and processing technologies for implants, more so for orthopaedic and dental applications.

Need for Prostheses

The first question to ask while undertaking such a study is "What is the need for implants to replace or fix human joints during traumatic conditions?" Human joints are complex and delicate structures capable of functioning under critical conditions, and it is a great challenge for doctors as well as scientists to develop site-specific implants that can be used in a human body to serve a specific purpose for orthopaedic, dental, ophthalmological, cardiovascular, cochlear, and maxillofacial applications.

Synovial joints such as hips, knees, and shoulders perform due to the combined efforts of articular cartilage, a load-bearing connective tissue covering the bones involved in the joints, and synovial fluid, a nutrient fluid secreted within the joint area (Ref 2–4). However, these joints are more often than not prone to degenerative and inflammatory diseases that result in pain and joint stiffness (Ref 5). Apart from the usual decay of articular cartilage due to age, there are illnesses such as osteoarthritis (inflammation of bone), rheumatoid arthritis (inflammation of synovial membrane), and chondromalacia (softening of cartilage). An astounding 90% of people above the age of 40 suffer from such degenerative conditions. The structure of a normal bone is distinctly different when compared to a bone that is suffering from osteoporosis, with the bone cell density being substantially lower for the osteoporotic bone as compared to the normal bone. Such premature joint degeneration may arise mainly from three conditions: deficiencies in joint biomaterial properties, excessive loading conditions, and failure of normal repair processes (Ref 2). Although minor surgical treatments are done to provide temporary relief to numerous patients, there is a consensus that the ultimate step is to replace the dysfunctional natural joints for prolonged pain relief and mobility. Thus, the field of arthroplasty has become popular in the surgical world and, according to the medical term, means surgical repair of joints (Ref 2). Currently, one of the main achievements in the field of arthroplasty is total joint replacement (TJR), where the entire load-bearing joint (mainly in the knee, hip, or shoulder) is replaced surgically by ceramic, metal, or polymeric artificial materials. As stated earlier, the problem is that not all artificial materials could be used for such purposes, only the ones that fulfill certain broad specifications.

In comparison, the human tooth, consisting of enamel, dentin, pulp, and cementum, is a highly specialized calcified structure used to break down food. It is a site where most surgical procedures in humans are performed, requiring implants of a subperiosteal (in contact with exterior bone surface) or endosteal (extending into the bone tissue) nature (Ref 6). The fixtures can be either fixed or removable, which really depends on the type of employed prostheses, a majority of which involve complete or partial dentures. In any case, the biomaterial interaction and tissue reaction of these implants, along with other intraoral devices, is critical for the stability and sustainability of dental prostheses.

The following section outlines some of the selection criteria that must be kept in mind when choosing an implant material for a specific purpose.

Implant Properties

The property requirements of a modern-day implant can broadly be categorized into three equally important features (Ref 7):

- The human body must be compatible with the material used for the prosthesis. While it is understandable that there is bound to be some amount of tissue reaction due to the introduction of a foreign substance, the resulting changes in mechanical, physical, and chemical properties within the localized environment should not lead to local deleterious changes and harmful systemic effects.
- The implant should have the desired balance of mechanical and physical properties necessary to perform as expected. The specific optimization of properties such as elasticity, yield stress, ductility, time-dependent deformation, ultimate strength, fatigue strength, hardness, and wear resistance really depends on the type and functionality of the specific implant part.
- The device under question should be relatively easy to fabricate, being reproducible, consistent, and conforming to all technical and biological requirements. Some of the constraints could include the techniques to produce excellent surface finish or texture, the capability of the material to achieve adequate sterilization, and the cost of production. The repair of such implants in case of failure is also very important. It has been noted that for any dental prostheses or TJR surgery, the revision surgery of an implant is more difficult, has lower success rates, and may induce additional damage to the surrounding tissues (Ref 8). Unfortunately, *in vivo* degradation, primarily due to the higher wear rates associated with artificial implant materials and the consequent adverse biological effect of the generated wear debris, results in a shorter lifetime for these artificial implants when compared with their natural counterparts. Thus, it is imperative to account for the physical stability of the foreign material once it is placed inside a human body.

Apart from these factors, the selection of the implant material itself is the principal criterion for proper functioning. No amount of design changes can help if the material is not biologically and mechanically compatible. That, along with the surgery location and desired functioning of the artificial joint, determines what material should be used. For example, smaller implants used for cochlear and dental prostheses are manufactured using a plastic or ceramic material. However, for making total hip replacements and total knee replacements, metals are considered the best candidate due to their higher tensile load-bearing capabilities. The various parts of hip and knee implants require different property characteristics. Thus, it is understandable that for best results, modern-day implants such as the Trapezoidal-28 (T-28) hip (Ref 9, 10), the Burstein-Lane (B-L) knee (Ref 11), or the Total Condylar Prosthesis Knee (Ref 12) are assembled by joining the various components made of metals, ceramics, and/or polymers to form one unit.

For metallic implants, casting and forging metallic components is still one of the most accepted techniques in the implant fabrication area, even though minuscule cracks and inhomogeneous composition of parts provide major hurdles for the process (Ref 13). Along with that, the fabrication technique itself has some impact on implant performance. For example, preparing rough, serrated implant surfaces helps in better cell adhesion, differentiation, and proliferation (Ref 14, 15). Having porous implants has shown to help in the growth and attachment of bone cells.

Ceramic devices are manufactured by a variety of techniques. Typical powder-metallurgy-based routes follow compaction and solid-state sintering of powdered ceramics (alumina and calcium phosphate) or metal-ceramic composites (CermeTi, Dynamet Technology, Inc.) (Ref 16). Depending on the property requirement, the heating schedules can be varied to determine grain size and crystallinity. For example, sintering at a higher temperature (liquid-phase sintering or vitrification) is often done to produce a combination of fine-grained crystalline matrix with reduced porosity (Ref 6). Other materials, such as hydroxyapatite, are used as coatings on various biomaterials and are plasma sprayed onto the material. Conventional casting routes are adopted to produce bioceramic glasses. For this, one must ensure that the solidification process in this method is slow enough to prevent crystallization (otherwise, polycrystalline products will form). This frustrated nucleation leads to the formation of glasses below the glass transition temperature (Ref 6). If required, these glasses can be annealed at higher temperatures to nucleate and grow crystalline phases in the glassy matrix, commonly forming a new class of materials called glass-ceramics.

Polymeric implants can be divided into two broad categories: natural and synthetic polymers. Natural polymers are made of an extracellular matrix of connective tissue, such as tendons, ligaments, skin, blood vessels, and bone. However, they are very difficult to procure and reproduce on a regular basis. Generally, synthetic polymers are synthesized by polymerization and condensation techniques to form long chains of the desired shape and property (Ref 6). Other synthetic materials, such as fibers and biotextiles, are prepared by melt spinning and electrospinning, while hydrogels are prepared by simply swelling cross-linked polymeric structures in water or other biological fluids.

Development of Implant Materials

Metallic Implants

In the early days of arthroplastic surgery, stainless steel was considered a viable implant material mainly because of its availability and processing ease. Alloying additions of chromium, nickel, and molybdenum were made to the ferrous matrix to prepare alloys such 316L, also known as ASTM F138 (Ref 2). They were primarily used to make temporary devices such as fracture plates, screws, and hip nails. However, as TJR surgery became popular, it was evident that the very high modulus of stainless steel (~200 GPa, or 29 $\times$ 10^6 psi) was a deterrent (Table 1). Also, researchers started looking for alloys that were more biocompatible and corrosion and wear resistant. Cobalt-base alloys came into the picture where wrought alloys were used to fabricate prosthetic stems and load-bearing components. Even though they offered excellent corrosion resistance, wear resistance, and fatigue strength, these Co-Cr-Mo alloys (ASTM F75 and F799) still had higher modulus (~210 GPa, or 30 $\times$ 10^6 psi) (Table 1) and inferior biocompatibility than what was desired for implant materials (Ref 2). After the early 1970s, titanium alloys started to gain much popularity due to their excellent specific strength, lower modulus, superior tissue compatibility, and higher corrosion resistance (Ref 17). Commercially pure titanium (ASTM F67) was the first to be used because its oxide (titanium in atmosphere readily forms a nascent oxide layer) had excellent osseointegration properties; that is, human bone cells bonded and grew on the titanium oxide layer quite effectively. However, due to its limited strength, the implants were confined to specific parts, such as hip cup shells, dental crown and bridges, endosseous dental implants, pacemaker cases, and heart valve cages (Ref 18). To improve the strength for load-bearing applications such as total joint replacements, the alloy Ti-6Al-4V ELI (ASTM F136, the extra-low interstitial, or ELI, alloy composed of titanium, 6 wt% Al, and 4 wt% V) was chosen. This Ti-6Al-4V alloy was originally developed for aerospace applications and had superior performance in the field of aviation, with an elastic modulus of approximately 110 GPa (16 $\times$ 10^6 psi) (Table 1), only half that of 316L stainless steel. It was used for TJR surgery with modular femoral heads and for long-term devices such as pacemakers. However, it was soon discovered that the presence of vanadium caused cytotoxicity and adverse tissue reactions (Ref 19, 20). Thus, niobium and iron were introduced, replacing vanadium, to develop alloys such as Ti-6Al-7Nb (Ref 21) and Ti-5Al-2.5Fe (Ref 22). Other alloys with aluminum additions, such as Ti-15Mo-5Zr-3Al (Ref 23) and Ti-15Mo-2.8Nb-3Al (Ref 2), were tried. Further studies showed that the release of both vanadium and aluminum ions from the alloys may cause long-term health problems, such as peripheral neuropathy, osteomalacia, and Alzheimer diseases (Ref 24, 25). Thus, Ti-6Al-4V somewhat lost its importance as the most viable orthopaedic alloy.

These circumstances led to an urgent need to develop newer and better orthopaedic alloys. This required the researchers to first identify those metallic elements that were completely biocompatible and could be alloyed with titanium. The ideal recipe for an implanted alloy included excellent biocompatibility with no adverse tissue reactions, excellent corrosion resistance in body fluid, high mechanical strength and fatigue resistance, low modulus, low density, and good wear resistance. Unfortunately, only a few of the alloying elements do not cause harmful reactions when planted inside the human body (Ref 26). These include titanium, molybdenum, niobium, tantalum, zirconium, iron, and tin. Of these, only tantalum showed an osseocompatibility similar to that of titanium. However, its high atomic weight prevented tantalum from being used as a primary alloying addition. In fact, the biocompatibility of higher amounts of tantalum and palladium additions was only tested for dental and craniofacial prostheses where implant weight would not be of much concern (Ref 27). For other types of load-bearing implants, several molybdenum- and niobium-base alloys were analyzed. Investigations on ternary Ti-Mo-Fe alloys were carried out,

Table 1 Comparison of mechanical properties of commonly used orthopaedic alloys

	Modulus		Yield strength		Ultimate tensile strength	
Alloy	GPa	10^6 psi	MPa	ksi	MPa	ksi
Stainless steel	200	29	170–750	25–110	465–950	(65–140)
Co-Cr-Mo	200–230	29–33	275–1585	40–230	600–1795	(90–260)
Commercially pure Ti	105	15	692	100	785	115
Ti-6Al-4V	110	16	850–900	120–130	960–970	140–141

where the strengthening effect of the iron addition was studied in a Ti-7.5Mo alloy (Ref 28, 29). Guillermot et al. conducted tests on Ti-Mo-Fe-Ta alloys with hafnium additions (Ref 30). The early works of Feeney et al. focused on one of the most promising quaternary molybdenum-base β-titanium alloys, Ti-11.5Mo-6Zr-4.5Sn, also known as βIII (Ref 31). The phase transformations occurring in these alloys were found to be similar to that of binary titanium-molybdenum alloys. At room temperature, the as-quenched βIII alloy showed low yield strength, high ductility, and high toughness. The effects of iron in titanium-molybdenum alloys (Ref 28) and the superior properties of βIII (Ref 31) were finally combined together to develop Ti-12Mo-6Zr-2Fe (Ref 32, 33), which recorded superior yield strength and modulus values. A parallel, if not better, effort was made to develop niobium-base β-titanium alloys. Karudo et al. (Ref 34) and Tang et al. (Ref 35) developed some alloys based on the Ti-Nb-Ta, Ti-Nb-Ta-Zr, Ti-Nb-Ta-Mo, and Ti-Nb-Ta-Sn systems. Of the different alloys that were chosen, the tensile strength and elongation of Ti-29Nb-13Ta-4.6Zr alloy were found to be greater than or equivalent to those of conventional titanium alloys for implant materials (Ref 36–38). On comparing the hardness values of the quaternary alloys, it was evident that the homogenized samples had higher hardness than the air- or water-quenched samples. Finally, the dynamic moduli were observed to be lowest at 5 at.% Zr and a niobium/tantalum ratio of 12.0, which was attributed to the preferred site occupancy of niobium, tantalum, and zirconium within the body-centered cubic unit cell and its effect on the nature of bonding (Ref 35, 39). The alloys that possessed the lowest moduli were Ti-35.5Nb-5.0Ta-6.9Zr and Ti-35.3Nb-5.7Ta-7.3Zr.

Based on this research, a number of contemporary and prospective alloys were developed, such as Ti-12Mo-6Zr-2Fe (Ref 32, 33); Ti-15Mo-3Nb-0.3O (Ref 40); interstitial oxygen, also referred as TIMETAL 21 SRx; Ti-13Nb-13Zr (Ref 41); and Ti-35Nb-7Zr-5Ta (Ref 42). Interestingly, all these alloys were primarily β-type titanium alloys. This shift in the search for better biomaterials from α/β-titanium to β-titanium alloys could be explained by the fact that the latter fit in very well with the tight mechanical property requirements of orthopaedic alloys. Two of those important properties include yield strength and elastic modulus.

Yield Strength. The yield strength determines the load-bearing capability of the implant. For example, in the case of TJR surgeries where a high load-bearing capability of the implant is essential, one ideally needs an appropriately high yield strength value of the alloy. Thus, the orthopaedic alloys should have a sufficiently high yield strength value with adequate ductility (defined by percentage elongation or percentage reduction of area in a standard tensile test). Table 2 lists the yield strength and ultimate tensile strength values of some of the common titanium alloys. Interestingly, some of the metastable β-titanium alloys do exhibit very high values in comparison to the α- or α/β-titanium alloys.

Elastic Modulus. A number of experimental techniques have been used to determine the elastic properties of solids (Ref 43). There is always a concern for the relatively higher modulus of the implant compared to that of the bone (~10 to 40 GPa, or 1.5 to 6 × 10^6 psi) (Ref 2). Long- term experiences indicate that insufficient load transfer from the artificial implant to the adjacent remodeling bone may result in bone reabsorption and eventual loosening of the prosthetic device (Ref 44, 45). It has been seen that when the tensile/compressive load or the bending moment to which the living bone is exposed is reduced, decreased bone thickness, bone mass loss, and increased osteoporosis occur. This is termed the stress-shielding effect, caused by the difference in flexibility and stiffness, which is partly dependent on the elastic moduli difference between the natural bone and the implant material (Ref 46). Any reduction in the stiffness of the implant by using a lower-modulus material would definitely enhance the stress redistribution to the adjacent bone tissues, thus minimizing stress shielding and eventually prolonging the device lifetime. In an attempt to reduce the modulus of the implant alloys to match that of the bone tissue, Ti-6Al-4V and related α/β alloys were considered to be inferior. The β-titanium alloys have a microstructure predominantly consisting of β-phase that exhibits lower overall moduli. Table 2 shows that Ti-15Mo-5Zr-3Al, Ti-12Mo-6Zr-2Fe, Ti-15Mo-3Nb-0.3O (21SRx), and Ti-13Nb-13Zr have elastic moduli ranging from 74 to 88 GPa (11 to 13 × 10^6 psi), which is approximately 2 to 7 times higher than the modulus of bones.

Fatigue. Variable fatigue resistance of the metallic implants is also a cause of concern while developing an alloy. The orthopaedic implants undergo cyclic loading during body motion, resulting in alternating plastic deformation of microscopically small zones of stress concentration produced by notches and microstructural inhomogeneities. Standard fatigue tests include tension/compression, bending, torsion, and rotation-bending fatigue testing (Ref 2).

There were several advantages and disadvantages of the various alloys that were researched, and many more will probably be developed and tested in the near future. Two of the most promising alloys appear to be the Ti-35Nb-7Zr-5Ta (often referred to as TNZT) and Ti-29Nb-13Ta-4.6Zr (often referred to as TNTZ) compositions, mainly because these alloys exhibit the lowest modulus values reported to date—~55 GPa (8 × 10^6 psi) in the case of TNZT, almost 20 to 25% lower than other available alloys (Ref 2, 42). While TNZT was developed at Clemson University by Rack et al. (Ref 42), TNTZ was developed at Tohuku University, Sendai, Japan, by Niinomi et al. (Ref 34). TNZT is now commercially sold by Allvac in the United States as TiOsteum and TiOstalloy. Its low yield strength value (547 MPa, or 79 ksi) was increased by adding interstitial oxygen; thus, Ti-35Nb-7Zr-5Ta-0.4O showed a strength of 976 MPa (142 ksi) and a modulus of 66 GPa (9.6 × 10^6 psi) (Ref 42).

Ceramic Implants

Ceramics, including glasses and glass-ceramics, are used for a variety of implant

Table 2 Mechanical properties of orthopaedic alloys developed and/or used as orthopaedic implants

		Elastic modulus		Yield strength		Ultimate tensile strength	
Alloy designation	Microstructure	GPa	10^6 psi	MPa	ksi	MPa	ksi
Commercially pure Ti	{α}	105	15	692	100	785	115
Ti-6Al-4V	{α/β}	110	16	850–900	125–130	960–970	140–141
Ti-6Al-7Nb	{α/β}	105	15	921	135	1024	150
Ti-5Al-2.5Fe	{α/β}	110	16	914	130	1033	150
Ti-12Mo-6Zr-2Fe	{Metastable β}	74–85	10–12	1000–1060	145–155	1060–1100	155–160
Ti-15Mo-5Zr-3Al	{Metastable β}	75	10	870–968	125–140	882–975	130–140
	{Aged β + α}	88–113	13–16	1087–1284	160–190	1099–1312	160–190
Ti-15Mo-2.8Nb-3Al	{Metastable β}	82	12	771	110	812	115
	{Aged β + α}	100	14	1215	175	1310	190
Ti-13Nb-13Zr	{α′/β}	79	11	900	130	1030	150
Ti-15Mo-3Nb-0.3O (21SRx)	{Metastable β} + silicides	82	12	1020	150	1020	150
Ti-35Nb-7Zr-5Ta	{Metastable β}	55	80	530	75	590	85
Ti-35Nb-7Zr-5Ta-0.4O	{Metastable β}	66	9	976	140	1010	145

Source: Ref 2

applications in dental and orthopaedic prostheses. Implanting ceramics in the body can present a number of different scenarios. The bioceramic-tissue attachment can occur due to physical attachment or fitting of inert ceramic to the tissue (morphological fixation), bone ingrowth and mechanical attachment into porous ceramic (biological fixation), chemical bonding of bones with the dense, nonporous ceramic (bioactive fixation), or temporary attachment of resorbable ceramic that is finally replaced by bones (Ref 6).

One of the most commonly known groups of bioactive ceramics is the calcium phosphates. They are naturally formed in minerals as well as in the human body. These bioceramics can be further classified in terms of their calcium-phosphorus ratios. For example dicalcium phosphate, tricalcium phosphate, and tetra calcium phosphate have calcium-phosphorus ratios of 1, 1.5, and 2, respectively. In the case of hydroxyapatite (HA, or $3Ca_3(PO_4)_2{\cdot}Ca(OH)_2$), which is considered a bioactive material, the calcium-phosphorus ratio is 1.67, and this ratio must be accurately maintained. Otherwise, during heat treatments the compound can decompose to more stable products such as α- or β-tricalcium phosphate. To prevent such an occurrence, many efforts have been directed toward the development of fabrication routes for HA that mainly involve compaction followed by sintering. Despite the enhanced efforts toward better processing routes, abnormalities such as dehydration of HA and formation of defects and impurities continue to arise, and such defects can be characterized by x-ray diffraction, infrared spectroscopy, and spectrochemical analyses. Calcium-phosphate-base materials can be used for bioactive as well as bioresorbable fixations in non-load-bearing parts and for coatings on metallic implants via sputtering techniques such as plasma spraying. Other commonly known processing routes are based on electrophoresis, sol-gel, and electrochemical processing (Ref 47). Recently, laser-induced calcium-phosphate-base surface coatings have been successfully deposited to obtain desired biological properties in terms of cell adhesion, differentiation, and proliferation (Ref 48). These coatings are ideally expected to be of desired thickness, have excellent adhesion strength, and prevent biodegradation. They are also used for making bone cements, a calcium-deficient HA-based product for anchoring artificial joints by filling in the space between prosthesis and bone. Such anchoring with soft tissues and bone can also be achieved by using glasses of certain proportions of SiO_2, Na_2O, CaO, and P_2O_5. Ideally, such glasses are processed so that they contain less than 60 mol% of SiO_2, a high Na_2O and CaO content, and a high CaO/P_2O_5 ratio (Ref 6). Depending on the relative amount of the aforementioned oxides, they can be bioactive (form an adherent interface with tissues) or bioresorbable (disappear after a month of implantation).

Among bioinert implant materials, alumina (Al_2O_3) is the most commonly known ceramic, used for load-bearing prostheses and dental implants. It has excellent corrosion and wear resistance and high strength. In fact, the coefficient of friction of the alumina-alumina surface is better than that of metal-polyethylene surfaces (Ref 6). It also has excellent biocompatibility that enables cementless fixation of implants. Purer forms of alumina with finer grain sizes can be used to improve mechanical properties such as strength and fatigue resistance, as well as increase the longevity of the prosthetic devices (Ref 6). Despite these advantages, the primary drawback of using alumina-base ball-and-socket joints is the relatively high elastic modulus of alumina (>300 GPa, or 44×10^6 psi), which can be responsible for stress-shielding effects. However, much of this is solved by using zirconia (ZrO_2)-base products that have lower elastic modulus (~200 GPa, or 29×10^6 psi). Again, while both alumina- or zirconia-ceramic femoral heads offer excellent wear resistance, these ceramics do not have the same level of fracture toughness as their metallic counterparts, leading to problems such as fracture of these heads in use. This has even led to the recall of hip implants using zirconia femoral heads (Ref 49). Furthermore, the use of a ceramic femoral head attached to a metallic femoral stem also leads to an undesirable abrupt ceramic/metal interface in the hip implant. These are outstanding issues in terms of optimized implant design and must be addressed. There are some efforts toward developing the concept of a unitized implant that uses a laser-based processing technique to fabricate a monolithic functionally-graded implant, the details of which are discussed in the section "Functionally-Graded Implants: Hybrid Processing Techniques" in this article.

Polymeric Implants

Polymers are the most widely used materials for biomedical devices for orthopaedic, dental, soft-tissue, and cardiovascular applications, as well as for drug delivery and tissue engineering. They consist of macromolecules having a large number of repeat units of covalently bonded chains of atoms (Ref 50). The polymers can include a range of natural materials, such as cellulose, natural rubber, sutures, collagen, and deoxyribonucleic acid, as well as synthetically fabricated products, such as polyethylene (PE), polypropylene (PP), polyethylene terephthalate (PET), polyvinyl chloride (PVC), polyethylene glycol (PEG), polycaprolactone (PCL), polytetrafloroethylene (PTFE), polymethyl methacrylate (PMMA), and nylon (Ref 6).

Natural polymers are often pretty similar to the biological environment in which they are used, because they are basically an extracellular matrix of connective tissue such as tendons, ligaments, skin, blood vessel, and bone (Ref 6). Thus, there is a reduced chance of inflammation and risk of toxicity when introduced into the body. The natural set of polymers perform a diverse set of functions in their native setting; for example, polysaccharides such as cellulose, chitin, and amylose act as membrane support and intracellular communication; proteins such as collagen, actin, myocin, and elastin function as structural materials and catalysts; and lipids function as energy stores (Ref 51). Also, it is a great advantage that these naturally occurring implants can eventually degrade after their scheduled "task" is complete, only to be replaced by the body's own metabolic process. This degradation rate can be controlled to allow for the completion of the specific function for which the implant was introduced. The main problem with these naturally formed polymers is their reproducibility; the material is very specific to where and which species they are extracted. Also, due to their complex structural nature, synthetic preparation of these materials is very difficult.

The synthetic polymers can be prepared by addition polymerization (e.g., PE, PVC, PMMA) or condensation polymerization (e.g., PET, nylon). In the former process, the monomers go through the steps of initiation, propagation, and termination to reach a desired length of polymeric chain. In contrast, the condensation polymerization process usually involves a reaction of two monomers, resulting in elimination of small molecules such as water, carbon dioxide, or methanol. These materials exhibit a range of hydrophobic to hydrophilic properties and thus are used for specific applications only. For example, soft contact lenses that are in constant contact with human eyes are preferably made of materials that are hydrophilic, such as poly 2-hydroxyethyl methacrylate (polyHEMA).

Table 3 lists the applications of various biopolymers (Ref 6).The mechanical and thermal properties of polymers are dictated by several parameters, such as the composition of backbone and sidegroups, structure of chains, and molecular weight of molecules (Ref 50). In the case of polymers, structural changes at high temperature are determined by performing differential scanning calorimetry experiments. The deformation behavior of polymers can be analyzed by dynamic mechanical analyses as well as via normal tensile testing of dog bone samples. It should be noted here that, compared to metals and ceramics, polymers have much lower strength and modulus, but they can be deformed to a much greater extent before failure.

A relatively new area of research has focused on biodegradable polymers that do not need to be surgically removed on completion of their task. They are used for five main types of degradable implant applications: temporary support device, temporary barrier, drug-delivery device, tissue scaffold, and multifunctional implants (Ref 6). The additional concern while designing this type of implant is the toxicity of the degradation products, along with the obvious

Table 3 Applications of various biopolymers

Polymer	Application
Polyethylene (PE)	Catheters, acetabular cup of hip joint
Polypropylene (PP)	Sutures
Polyvinyl chloride (PVC)	Tubing, blood storage bag
Polyethylene terephthalate (PET)	Tissue engineering, fabric tubes, cardiovascular implants
Polyethylene glycol (PEG)	Drug delivery
Polylactic and polyglycolic acid	Tissue engineering
Polytetrafloroethylene (PTFE)	Vascular grafts
Polymethyl methacrylate (PMMA)	Hard contact lenses, bone cement for orthopaedic implants
Polyacrylamide	Swelling suppressant
Polyacryl acid	Dental cement, drug delivery
Polydimethyl siloxane (PDMS)	Heart valves; breast implants; catheters; insulation for pacemaker; ear, chin, and nose reconstruction
Cellulose acetate	Dialysis membrane, drug delivery
Nylon	Surgical sutures

Source: Ref 6

biocompatibility issues of all implant materials. The terms *biodegradation*, *bioerosion*, *bioabsorption*, and *bioresorption* are all loosely coined in the medical world to indicate that the implant device would eventually disappear after being introduced into the body (Ref 6). The successful use of a degradable polymer-based device depends on understanding how the material would lose its physicochemical properties, followed by structural disintegration and ultimate resorption from the implant site. Despite their potential advantages, there are only a limited number of nontoxic materials that have been successfully studied and approved by the U.S. Food and Drug Administration as degradable biopolymers. These include polylactic acid, polyglycolic acid, polydioxanone, polycaprolactone, and poly(PCPP-SA anhydride), along with the naturally occurring collagen, gelatin, and hyaluronic acid (Ref 6).

Several totally or partially biodegradable self-polymerizing composites are being used for orthopaedic surgery and dental applications. For fixation of endoprostheses, self-curing acrylic resins based on blends of PMMA particles and MMA monomer or a copolymer of MMA with styrene are often used (Ref 52). The slurry containing the aforementioned blends can be introduced into the bone cavity. The use of biodegradable composites is greatly encouraged for making bone cements and beads for drug-delivery applications. This is primarily due to their minimal release of residual monomers along with their ability to control the resorption rates in conjunction with bone ingrowth. Biodegradable antibiotic-loaded beads have the advantage of releasing the entire load of drug as they degrade (Ref 52). Composites based on polypropylene fumarate and PMMA are being used extensively for these purposes. For example, partially resorbable polymeric composites with bioactive properties have been prepared by adding aqueous α- tricalcium phosphate dispersions to PMMA bone cement (Ref 53). The resulting composite was a suitable bone substitute with a polymeric porous body and bioactive inorganic phase confined inside the pores. Again, PMMA/PCL beads formulated with partially biodegradable acrylic cements were used for delivery of drugs such as antibiotics, analgesics, or antiinflammatories (Ref 53).

Functionally Graded Implants—Hybrid Processing Techniques

As amply evident from the discussions in the preceding sections, the need for prosthesis implants, ranging from dental to orthopaedic applications, is increasing at an alarming rate. While currently-existing implants function appropriately, they do not represent the best compromise of required properties. Furthermore, the present manufacturing of implants is largely via subtractive technologies involving substantial material waste, leading to increased costs and time of production. Therefore, an imperative need exists for functionally-graded implants representing a better balance of properties and manufactured via novel additive manufacturing technologies based on near-net shape processing.

Some specific problems associated with currently-used implant manufacturing processes and the consequent compromise in properties are listed as follows:

- The manufacturing is based on conventional casting and forging of components, followed by material-removal steps via subtractive technologies such as precision machining. These technologies not only involve substantial material waste but are also limited to monolithic components without any compositional/functional changes within the same component.
- Diverse property requirements at different locations on an implant are satisfied by joining different components (e.g., femoral stem and femoral head) made of different materials in a total hip replacement system. This always leads to the formation of chemically abrupt interfaces that are detrimental to the properties of the implant. For example, it was a standard convention of using titanium alloy stems for orthopaedic applications to be fitted with more wear-resistant cobalt alloy for the head. However, some of the designs showed significant fretting corrosion effects due to micromotion between these components (Ref 54).

The current manufacturing route for implants does not allow custom designing for specific patients with rapid turnaround times. Consequently, instead of custom designing the implant, the surgeon is often forced to adapt the pre-existing design to fit the patient's requirements. This can become particularly challenging if the required physical dimensions of the implant differ substantially from those of the standard manufactured ones, for example, implants to be used for children.

To get around this problem, a novel processing technique called Laser Engineered Net Shaping (LENS) (Sandia National Laboratories) shows great promise. Similar to rapid prototyping technologies such as stereolithography, the LENS process (Ref 55, 56) begins with a computer-aided design file of a three-dimensional component, which is sliced into a series of layers electronically. The information about each of these layers is transmitted to the manufacturing assembly. A metal or alloy substrate is used as a base for depositing the component. A high-power laser (capable of delivering several hundred watts of power) is focused on the substrate to create a melt pool into which the powder feedstock is delivered via an inert gas flowing through a multinozzle assembly. The powder-feeder system of the LENS system consists of multiple hoppers. By controlling the deposition rates from individual hoppers, it is possible to design compositionally-graded and, consequently, functionally-graded materials, as demonstrated in a number of previous papers on laser-processed compositionally-graded titanium alloys (Ref 57–59). The nozzle is designed such that the powder streams converge at the same point on the focused laser beam. Subsequently, the substrate is moved relative to the laser beam on a computer-controlled stage to deposit thin layers of controlled width and thickness. There are four primary components of the LENS assembly: the laser system, the powder-delivery system, the controlled-environment glove box, and the motion-control system. A 750 W neodymium: yttrium-aluminum-garnet (Nd:YAG) laser, which produces near-infrared laser radiation at a wavelength of 1.064 μm, is used for all the depositions. The energy density is in the range of 30,000 to 100,000 W/cm^2. The oxygen content in the glove box is maintained below 10 ppm during all the depositions. The powder flow rates are typically 2.5 g/min, while the argon volumetric flow rate is maintained at 3 L/min. The LENS offers a unique

combination of near-net shape manufacturing and rapid solidification processing that can be particularly useful for manufacturing orthopaedic implants. A schematic representation of the LENS process is shown in Fig. 1. From the viewpoint of making implants based on metallic, ceramic, or even hybrid materials, compositional gradation can be particularly beneficial because it will enable the development of custom-designed orthopaedic implants with site-specific properties. Furthermore, engineering functional gradation in these implants will allow for a single unitized component to be manufactured without any chemically or structurally abrupt interfaces, leading to enhanced properties and performance.

Surface engineering of the near-net shape laser-processed implant can be carried out using a number of related processing techniques. Examples of these include the addition of bioceramic surface layers via a different type of laser deposition to improve osseointegration of the implant, and the addition of wear-resistant coatings via sputter deposition or other physical vapor deposition techniques.

Functionally Graded Hip Implant

Fabricating implants for total joint replacement surgeries such as total hip replacement (THR) is rather challenging because the property requirements at different locations of the monolithic implant are quite different. As discussed earlier, the LENS technique with multiple powder feeders is a viable tool to produce a functionally graded implant in its near-net shape form with site-specific properties. The basic core structure (hollow or similar to the prototype shown in Fig. 2) of the femoral stem and head assembly can be fabricated using LENS.

However, instead of conventional alloys such as Ti-6Al-4V, the material of choice for the core of the femoral stem and head assembly could be based on one of the newer-generation low-modulus, biocompatible beta-titanium alloys, such as those based on the Ti-Nb-Zr-Ta system. To achieve an optimal balance of mechanical properties, both solid geometries in terms of femoral head and stem, along with internal cavities, can be processed together. Because the surface of the femoral stem is required to exhibit excellent osseointegration properties, additional roughness can be introduced on the surface of the stem by laser depositing lines of the same alloy or even biocompatible coatings such as calcium phosphate in the form of a grid (Ref 48). The pattern of these lines/grids can be optimized for achieving the best potential of osseointegration based on trial *in vitro* studies.

In contrast, the femoral head material must possess excellent wear resistance, especially in the regions that rub off against the internal surface of the acetabular cup made of ultrahigh-molecular-weight polyethylene (UHMWPE). Thus, ceramic-based materials (e.g., ZrO_2) are generally preferred over titanium and its alloys. As mentioned earlier, one drawback of using ceramic materials is that they exhibit poor fracture toughness, and thus, the joint between the head and the stem (made of titanium alloy) creates a weak interface between two dissimilar materials. The tendency for high-impact fracture makes these materials fragile. A more appropriate approach may be to manufacture the core of the femoral stem and head assembly in the form of a single monolithic component and use surface engineering to improve the wear resistance of the base titanium alloy locally in the femoral head section. The LENS process could be quite handy in implementing such an idea, where the core of the femoral head could be made of tough β-titanium alloy (such as Ti-Nb-Zr-Ta), and there could be a radial gradation of optimal amounts of boride (or carbide) precipitates dispersed within the matrix. This comes from the idea that hard titanium boride (or titanium carbide) precipitates within the soft beta-titanium matrix can enhance the wear resistance of these metal-matrix-based hybrids quite substantially (Ref 60).

The basic parts of the functionally-graded hip implant that can be manufactured by using the LENS process include:

- *Femoral stem:* Made of beta-titanium-base Ti-Nb-Zr-Ta alloys
- *Femoral head:* Made of metal-matrix-based hybrid materials with radial gradations from Ti-Nb-Zr-Ta- to Ti-Nb-Zr-Ta-reinforced borides (or carbides)

Subsequent to LENS processing of the femoral implant, surface engineering strategies can be used to enhance the osseointegration of the femoral stem. For example, laser-based direct melting techniques may be used to simultaneously synthesize a physically textured surface involving a substrate (such as Ti-6Al-4V) and a coating (such as calcium phosphate) (Ref 48). Such a process can help in systematic organization of the calcium-phosphorus coating by effectively controlling the thermophysical interactions. Furthermore a metallurgically-bonded interface can be obtained by controlling the laser processing parameters, because both the coating and substrate material are melted and solidified at very high cooling rates ($\sim 10^4$ to 10^8 K/s). Again, laser-induced surface modification techniques can be used to increase the wear resistance of the femoral head in hip implants. Reinforcing the soft matrix of metallic components (such as new-generation β-titanium alloys) with hard ceramic precipitates such as borides offers the possibility of substantially enhancing the wear resistance of these composites (Ref 61). The wear resistance seems to further improve when lubricious ZnO coating is sputter deposited on the surface of these boride-reinforced composites.

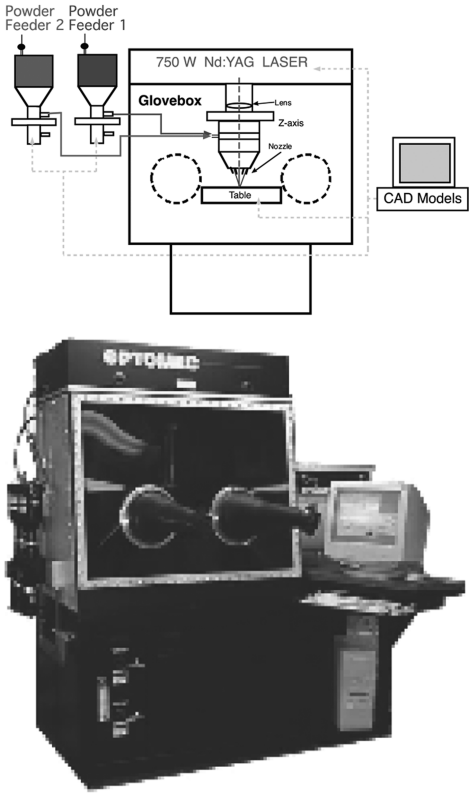

Fig. 1 Schematic representation and image of the Laser Engineered Net Shaping (LENS) laser deposition system

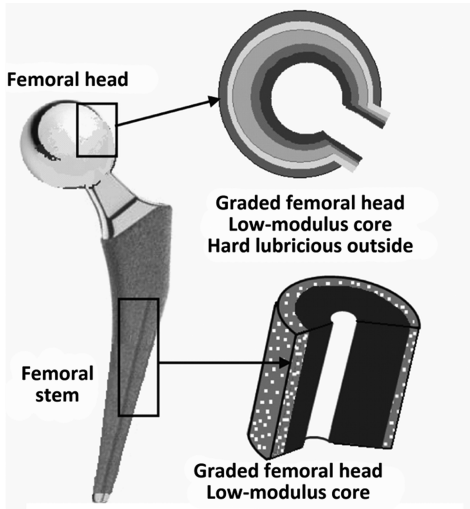

Fig. 2 Schematic diagram illustrating the functionally graded femoral head and stem of a hip implant that can be fabricated using the LENS system

Host Response to Biomaterials

The first thing that happens to a living organism after a foreign implant material is introduced into the body is its interaction with proteins such as fibrinogen, albumin, lysozyme,

high- and low-density lipoprotein, and many others. These proteins are present in large numbers within body fluids such as blood, saliva, and tears. Within seconds, the implant surface becomes coated with these proteins that, in turn, play a vital role in determining the tissue-implant interaction. In fact, the preferential adsorption of proteins (at much higher concentrations than the bulk) onto the biomaterial surface makes it a biologically recognizable material. This not only affects subsequent blood coagulation and inflammation, but it is what the cells "see" and respond to. The type of protein as well as the nature of the biomaterial surface is responsible for the aforementioned factors. For proteins to react more readily with the surface, they must be larger in size and should be able to unfold at a faster rate. Surfaces, on the other hand, play their part depending on their texture, nonuniformity, hydrophobicity, and composition (Ref 50). Typically, proteins are brought onto the surface of the foreign body via diffusion and/or convection. Variables such as concentration, velocity, and molecular size are important factors that determine such a movement. At the surface, the protein molecules selectively bind with the substrate at different orientations (to minimize repulsive interactions) via intramolecular forces such as ionic bonding, hydrophobic interactions, and charge-transfer interactions (Ref 50). In terms of kinetics of adsorption of proteins, the proteins initially attach quite rapidly to the largely open surface. However, at later stages, it is very difficult for the arriving proteins to find and fit into the empty spaces. This causes conformational changes so as to increase their contact points with the surface, by molecular spreading or by increasing the concentration of these molecules. Most adsorbed proteins are irreversibly attached to the surface, meaning that once they are attached, it is very difficult to detach them. In fact, desorption of protein molecules would require a simultaneous dissociation of all interactions between the molecule and the surface (Ref 50). Nevertheless, at longer times, the adsorbed molecules can eventually exchange with other competing protein molecules that have stronger interaction with the surface (Vroman effect). For example, in blood, which has more than 150 proteins, albumin dominates the initial interaction with the surface, primarily due to its high concentration and mobility. However, in due course, other proteins such as immunoglobulin G and fibrinogen, which have much less mobility but a higher affinity with the surface, can exchange with the albumin molecules and form a stable coating (Ref 50).

During implantation of a biomaterial, knowledge of the aforementioned processes is very important, because bleeding and injury of cells is a part of the wound-healing process. (While blood is a mixture of plasma, red blood cells, white blood cells, and platelets, cells join together to form tissue, muscle, nerves, and even the epithelium.) During injury, the endothelial cells and collagen fibers are exposed to blood. Fibrinogen, a protein present in blood, reacts with enzymes such as thrombin to form polymerized fibrin threads or clots.

The cells, on the other hand, constantly adapt themselves to the changes in environments around them. Due to the presence of implants, the cells can face trauma by way of physical, chemical, or biological agents, causing inflammation. If the tissue injury is minimal or if it can regenerate (e.g., skin tissue forming due to proliferation and differentiation of stem cells), then after complete healing, the normal functionalities can be achieved. However, scarring can occur, causing permanent loss of cell functionality if the injury is extensive or the tissue cannot regenerate, for example, heart muscle cells. Inflammation is an important part of the wound-healing process following implantation, often resulting in swelling and redness accompanied by heat and pain. It involves the migration of cells to the injury site via a process called chemotaxis, removing the dead cellular and tissue material from the site, destroying or quarantining all the harmful biological and chemical substances, and making sure that tissue rebuilding can start. During inflammation, blood flow to the injury site is increased by dilation of blood vessels (vasodilation) along with increased vascular permeability. Increase in blood circulation and metabolism rate causes the region to feel warm. Also, the endothelium becomes more adhesive, thus trapping and retaining the leukocytes, present in eosinophil, neutrophil, and basophil, at the trauma site. These cells are responsible for killing the invading pathogens, such as viruses, bacteria, and fungi, and consuming the foreign objects, such as debris from biomaterials, damaged tissue, and dead cells (Ref 50). While basophils and eosinophils are responsible for releasing harmful chemicals to kill the attacking foreign parasites, the neutrophils help in phagocytosis of foreign particles. Phagocytosis at all levels involves identifying or marking the foreign objects, surrounding and engulfing them, and finally releasing harmful chemicals to destroy them. Phagocytosis is also the primary function of macrophages that form during the phase of chronic inflammation, leave the blood stream, and attach themselves to tissues at the site of implantation (biomaterial surface). These take some time to form, unlike the neutrophils that result from an immediate response to injury (active inflammation). The macrophage cells usually span close to 50 to 100 μm, can live from a couple of months to a year, and are considered the first line of defense. These macrophages can also fuse together and form multinucleated foreign body giant cells that can phagocytose even larger particles.

Along with inflammation, there may be undesired colonization of tissue by bacteria, fungi, or viruses during biomaterial implantation. This is called infection, which is a serious cause of concern during surgery. It should be noted that infection can result in inflammation, but the reverse may not be true. One of the indications of infection is pus formation, which is a result of neutrophils and macrophages that die after killing the foreign parasites. To prevent the spread of infection, fibrous tissues usually form around the pus. If these form at the surface of the skin, as in the case of superficial immediate infection, the region stretches until it bursts open or is surgically drained (Ref 62). The second type of infection, called deep immediate infection, is the primary effect of the implantation procedure and is caused by airborne or skin bacteria that are introduced into the body involuntarily. The biggest threat to smooth surgery is deep late infection, which occurs several months after the procedure. It may be caused by a longer incubation period of the bacteria or even by slower development of the infection.

As mentioned previously, tissue injury due to implantation can affect the morphology, function, and phenotype of the cells (Ref 50). The change in environment due to the presence of implants can temporarily or permanently alter the functionality of surrounding tissues, for example, bone loss due to the stress-shielding effect. When blood vessels are damaged, blood clotting provides essential time for cell migration and proliferation to start the rebuilding process. This involves inflammation, which is also a necessary step toward successful would healing. The cells, promoted by growth factors, synthesize extracellular matrix proteins from the point of the wound inward (Ref 50). Next comes the formation of new blood vessels that are necessary to aid the newly formed tissues. Due to the macrophages, endothelial cells, and several growth factors, the environment at the wound site is made suitable for development of endothelial cells to form capillaries. The newly formed tissue, called granulation tissue, consists of smaller blood vessels and is very delicate. At a later stage of wound healing, the remodeling phase begins, where the newly formed tissue may have the structural and functional characteristics of the original tissue. Otherwise, remodeling may cause scar tissue formation with reduced functionality.

How long does it take for the entire wound healing to successfully take place? It depends on several factors, from the proliferative capacity of cells to the type of tissue and from the severity of wounds to the health condition and age of the patient (Ref 50). Typically after surgery, the clotting of blood occurs almost instantaneously. The migration of leukocyte cells takes place within a couple of days. In contrast, the macrophages migrate to the trauma site within a week. The tissue rebuilding and repair can last for several weeks, with the remodeling phase extending for as much as a couple of years (Ref 50).

Implant Failure

From the time an implant is introduced into the body via invasive surgery, the biomaterial

remains in prolonged contact with the cells and tissues. There are four different types of tissue responses to the biomaterial:

- The material is toxic, and the surrounding tissue dies.
- The material is nontoxic and biologically inactive, and a fibrous tissue forms.
- The material is nontoxic and active, and the tissue bonds with it.
- The material is nontoxic and dissolves, and the surrounding tissue replaces it (Ref 6).

The implant material, its geometry, and the environmental conditions around it play a very important role in governing how the proteins interact with the foreign substance, and the ensuing cell adhesion occurs via receptors in the cell membrane. The various steps of the physiological wound-healing process, including the activation of neutrophils and macrophages, and the differentiation and proliferation of the adhered cells in turn determine the structure and functionality of the neighboring tissues. In fact, evidence has shown that macrophages and foreign body giant cells can be present at the implant-tissue interface throughout the entire period of implantation, with all of this being a part of foreign body reaction (Ref 50). In an ideal situation, one would expect that the wound-healing process should be smoothly completed and proper function of the tissues around the implant should be restored. Also, one would hope that the implant should be integrated with the body, with no short- or long-term repercussions (failure of implant, infection, etc.).

However, in real life a number of processes can delay and complicate the wound-healing process. Sometimes, the cells around the implant completely reject it, leading to chronic inflammation, which can lead to removal of the biomaterial. This type of situation may arise for various reasons, such as inappropriate healing (too little or overgrowth of the tissue) and structural failure or migration of the implant (wear, fracture, stress shielding) (Ref 6). Wearing or fracture of implants can cause debris formation, which is more often observed in metallic materials. During dynamic loading/unloading of load-bearing implants (hip, knee, etc.), constant friction between two articulating parts can lead to the release of small particulates that are detrimental to the body. Stress shielding is also a serious problem for load-bearing implants, where unequal distribution of the load between the implant and the bone around it may lead to reabsorption. Other physiological reasons for implant rejection could be leaching out of ions (metals), degradation of material due to interaction with enzymes (polymers), and inadequate encapsulation of the implant surface via proteins and cells (Ref 50). Although introduction of biodegradable polymers can minimize issues in this aspect, upon completion of their scheduled task, these materials degrade into by-products that are degradable and/or can be removed by existing metabolic pathways (Ref 50). Another complication of implant surgery is the formation of fibrous tissue around the surface. The thickness and texture of fibrous tissues formed around the implant can depend on the type of implant material, size and shape of the implant, site of surgery in terms of functionality, and type of tissue that needs to be healed. The problem occurs when such layering prevents the normal operation of the implant in terms of mechanical function and drug delivery (Ref 50). These issues are further complicated if superficial and deep infections occur due to the colonization of bacteria, fungi, and viruses around the implant. Medications may not work due to the presence of an impervious fibrous layer, and the removal of the implant may be the only option.

To prevent such failures, several precautions are usually taken before using an implant for a prosthesis. The first step is to evaluate the material itself, because it is known to be the most common reason for implant failure. Unsuitable materials used for a prosthesis would mean that its physical, chemical, and biological properties are not suitable or compatible for the specific implant application. The design of the device is the next critical item. Information from past failures as well as upcoming experimental and modeling results must be incorporated to arrive at better designs. For example, while designing orthopaedic load-bearing implants, data from finite-element analyses of stress-concentration points as well as stress-strain results from walk simulators are taken into account. During fabrication, the implant should be free of any defects and inclusions that may lead to implant failure. In some cases, the sterilization process itself may cause changes in the structure and property of the prosthetic device. On the other hand, incomplete sterilization can also lead to infection, as with improper packaging and shipping. After the implant is fabricated, both mechanical (tensile, wear, fatigue) and biological (*in vitro*, *in vivo*) testing must be conducted to determine its feasibility. While the mechanical testing processes have been discussed in the section "Development of Implant Materials" in this article, a brief discussion of the biological tests follows.

***In Vitro* Assessment of Tissue Compatibility.** This usually involves performing cell cultures for a wide variety of materials used in medical devices. Three different cell culture assays are used for *in vitro* study: direct contact, agar diffusion, and elution. In all the tests, experimental variables such as cell type (usually L-929 mouse fibroblast), number of cells, duration of exposure, and test sample size are kept constant (Ref 6). Positive and negative controls are often used during the assay test to determine the viability of the test. In all cases, the amount of affected or dead cells in each assay provides a measure of the cytotoxicity and biocompatibility of the biomaterials. In the direct contact test, the material is placed directly on the cell culture medium. After the test, the cells are stained by hematoxylin blue, and the toxicity is evaluated by the absence of stained cells, because dead cells do not stain. The main problem with this type of test is cell trauma and death due to movement of the sample or the weight of highly dense materials. This is overcome by the agar diffusion test, where the agar (colloidal polymer from red algae) forms a layer between the test sample and the cells. In this assay, the healthy cells are stained red as compared to dead or affected cells. The main problem with this type of test is the risk of the sample absorbing water from the agar, thus causing dehydration of the cells. The third type of test, elution, is conducted in two separate steps: extraction of fluid (0.9% NaCl or serum-free cultural medium) that is in contact with the biomaterial, and biological testing of the medium with cells. Although this type of testing is time-consuming, it is very effective. It is universally observed and accepted that materials found to be nontoxic *in vitro* are nontoxic in *in vivo* assays as well (Ref 6).

***In Vivo* Assessment of Tissue Compatibility.** This type of test is conducted to determine the biocompatibility of a prosthetic device and also to assess whether the device is performing according to expectations without causing harm to the patient. It provides valuable data about the initial tissue response to the biomaterial, which in turn helps in selection and design of the device. Some tests, such as toxicity, carcinogenicity, sensitization, and irritation, determine if the leachable products of the medical device affect the tissues near or far from the implant site. Other tests, such as implantation and biodegradation, study the postsurgery changes in the implant material itself and their ensuing effect on the body. Overall, there may be an array of tests that must be conducted and evaluated, depending on where and why a specific device is used, before certifying an implant. For conducting the actual *in vivo* tests, animal models (sheep, pig, rat) are usually selected after weighing the advantages and disadvantages for human clinical applications.

As evident from the previous discussions, a variety of tests can be conducted before a prosthetic device is considered suitable for implantation. The choice of test depends on the specific application of the implant under consideration. Sometimes, it is very difficult to replicate the exact test, even while performing *in vivo* tests. For example, there is no adequate animal model to study the inflammatory reaction to wear debris near hip joints (Ref 6).

After successful completion of all these steps, the implant is finally ready to be surgically inserted into a patient. The prosthetic device is chosen based on the patient and the site of implantation. Each patient is different. He/she may have different allergic reactions to implant materials, may have previous health conditions unsuitable for the prosthesis, or may even have different immunological responses to fighting infection. Failures can

also be caused by the misuse of implants. For example, a patient who has undergone total hip replacement surgery can cause severe damage and loosening of the implant by excessive exercising before proper healing takes place (Ref 6). All of these factors can single-handedly or jointly contribute to improper functioning and eventual failure of implant devices.

The implant structure should be carefully analyzed postfailure to determine the exact cause and mechanism by which it failed. This can lead to the improvement of processing techniques and materials used for fabricating the device, can help in bettering the design and testing mechanisms used for these products, and can provide enough insight into adopting alternate surgery procedures and drug therapy postimplantation (Ref 6). Thus, implant retrieval and evaluation is a vital study to determine the safety and biocompatibility of implants. Along with the implant material, examination of the tissue must be conducted to assess the implant-tissue interface. At first, the overall implant and tissue specimen can be analyzed by light microscopy and cell culture, respectively. Consequently, specific aspects of the material can be studied using techniques such as scanning electron microscopy, transmission electron microscopy, energy-dispersive spectroscopy, contact-angle measurement, Fourier transform infrared spectroscopy, and scanning ion mass spectroscopy. Similarly, studies of proteins and genes can be conducted on the tissue sample. Compilation of these data can aid in the development of next-generation implants. A good example of the benefits of implant evaluation is the modern use of UHMWPE as a polymeric cup instead of synthetic fluorine-containing resin, with which some biological problems were encountered. In the case of dental implants, the integration of bone with the metal was far better understood after evaluation of failed fixtures.

Summary

According to D.F. Williams in 1987, *biocompatibility* can be defined as the capability of a medical device (implant) to perform with an appropriate host response in a specific application (Ref 63). Various parts of the device may be individually assessed, or every part may be considered separately. While the former is the biocompatibility of the device, the latter is the biocompatibility or bioresponse of individual materials (Ref 6). Either way, it is important to note that no material is suitable for all biomaterial applications. Nevertheless, implant science has been developing new technologies for implant devices as well as improving cell tissue interactions with biomaterials, some of which is discussed next.

Over the years, the use of polymers as biomaterials has increased considerably. Scientists are taking a very active interest in the development of newer stimulus-responsive smart polymers. In the presence of various physical, chemical, and biological stimuli, the polymers exhibit different responses, such as gelation, surface adsorption, and collapse of hydrogel. All of these responses are reversible processes, and, in the absence of the stimuli, the response is also reversed (Ref 6). These smart polymers are even combined with biomolecules to enhance their use beyond implant devices. These types of polymers, in combination with proteins and drugs, can be used in solution, in surfaces, and as hydrogels for applications such as drug delivery, removal of toxins, and enzyme processes (Ref 6). To improve the osseointegration properties, the polymer matrices are filled with HAs. These materials contain approximately 50 vol% HA in a polyethylene matrix and are used to make implants for ears (Ref 64).

Similarly, the osseointegration properties of ceramics and metals can be improved by introducing porosity on those surfaces that are in direct contact with the bone. The growth of bones into these pores would also ensure good mechanical stability of both load-bearing and non-load-bearing implants. Research has shown that optimal engineered porosity, fabricated by laser-deposition processes such as LENS with pore sizes in the range of 100 to 150 μm, can promote the growth of osteoblast cells within these pores (Ref 65). Figure 3 shows one such study, where Ti64 samples containing different sizes of engineered porosity were fabricated by LENS. The implant in this case acts as a scaffold for bone formation. For smaller pores, the fibrous tissue occupies the void space, because an extensive capillary network for osteogenesis does not occur (Ref 50). The degree of porosity of these materials has a big impact on bone integration and modulus, with substantial reductions in modulus with increasing porosity. However, with increase in porosity, the strength of the implant material reduces drastically, which could be a big challenge for load-bearing implants. Other surface-modification techniques are currently being studied to promote bone growth, including increasing the surface roughness of the device, using nanograined materials (Ref 66) to increase the surface area, and coating the implant with bioactive materials such as calcium phosphate (Fig. 4) (Ref 48, 67). Laser-engineered textured materials can also promote directional growth and movement of cells. Other physicochemical methods are also being used to change the surface composition as well as the biochemical properties of the surfaces. The latter approach uses the organic components of bone to affect tissue behavior by introducing peptides and proteins. Many bone growth factors could be used to influence the growth and differentiation of osteoblasts (Ref 50). Even tissue engineering approaches have been used to stimulate precise reactions with proteins and cells at a molecular level. As mentioned previously, the cell and tissue response to implantation is greatly dependent on what they "see" on the surface of the foreign device. Even the interaction of cells with the extracellular matrix (ECM) depends on the rigidity of the substrate. Adhesive surfaces created by targeted use of proteins, peptides, and other biomolecules help in mimicking the ECM environment (Ref 6). Even chemically patterned surfaces, aided by techniques such as photolithography, could be used to control cell adhesion at certain specific regions. In the future, several of the aforementioned surface-modification techniques could be combined to design devices with chemically engineered surfaces and controlled scaffold architecture that could manipulate specific cell growth, which in turn develops into specialized tissues.

Using this same concept has led to the design of multifunctional devices. Their application is thought to be a combination of a variety of functions that require the design of materials with specific properties. For example, the development of biodegradable bone nail can provide mechanical support to fracture sites as well as ensure growth on new bone at implant sites (Ref 6). As mentioned previously, biodegradable materials are used more and more for this purpose, and the use of other functional combinations involving tissue-engineering scaffolds is also being actively considered. In the future, these scaffolds could provide structural stability as well as serve as a means for drug delivery (Ref 6).

Similar to cell-biomaterial interaction, another cause of concern is the blood- biomaterial

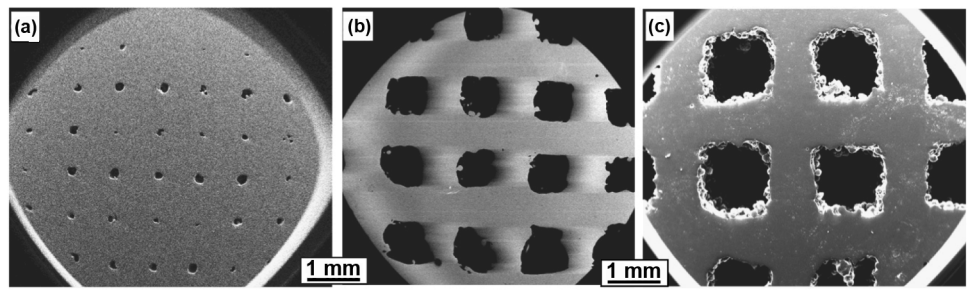

Fig. 3 Scanning electron microscopy backscattered electron images of Ti64 samples that were deposited via the LENS system using hatch widths of (a) 0.89 mm (0.035 in.), (b) 1.5 mm (0.06 in.), and (c) 2.0 mm (0.08 in.). The images show three different-sized scales of engineered porosities, resulting in different elastic moduli and cell responses.

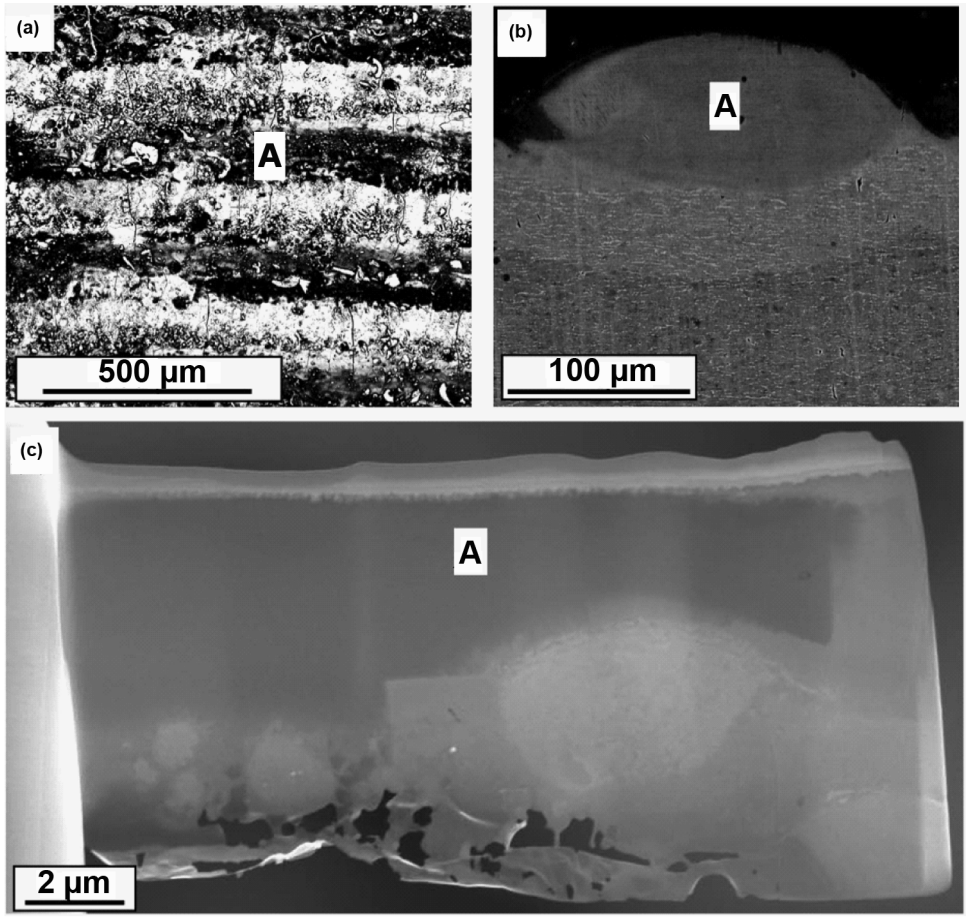

Fig. 4 (a) Top and (b) cross-sectional scanning electron microscopy backscattered images of laser-induced calcium phosphate coating on Ti64 substrate. (c) Cross-sectional transmission electron microscopy image of the same sample. All images show the calcium- and phosphorus-rich region, denoted by "A."

interaction for implants such as vascular grafts and heart valves. Ongoing efforts have been directed toward producing blood-compatible biomaterials that have properties similar to the endothelium (Ref 50). Usually, these materials are hydrophilic in nature, which reduces platelet adhesion and coagulation. Even anticoagulants applied along blood-contacting surfaces or incorporated in the chemical structure of polymers have shown promise in terms of reduction of thrombus formation.

Another major concern about introducing a foreign material into the body, apart from the body's normal foreign body reaction, is the undesired colonization of bacteria, viruses, or fungi, causing short- and long-term infections. Many researchers have been working to design biomaterials that discourage germ adhesion and growth. Some biomaterials have been designed to release antibiotics via diffusion or dissolution of material (Ref 50). However, it is difficult to predetermine the dose without prior knowledge of the type and extent of germs that can affect the implantation site. In addition, there are various concerns, such as patients becoming sensitive to the antibiotic dose and germs mutating to develop antibiotic-resistant strains. Thus it is clear that more research needs to be conducted before successfully implementing this concept.

The design and development of new types of implant devices and their targeted application will also dictate newer test protocols to analyze and evaluate these biomaterials. With newer devices such as smart polymers and bioactive glasses, more studies have been focused on active tissue-biomaterial interactions. *In vivo* testing and assessment of the targeted biological response of a tissue-engineered device would, in turn, provide pivotal information toward research and development of the device (Ref 6). The ultimate goal would be to use these devices universally with minimum inflammatory and reactive response from the patient, quick healing of tissue (with no fibrous tissue formation), and successful integration of the device within the body, with desired performance and no long-term repercussions.

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