# Biomaterials and Biomedical Devices

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**This review discusses the factors important in the incorporation or integration of biomaterials and devices by tissue. Methods for surface modification and surface-sensitive techniques for analysis are cited. In vitro methods to evaluate the biocompatibility or efficacy of certain biomaterials and devices are presented. Present and future directions in neural prostheses, cardiovascular materials, blood or bone substitutes, controlled drug delivery, orthopedic prostheses, dental materials, artificial organs, plasma- and cytapheresis, and dialysis are discussed.**

BIOMATERIALS ARE AS OLD AS MEDICINE ITSELF AND THEY have been very widely used for tooth restorations since the beginning of this century. Their successful use in reconstructive surgery, however, did not develop until after World War II. Since that time, research and application have progressed exponentially each decade principally for two reasons, the first and foremost being the tremendous need for strengthening or replacing body components that transplantation cannot accommodate. The other factor is the technologic breakthroughs that have resulted from the interdisciplinary focus of physicists, chemists, engineers, and biomedical and clinical scientists on these problems. This has led to the successful employment of artificial materials to replace structural components of the body; that is, to surgical reconstruction with materials that have been assembled and processed in such a manner that: (i) they are biocompatible and (ii) they can assume the mechanical (for example, load-bearing) and other functional roles of the components they are replacing.

In order to accomplish this, implants cannot merely become walled off or encapsulated, but they must deceive adjacent tissue structures at the implant site to the extent that they can become integrated into the body. A successful implantation can best be achieved by a team that understands not only the anatomical, physiological, biochemical, and pathological aspects of the problem, but also comprehends bioengineering, including the mechanics of tissue components, rheological and electromechanical phenomena, and stereological analysis. A thorough understanding of the chemical, physicochemical, materials science, and biocompatibility aspects of the implant components is also required. Indeed, the surface characteristics of the materials and the events at the tissue biomaterial interface are critical for acceptance, integration, and durability of an implant (*1*). An implant employed for surgical reconstruction must first of all have surface characteristics that promote the adhesion of appropriate eukaryotic cells and tissue preferentially to that of bacteria. The latter situation would result in infection and rapid rejection (*2*). In order for ideal tissue integration to occur, the adhesion of the implant surface to, and possibly even its chemical bonding with, tissue and appropriate eukaryotic cells should be followed by infiltration or encapsulation of the implant by fibrovascular tissue and appropriate cells. The implant surface may require different characteristics in different situations. Generally porosity or roughness of the implant surface is preferable to smoothness although in certain situations this may promote bacterial colonization. Blood cells or marrow-derived cells such as neutrophils, macrophages, epithelioid cells (derived from macrophages), foreign-body giant cells (also usually considered to be derived from macrophages), and platelets play very important roles in implant incorporation. Lymphocytes, plasma cells, natural killer cells, and macrophages are very actively involved in the complex antigenic or immunologic reactions that accompany the incorporation of transplants or implants of natural origin. With foreign materials such as synthetic polymers (plastics, metals, ceramics, and carbon or their composites) they are usually less important. In some situations, however, such as implantation of the total artificial heart, an immune deficiency resulting from drug therapy can lead to bacteria (Fig. 1) that are ordinarily commensals such as *Staphylococcus epidermidis* becoming infectious agents (*3, 4*).

Also important are fibroblasts that are involved in the fibrosis or formation of granulation tissue surrounding implants, or of the capsules around implant particles. Their products such as mucopolysaccharides and acid mucopolysaccharides, the primary constituents of connective tissue matrix, and the different collagens are involved in adherence to biomaterials. The fibroblasts and their products along with endothelial cells are also involved in the formation of the microvasculature important for implant incorporation. Indeed, both

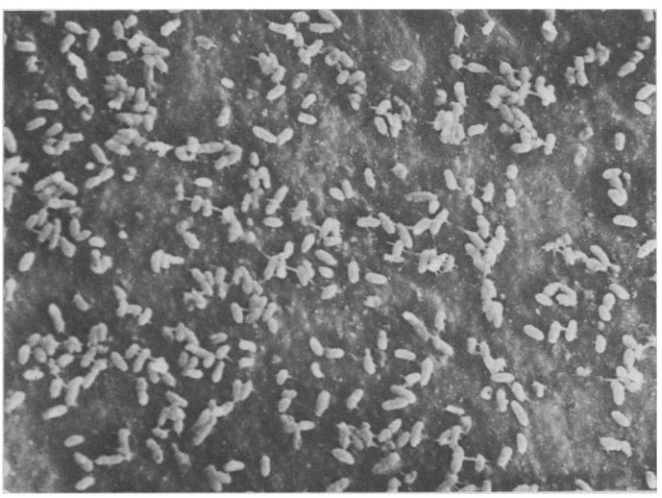

**Fig. 1.** *Pseudomonas aeruginosa* cultured from a total artificial heart implant patient. The bacteria were then allowed to adhere to a new sample of biomaterial driveline. Specimens courtesy of W. C. DeVries and J. J. Dobbins (magnified 2400 times).

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neutrophils and macrophages are involved in the wound repair and healing processes as well as in killing the bacteria that cause the infections that threaten implantation. Neutrophils, however, are principally involved in the acute phase of inflammation and are relatively short-lived compared to macrophages (and their derivatives) that are involved in the chronic inflammatory and healing phases. Indeed, once the adherence of eukaryotic cells and tissue has superseded that of bacteria, then the competition of adherence between the macrophages (and their derivative cells) and fibroblasts becomes important in implant integration. The macrophage appears to play a significant role in the regulation of wound healing (*5*), and macrophage infiltration always precedes the onset of fibroplasia. Activated macrophages stimulate collagen synthesis, deposition, and neovascularization (*6*). They also produce factors chemotactic for fibroblasts (*7*) and secrete collagenases involved in the breakdown of connective tissue (*8*). Foreign body giant cells (also called macrophage polykaryons) are frequently intimately involved with the fibroblasts and collagen fibers encapsulating implants. Indeed, in some situations, it appears that fibroblasts rather than macrophages may primarily be responsible for the reparative granuloma at implant sites and that their foreign body giant cells are formed by fusion of fibroblasts rather than of mononuclear phagocytic cells (*9*).

Recently, platelet adherence to implant surfaces has been recognized as being of importance in the failure of certain polymers to form useful smaller vascular grafts although they can form suitable prostheses for larger vessels. Although platelets counteract the effects of tissue injury on the walls of the smaller grafts they are also components of the intravascular thrombi which can occlude these smaller prostheses and result in ischemia and infection. Endothelial cell lining or seeding of the prostheses tends to prevent this (*10*).

Research on skin substitutes has suggested that natural cryopreserved cadaver skin, collagenous materials, cross-linked dextran gels, or synthetic polymeric biodegradable materials might serve as substrates for the engraftment of cultured or uncultured autogenous or autologous keratinocytes or epidermal cells to treat dermatologic disorders or skin wounds. Yannas *et al.* (*11*) had previously described a biodegradable, highly porous cross-linked collagen-glycosaminoglycan (CG) network that acts as a template to induce wound tissue to synthesize new skin. Yannas and his colleagues described three parameters (including seeding with epidermal and dermal cells) critical for maximal skin regeneration (Yannas *et al.*). [See (*12*) for an explanation of names in parentheses.] Stra-Cor membranes, bioplastic skin substitutes, are hydrogels formed by the coprecipitation of two oppositely charged polyelectrolytes derived from a field of three biopolymers—keratin, collagen, and chitin. These membranes have many properties considered desirable for wound coverings (A. Widra and M. N. Cohen). Human epidermal cells generated on basement membrane Matrigel appear to have the potential for use as autografts in the treatment of ulcerative lesions that occur in sickle cell disease and other disorders (D. G. Walker-Jones *et al.*).

Cellular and tissue engineering is important in the development of biomaterials and in reconstructive surgery. The relationship between tissue structure and mechanical properties, the endothelium-like membrane formed by cells such as macrophages in pseudokeratoplasty [a surgical procedure utilizing a synthetic plastic to replace the central cornea (*13*)], and the use of harvested or cultured endothelial cells for lining vascular prostheses are other examples of cellular and tissue engineering.

Engineering relevant to the levels of organization of the body comprises an important current approach to the fabrication of biomedical materials and devices. Thus molecular (including phospholipid and protein), enzyme, genetic, and organellar (including liposomal) engineering, as well as cellular and tissue engineering, can be important in the achievement of required biomaterials and therapeutic devices. New protein catalysts known as catalytic antibodies (*14*) should also be important in this regard.

## Neural Prostheses and Devices for Pain

New types of miniscule implantable electrodes for neural or neuromuscular stimulation (W. Anderson, Y. Lee, F. Mendel, and D. Fish), including one for spinal cord stimulation to control movement disorders and pain, and one for stimulating the central gray matter of the brain to control chronic pain have been described. A multichannel analog-stimulation cochlear implant for patients with total or profound deafness who receive no benefit from a hearing aid has been developed (*15*). This is the first neural prosthesis designed to replace part of the sensory system that has been approved for marketing by the Food and Drug Administration (FDA). Of 16 patients receiving this implant in an earlier study, 11 were evaluated and all but one demonstrated some degree of auditory-only speech recognition (R. Schindler and D. Kessler). It has been shown that some patients who do not benefit from analog-stimulation as a result of poor nerve survival may be helped by pulsatile stimulation (*16*). Important work has been done on synthetic degradable and nondegradable polymeric guide tubes to promote the regeneration of severed peripheral nerves. The same biodegradable CG polymer mentioned above for skin wound repair has been placed between the ends of transacted peripheral nerves inside a silicone tube graft and appears to promote regeneration (*17*). Conduction properties resulting from regeneration across extended distances with this system have been reported (A. S. Chang *et al.*). Previous studies by another group from Boston had shown the effects on peripheral nerve regeneration of a laminin-containing gel in biodegradable polylactate versus polyethylene tubes (*18*). Dr. Madison has developed collagen-based nerve guide tubes having the laminin-containing gel incorporated into their walls (R. Madison).

## Vascular and Cardiovascular Materials

Interesting work has been reported in a variety of areas, including synthetic microcellular polymeric foam for small diameter vascular replacement (A. Sylwester, J. Aubert, and P. Rand); the permeability of certain cardiovascular polymeric biomaterials to lipophilic drugs (S. D. Bruck and M. Kojima); the properties of polyurethane vascular grafts that mimic arterial behavior (M. L. Weygang); studies of the glycomacromolecular coating of certain strains of cocci that promote their adherence to both Dacron and polytetrafluoroethylene (PTFE) polyvascular grafts (B. M. Evers, B. L. Giammara, D. Jubenville, and M. A. Malangoni); how sulfonation of polyurethanes affects their surface properties such as fibrin sorption (increased) and platelet deposition (decreased) (A. S. Okkema, T. A. Giroux, T. G. Grasel, and S. L. Cooper); the description of a glutaraldehyde-tanned bovine collagen vascular graft (B. N. Sawyer); and the significance of medical grade polyurethanes in the development of the artificial heart (M. Szycher). Important in this regard are alterations of the polymeric structure of the polyurethanes so that functionalities resembling heparin are incorporated (*19*). Another approach is to coat the surfaces of the polyurethane tubes so that they can absorb substances like albumin, resulting in surface passivation that prevents clotting. An aliphatic polyurethane that appears especially promising in this regard has been described by Szycher *et al.* (*20*). Fiberoptic scanning densitometry was shown to be useful for quantifying the radiopacity of vascular catheters (D. D. Solomon, M. P. Byron, and M. J. Lipton).

The structures of thromboemboli formed in vitro on Biomer-coated surfaces were compared by image analysis (G. A. Adams *et al.*). The role of fibrinogen in the adhesion of platelets to, and their activation on, methacrylate polymers has also been reported (J. N. Lindon *et al.*).

## Blood Cell and Plasma Substitutes

One reason for a good deal of interest in this area is the reticence of people to be transfused for fear of hepatitis or AIDS infection. Progress has been made in hemoglobin and erythrocyte substitutes (R. D. MacGregor, N. Taylor, B. Lubin, and C. A. Hunt), plasma substitutes (L. C. Cerny and E. L. Cerny), and oxygen-carrying perfluorochemical (principally perfluorocarbon) blood substitutes. L. C. Clark, Jr., who first suggested the use of perfluorocarbons for this purpose (*21*), has been active in the physiological evaluation of the fluorocarbon red blood cell substitutes (L. C. Clark, Jr., R. B. Spokane, R. E. Hoffman, and S. J. Jacobs). Fluosol-DA 20% may be marketed for certain purposes this year. Further studies will be required, however, before its approval as a general blood substitute. Its use in localized focal ischemic events where, combined with oxygen administration, it can deliver increased amounts of oxygen at high tension appears warranted, however. These situations could include cerebrovascular accidents, myocardial infarction, peripheral ischemia, sickle cell crises, and trauma, including certain burn cases. In the future, perfluorochemicals could also find use for treating tumor hypoxia and for nuclear magnetic resonance (NMR) imaging, especially of the vascular system. The evaluation of a pyridoxalated-hemoglobin-polyoxyethylene conjugate as an oxygen-carrying plasma expander in lethal anemia (M. Matsushita, A. Yabuki, P. S. Malchesky, and Y. Nose), a study of the rheological effect of mixtures of perfluorotributylamine and stroma-free hemoglobin on sickled erythrocytes (C. A. Reindorf and N. E. Thompson), and the effect of hemodilution with Fluosol-DA on antipyrine metabolism in the rat (R. P. Shrewsbury *et al.*) have been described. Liposome-encapsulated hemoglobin as a potential blood substitute has also been described (A. S. Rudolph *et al.*). The potential therapeutic uses of plasma, hemoglobin, and erythrocyte substitutes (including microencapsulated hemoglobin or artificial red blood cells), other artificial cell types (including hepatocytes and pancreatic islet cells), and relevant therapeutic modalities, such as hemosorption, hemodialysis and hemoperfusion, have been summarized by Chang (*22*), the inventor of microencapsulation.

## Standardization of Biomedical Devices

An overview on the standardization and control of biomedical devices has recently been collated by D. G. Singleton (*12*). Papers have covered in depth the FDA Premarket Approval Process (J. L. Ely) and FDA regulations governing Class III devices (*23*). Two papers have described how the National Bureau of Standards, American Dental Association, National Institute of Dental Research, and private dental companies have collaborated in a number of important advances in dental materials, devices, and analytical systems (*24*).

## Bone Graft Substitutes

Over the years P. J. Boyne has defined the parameters essential for the integration of bone implants, that is, their incorporation by host bone (*25*). Calcium phosphate (TCP) or hydroxylapatite (HA) bioceramics can be placed in bone defects in non–load bearing or low-stress areas and may promote infiltration by host bone. Even though the implanted material may be resorbed to some extent, the integrity of the implant may be maintained by its infiltration with, and chemical bonding to, bone. Composites of these bioceramics with fibrillar collagen, or autologous or banked bone were shown to be successful in certain craniofacial and orthopedic defects. In certain procedures, slivers of bone containing osteoprogenitor cells or autologous cultured osteoblasts may promote bone infiltration. Plaster of Paris, calcium sulfate hemihydrate, can be used as a binder for hydroxylapatite particles (*9, 26*). Although the plaster is resorbed in a period of weeks, it is replaced at the same rate by the infiltration of fibrovascular tissue that maintains the integrity of the implant (*27*). This connective tissue may later be converted to bone. These implants can be used to repair periodontal osseous defects. Teeth that ordinarily would have been extracted as a result of these defects can now be saved by implantation with the plaster/hydroxylapatite composite (R. A. Carnevale, C. M. Bullard, G. W. Greco, and J. Hanker). These implants also appear to be beneficial for certain endodontic (periapical and endo-perio) bony lesions. In two types of endodontic periapical defects, one of which is very large and the other in which dehiscence is present, the prognosis for tooth retention postsurgically is very low. After HA/plaster implantation, however, the prognosis is considerably improved (R. D. Lewis, R. A. Carnevale, B. L. Giammara, and J. Hanker). HA/plaster implants are also valuable for cranioplasty inasmuch as the implantation procedure is much simpler than that required when methacrylate is employed. These composite implants become infiltrated with, and incorporated into, new bone even in the skull [see (*28*) and paper by Hanker *et al.* (*12*)]. Rounded HA particles are considered less likely to elicit an inflammatory response than those having sharp edges (*29*). The use of bone substitutes consisting of fibrillar collagen and HA/TCP (M. Uratsuji, T. W. Bauer, and S. I. Reger), ceramic/bone composites (M. B. Habal), and porous HA (E. C. Shors, E. W. White, and G. Kopchok) have also been described. Bone infiltration was much more rapid in porous HA/plaster than in dense HA/plaster implants (S. A. Fredette *et al.*). Research was also done on intraosseous devices placed in HA-implanted defects (P. J. Boyne and P. M. Scheer), on biodegradable TCP-containing bone cements (T. N. Gerhart *et al.*), and on factors affecting strength performance of HA/plaster implants (T. R. Devine and K. A. Johnson). Research on HA/silver phosphate ceramics (K. Hangst; J. Eitenmuller, K. Hangst, G. Peters, and W. Golsong), on resorbable TCP/amino acid composites (L. M. Morris and P. K. Bajpai), and on computergraphic analysis of the efficacy of HA implant procedures (A. Molina *et al.*) was also described. Studies were also done on the effects of blood and marrow components on the setting of calcium phosphate cement binders for HA particles (R. Noecker *et al.*) and on the effects of compression on the mechanical and physical properties of composite HA/plaster implants (K. Cowden *et al.*).

## Tissue/Biomaterial Interface

The events occurring at this juncture are of prime importance for the incorporation and durability of biomaterial implants (*1*). Recent publications have gone into further detail on important factors present in tissue at the interface and on the properties of the surfaces of biomaterials that contribute to the successful integration of implants [(*30, 31*); see also paper by J. E. Lemons (*12*)]. Many papers focusing on individual aspects such as platelet-biomaterial interactions, endothelial cell-prosthetic vessel interactions, and the competition between bacteria and host cells on the biomaterial surface have appeared (*4, 32*). Analytical and high-resolution elec-

tron microscopy studies of cells growing on metal substrates are of interest (N. A. Coombs, R. M. Pilliar, and G. C. Weatherly) as is a new technique, low-voltage scanning electron microscopy. The latter appears to be particularly useful for the surface analysis of prosthetic devices (E. Goldberg, M. Yalon, and W. E. Longo). Surface-sensitive analytical techniques that permit near-atomic resolution of either the outermost layer or a few atomic layers of material surfaces have been reviewed (*33*).

The surfaces of different biomaterials such as ceramics and polymers apparently provoke different morphologic changes in cultured osteoclasts because of different functional challenges (J. T. Lambrecht, R. Ewers, A. Kerscher, and R. Jentzsch). An in vitro system for measuring platelet reactivity of biomaterials for use in vascular grafts has been described (R. Connolly, N. Schoenfeld, K. Ramberg, and A. D. Callow). A baboon model for screening the same interactions in vivo has also been developed (A. Yeager *et al.*). Special methods that facilitate study of the bacterial-biomaterial interface in implant specimens and even permit direct morphologic identification of some of the principal microbial pathogens have been described (B. Giammara *et al.*).

## Controlled Drug Delivery

Biomaterials and biomedical devices are improving at such a rate that it might be expected that in the future they will be used to treat many ailments currently approached with drugs and routine surgery. But the design and synthesis of new medicinal agents by synthetic chemistry, molecular engineering, biotechnology, and genetic approaches are also entering an era of increased sophistication and rapid progress. Moreover, the development of these new agents has been accompanied by similar sophistication in systems for their controlled release and delivery. Recent reviews (*34*) have covered many different types of approaches now available for the targeted, sustained, and controlled delivery of medicinal agents. Again, this has been made possible by the collaboration of pharmacologists, medicinal chemists, polymer chemists, immunobiologists, biochemists, and engineers. Systems have been described where liposomes, macromolecules, bioactive polymers, or ceramics are used for targeted as well as controlled or sustained delivery. The feasibility of an implanted, miniaturized semiconductor laser–based system for glucose estimation in conjunction with insulin pump therapy has been demonstrated (I. C. Arrieta, D. E. Burk, and C. Batich). A dressing for burn wounds for the release of silver sulfadiazine in a controlled-sustained fashion has also been described (L. M. Miller and J. F. Hansbrough). A unique microencapsulation procedure for forming bilayer and liposome-like systems similar to the one described (*35*) for forming artificial red cells (neohemocytes) has also been developed (R. D. MacGregor, N. Taylor, and C. A. Hunt). Indeed, artificial cells containing various enzyme or multienzyme systems have been synthesized (*36*). Their sizes vary from that of true cells to that of soluble cross-linked proteins (*37*). They have been studied for routine treatment of acute poisoning and chronic renal or fulminant hepatic failure. They are also under investigation in animals for the therapy of hereditary enzyme deficiencies, diabetes, and other metabolic disorders.

The microencapsulation of cultured human cells such as islet cells or hepatocytes in biocompatible, protective synthetic membranes appears to diminish their immunologic rejection. On the other hand, the microencapsulation of enzymes as liposomes appears to enhance the immune response to the entrapped protein (*38*) although there is an advantage in that liposomes are biodegradable. Injectable and oral microsphere, microcapsule, and liposome systems are under development where the drug is released gradually and the encapsulated microparticle is engineered to attach to specific cells. The active ingredient is not released until it is ingested by the target cells; this reduces overall toxicity of the agent.

In addition to the microparticles described above, systems employing biodegradable polymers and other matrices in larger dimensions for the release of therapeutic agents are under investigation (*39*). Thus skin sponges known as microsponges can be used to release skin lotion or topical antibiotics. Transdermal patches have been approved by the FDA for the continuous release of drugs for motion sickness or heart disease. Contact lenses and biodegradable eye patches are being studied for the improved delivery of antibiotics and other eye medicaments. Match-size capsules implanted subdermally, vaginal rings, and biodegradable implants are under study for long-term controlled release of contraceptives. Biodegradable or bioresorbable polymers as the matrices for such implants eliminate the need for surgery to remove the device. The polyanhydrides are a class of biocompatible, biodegradable polymers that appear particularly suited for drug delivery (*40*). They can be produced in rigid or flexible forms as either disks, rods, microspheres, or flexible sheets. Their biodegradation times can be tailored to range from a few days to a few years. They can be used to deliver the usual drugs as well as peptides and proteins such as insulin or enzymes. They have been approved for experimental use by the FDA and are currently under study as 1-inch-diameter implants for increasing dopamine levels in brains of Parkinson's disease patients and also for the delivery of chemotherapeutic agents directly to brain tumors (*39*).

## Novel Materials and Techniques

The hydrothermal synthesis of hydroxylapatite by zirconia dispersion is reported to form an exceptionally dense and tougher material (K. Ioku, M. Yoshimura, and S. Somiya). New low toxicity epoxy-diepisulfide-polyamide resins have been produced with adjustable setting times; they show potential for dental and orthopedic applications (I. N. Hadjinikolaou, J. P. Bell, and L. Spangberg).

Hyaluronic acid is a high molecular weight polysaccharide composed of repeating subunits of glucuronic acid and glucosamine. This polymeric material is widely distributed in connective tissues and cartilage and is an important tissue lubricant (*41*). In physiologic solutions, sodium hyaluronate (NaHA) molecules act like stiff random coils. The coils become rod-like as the *p*H is lowered and expand as it is elevated (*42*). Thus the rheologic and viscoelastic properties of NaHA make it ideal for use as a sponge-like biomaterial (*43*). It is currently used in cataract surgery to maintain tissue separation and to cushion the cornea from mechanical damage. The ability of the coils to store mechanical energy, or the elasticity of hyaluronate, is of particular importance in its use as an interarticular implant in damaged joints. These properties and their importance in the use of NaHA solutions as implants are thoroughly discussed in a recent paper (D. P. DeVore and S. A. Loftus).

The use of polyvinyl alcohol and other synthetic polymers of optimum viscosity (10 to 25 cP) as lubricant films for ophthalmic use in "dry eye" syndrome and in cataract surgery have also been reported (S. Kalachandra and D. O. Shah).

## Bone as a Biomaterial

In experimental studies of bone as a biomaterial, an understanding of the fracture mechanics of bone can be helpful (*44*). The use of very small specimens in these studies can lead to inaccurate results because of material heterogeneity (D. D. Moyle).

Also important for the use of bone as a biomaterial is a materials characterization of the extracellular matrix of living bone. An analysis and review of the effects of extracellular fluid on the electrical and electromechanical properties of bone have been collated from in vitro and in vivo studies (D. A. Chakkalakal).

A comparison of the relationship between the structure and elastic properties of normal and pathologic bone by ultrasonic techniques could help define some of the requirements for utilizing bone as a biomaterial (J. L. Katz *et al.*). Ultrasonic techniques appear to be important in evaluating bone remodeling about femoral prostheses in total hip arthroplasty (M. Zimmerman *et al.*). A study has been done on the importance of biomechanical factors at the tissue-biomaterial interface for fixation of bony implants (J. Brunski). Relative motion and interfacial stresses and strains appear to be the more important factors.

Osteoporosis or the loss of bone mass in persons over 40 might be expected to present a special problem for the fixation of implants such as porous-coated hip prostheses. A detailed study in dogs with nutritional secondary hyperparathyroidism, a model for osteoporotic bone, suggests that this is not the case. The results of this study suggest that stress-induced bone remodeling and ingrowth override the slower osteoporotic process (K. A. Thomas, S. D. Cook, M. A. Kester, and A. F. Harding).

## Orthopedic Materials and Prostheses

Excellent articles have appeared on the surface modification and tribology of orthopedic and joint prosthesis materials and devices (*45*) and on the mechanical properties of load-bearing implants (*46*). Bone formation has been seen adjacent to porous-coated alloys, such as those obtained by coating cobalt-chromium-molybdenum implants with a porous layer of beads, and next to intraosseous titanium implants (P. J. Boyne). In the latter study interface bone formation was studied by different modes of microscopy after the implantation of eight varieties of titanium prostheses (screw-type, vented-cylinder, smooth-surfaced, HA-coated, or plasma spray-coated) in the femurs of baboons. Good osteointegration was obtained with all of the implants with the exception of smooth-surfaced titanium. New analytical methodology has been developed for evaluating orthopedic implants or prosthetic devices by computer graphic analysis for fracture resistance. In addition, biodegradable polymeric biomaterials for internal fixation of fractures have been described. These eliminate diminished bone formation due to "stress-shielding" that is observed when metal plates are used. The most promising of these materials appear to be the biocompatible and biodegradable polyesters such as polylactic and polyglycolic acids, their copolymers, and polydioxanone (PDS). They can be tailored to any degree of hardness, tensile strength, flexibility, and degradation rate required (*47*). These materials as compression-molded plates with screws of the same polyester give excellent results for internal fracture fixation. They are also promising when reinforced with high-strength carbon fibers to produce partially degradable bone plates for internal fracture fixation. Flexible, degradable polyester fibers reinforced with carbon fibers are also under study for tendon and ligament repair. There is no question that in the near future many bone defects will be implanted more satisfactorily and with less trauma to the patient with biomaterials than with autogenous bone. This will eliminate the need for secondary surgery to obtain the graft. Moreover, sintered ceramic implants show much less tendency to be resorbed than autogenous bone grafts. There is even some question as to whether or not homologous or banked bone could be a source of human immunodeficiency virus (HIV) infection.

The finite element method in biomechanics is useful for predicting the stress state in bone as well as for the stress analysis of orthopedic devices (J. B. Koeneman). Inasmuch as electrical stimulation is finding greater use to enhance healing in treatment of fractures, there has been interest in whether or not this affects the corrosion of stainless steel internal fixation devices. In vitro studies suggest that at a 95 percent confidence level the stimulator does not affect the corrosion of certain of these devices (B. Edwards, J. Posey-Dowty, and P. Higham).

The fixation or permanent attachment of metallic hip or knee prostheses to bone can now be done by biologic fixation rather than bone cement (*48*). There is a need for materials other than metal to attach to bone. A study was performed (E. C. Shors, G. W. White, and G. Kopchok) comparing the ingrowth of bone into porous implants of metals, vitreous carbon, silicone rubber, or hydroxylapatite (HA). The implants of these different materials were manufactured to nearly identical macroscopic morphologies (and pore size ranges) with the Replamineform process (*49*). More bone grew into porous HA than the other porous materials. Metal implants with HA-coated pores also showed greater bone ingrowth and bonding (E. C. Shors, G. W. White, and G. Kopchok).

The application of porous metallic coatings to cast Vitallium$^{R}$ alloy appeared to result in a superior femoral hip prosthesis than its application to stems of other alloys (L. Gustavson, T. Crippen, and J. H. Dumbleton). Polymethylmethacrylate (PMMA)-based bone cements are routinely used for fixation of total joint replacements. The fracture of bone cement, however, appears to be a major factor in fixation failure resulting from implant loosening. A toughness test to assess the fracture resistance of bone cements is therefore of interest (R. M. Pilliar and C. T. Wang).

## Dental Materials

A castable glass-ceramic system became available for commercial use for the fabrication of dental restorations such as crowns in 1984 (*50*). Another glass-ceramic system called castable apatite ceramic (*51*) is similar in composition and crystalline structure to enamel and may be available soon. The successful use of resin dentine-bonding agents as root canal sealers has been reported although evidence of their long-term efficacy is lacking. These developments have been reviewed by Brackett and Duncanson (*12*).

Recent studies suggest that the complex dielectric properties of tooth constituents could be important in tooth formation, in caries, in other enamel and dentine problems, and in the healing of tooth fracture. There appears to be some correspondence to observations in bone formation, defects, and healing (J. V. Masi and L. C. Masi). Polymer composites are the most popular materials in use for anterior tooth restoration. Their load-bearing abilities depend upon their microstructure and mechanical properties such as elasticity. These can be readily assessed by x-ray diffractometry and scanning electron microscopy including energy-dispersive spectroscopy (EDS) (S. Singh, J. L. Katz, J. Antonucci, and J. A. Tesk).

Unlike polymers and ceramics, metals are degraded by tarnish and corrosion. These reactions involve electrochemical charge transfers, and the magnitude of the current determines the extent of degradation. In these degradative reactions, the charge transfers and the currents are strongly influenced by salivary proteins adsorbed on the surfaces of crown and bridge alloys. The formation of corrosion products with inorganic components may mask the positive charges of proteins and decrease their adsorption.

The relatively poor wear resistance of dental composite resins (*52*) limits their utility for stress-bearing posterior applications. Scanning electron microscopy studies suggest that the use of resins with

enhanced adhesion to fillers might increase the fracture toughness of these materials (J. L. Ferracane).

Bioglass or biocompatible glass coatings have been used by a number of investigators in an attempt to improve the bony anchoring of stainless steel cobalt-based titanium alloys or alumina ceramics. Poor bonding of the glass coating to the alumina substrate of the implant is often observed. Perfect adherence can be obtained, however, at 1400°C (D. Muster *et al.*).

The current clinical use of hydroxylapatite/plaster composites for bone defects discussed above has shown the advantage of having a material that is malleable during placement, hardens quickly after implantation, and becomes incorporated into host bone. This stimulated interest in the development of a calcium strontium phosphate glass powder that can be mixed with an appropriate liquid that allows it to be implanted when in the plastic stage. But the mixture is also able to harden readily like acrylic bone cements (W. S. Chen and E. A. Monroe).

A detailed review of all aspects of dental materials has recently appeared (*53*).

## New Directions for Processing Prostheses, Implantable Devices, and Their Analysis

Neural prostheses are, or will be, finding increasing use for restoring partial functions of muscles in paralyzed limbs and some degree of hearing in selected deaf people. These devices are subjected to a number of biological rejection processes as well as corrosion. It is therefore important to find durable, biocompatible polymeric coatings that will provide electrical isolation or insulation of the covered circuits. Polyamide coatings appear to offer promise for this purpose (R. N. Leyden).

Pure titanium is perhaps the most biocompatible inorganic material. Another consideration in the widespread use of titanium alloys as the anchorage part in artificial hip joints is their better machining and mechanical properties. The biocompatibility of titanium implants and their adhesion properties are associated with their passivating surface oxide (*54*). Analytical techniques for surface analysis (*55*), x-ray photoelectron spectroscopy (XPS), Auger electron spectroscopy (AES), and secondary ion mass spectroscopy (SIMS) show that the elements of the titanium alloys are present in their surface oxides (B. Kasemo, M. Ask, J. Lausmaa, and U. Rolander). Transmission electron microscopy (TEM) and scanning transmission electron microscopy (STEM) studies show that the oxides of the Ti-6Al-4V alloy have a more complex microstructure and a different crystallinity. These properties could affect the biocompatibility of these titanium alloy implants.

Two processes have been studied in an attempt to smoothen the surfaces of small diameter polymeric vascular implants to diminish the adherence of platelets and leukocytes that result in thrombosis (D. A. Wrobleski *et al.*). The surfaces of PMMA samples were treated by a chemical infusion process, that is, with a solution containing polyvinylpyrrolidone (PVP). Surfaces of silicone rubber samples were coated with titanium dioxide by an ion beam sputtering technique. Only the PMMA samples showed smoother surfaces by SEM analysis and better blood compatibility by two bioassays.

## Effects of Ion Implantation on Biomaterials

This treatment can modify the surfaces of biomaterials by the introduction of almost any ion in the periodic table (*56*). This can increase corrosion resistance, fatigue resistance, and hardness. Ion implantation can improve the surface properties of glassy carbon by several orders of magnitude so that it has similar wear resistance to pyrolytic carbon (L. S. Wielunski). This could increase its potential for use in tooth, bone, and heart valve replacement. The results of a detailed study of the effects of $C^+$, $Ar^+$, $N_2^+$, and $O_2^+$ ion implantation on the adsorption of plasma proteins such as albumin and fibrinogen on silicone rubber have also been presented (Y. Suzuki *et al.*). Papers have appeared on various aspects of the modification of the surfaces of titanium or titanium alloy orthopedic prostheses by ion beam implantation (*57*). Of particular interest are the effects on cell adhesion (K. S. Grabowski, F. A. Young, and J. C. Keller) and wear (Z. Xiaozhong and O. Qin). The effects of implantation of surgical alloys with rhodium resulted in short- and long-term improvements in corrosion resistance (R. A. Buchanan, I.-S. Lee, and J. M. Williams). Calcium hydroxylapatite has been sputtered on glass and Ti-6Al-4V substrates with a 1.5-kV argon ion beam (B. L. Barthell and T. Archuleta) and on metals and polymers by a combination of radio-frequency sputter and ion implantation techniques (J. R. Stevenson, H. Solnick-Legg, and K. O. Legg). It is expected that enhanced load-bearing fixation could result with such orthopedic devices.

## Artificial Organs: Devices for Therapeutic Plasmapheresis, Cytapheresis, and Dialysis

It was recently pointed out (Y. Nose and P. Malchesky) that although serious experimentation in artificial organs has occurred only for 35 years, their current therapeutic use is enormous. In the United States nearly 13 million procedures are performed annually. Worldwide, relatively few total artificial heart or cardiac prostheses (about 300, mostly as a bridge to cardiac transplantation) are performed. Insulin perfusion pumps are now used in approximately 10,000 patients. Worldwide, 10,000 heart valve, 300,000 pacemaker, 400,000 orthopedic prosthesis, and 400,000 blood oxygenator procedures are performed annually; and about 300,000 patients are living by virtue of artificial kidneys. In the future the number that will be kept alive by improved and by even more sophisticated biomaterials, devices, and procedures is inestimable.

Affinity adsorbents or immunoadsorbents have been investigated experimentally and clinically for blood purification by the selective removal of pathogenic macromolecules in the treatment of immune diseases such as rheumatoid arthritis, myasthenia gravis, systemic lupus erythematosus, and multiple sclerosis (Z. Yamazaki *et al.*). The same investigators employed a special filter for absorptive cell separation to achieve leukocyte-free blood transfusions. A filter for cytapheresis has also been developed. These developments offer promise for the immunomodulation of immune diseases.

The presence of specific cell membrane receptor molecules certainly offers an approach to the separation and purification of cell populations for medical and biotechnological purposes. Cell affinity chromatography utilizes this principle but often physical factors such as van der Waals, electrostatic, and fluid-mechanical forces affect the cell adhesiveness and selectivity (D. A. Lauffenberger and D. A. Hammer).

It is generally acknowledged that artificial biomaterials are much less immunologically active than transplants or tissue-derived biomaterials. The propensity of certain biomaterials, however, to interact with the complement system and produce the inflammatory mediators C3a and C5a that interfere with successful hemodialysis has recently been recognized (R. J. Johnson and D. E. Chenoweth). The design of dialysis membranes that are more compatible and the development of methods to measure their degree of complement activation should result in better hemodialysis device performance. Therapeutic plasmapheresis, that is, removal of pathologic protein

macromolecules such as immune complexes, cryoprecipitable proteins, and low density lipoproteins from essential plasma proteins can be achieved more effectively by membrane filtration than by plasma exchange (P. S. Malchesky, Y. Nose, and T. Horiuchi).

Another device that appears to be very effective for the selective removal of abnormal macromolecules from plasma is the Prosorba$^R$ Treatment Column. It consists of highly purified protein A (isolated from *Staphylococcus aureus*) covalently linked to inert silica housed in a polycarbonate device. The protein A immunoadsorbent selectively removes circulatory immune complexes, immunoglobulin G, and autoimmune antibodies from the plasma of patients with certain malignancies and autoimmune diseases (*58*). The column has been effective, for example, in eliciting antitumor responses in end-stage breast cancer patients and in increasing platelet counts in patients with immune platelet deficiency.

It has recently been noted that many devices utilized in blood storage and transfusion, as well as devices used in medical and surgical procedures, are manufactured with polyvinylchloride (PVC) plastic. The latter contains a plasticizer that produces a toxic metabolite that also has carcinogenic effects. The most common source of the toxin is blood that has been collected and stored in flexible PVC containers (*59*).

The standard hemodialysis machine propels a balanced salt solution and the patient's blood through opposite sides of cellulose membranes. Since 1984 a dialysis system has been undergoing development that will use different disposable sorbent packs to treat patients with liver or respiratory failure as well as patients with kidney failure (*60*). This could be a very significant contribution to the treatment of many thousands of patients annually.

## Implantable Electrical Devices

These devices or prostheses are being developed to assist or augment many body processes. They are in use or under study for cardiac pacemaking, bone growth and repair, hearing aids, automated drug delivery systems for diabetes, pain control and cancer chemotherapy, defibrillation, cardiac assist and the artificial heart, central nervous system stimulation to treat epilepsy and multiple sclerosis, peripheral nerve or gut stimulation, pain control, scoliosis treatment, artificial vision (*61*), and biosensing (*62*). Although most of these items may not be in general use until the 1990s, it is expected that they will represent a substantial market because they will probably have a greater unit cost than the pacemaker. The successful widespread use of the cardiac pacemaker has led to the development of the automatic implantable defibrillator, a related device that has been successfully implanted in over 300 individuals in clinical trials (*61*).

Biosensors such as glucose and lactate electroenzymatic systems are being widely applied in vitro in clinical medicine for glucose (*63*) and lactate (*64*) analysis. The in vivo use of glucose electrodes for the control of insulin pumps and lactate sensors for controlling cardiac pacemakers or defibrillators will occur when stabilization of these sensing devices in contact with body fluids at room or body temperature is achieved (*65*). It is expected that their widespread use as intravascular biosensors in critical care medicine will stem from these studies of Leland C. Clark, Jr. (who also introduced fluorocarbons as potential blood substitutes), and his co-workers since 1962 on enzyme electrodes. The potential use of biosensors in veterinary medicine, animal husbandry, fermentation monitoring, and biological and chemical warfare defense are also noteworthy (*66*). Bioelectrodes, biocatalytic membrane electrodes, and other biosensors appear to have potential use in renal disease, arthritis, blood gas determination, and the measurement of many other molecules, including immunoglobulins and circulatory immune complexes (CIC) for the critical care or management of patients (*66*). It is envisaged that certain of these immunobiosensors could eventually be used in conjunction with the Prosorba$^R$ Treatment Column. This column (which was approved by the FDA in December 1987) can effect the selective removal of immunoglobulin G, CIC, and autoimmune antibodies resulting in tumor regression, autoantibody clearance, and immune modulation as discussed above (*58*).

## Artificial Lymph Gland

A form of cancer biotherapy in which there has been much recent interest is adoptive cellular immunotherapy (*67*). This promising cytapheresis approach involves the readministration of a leukocyte subset whose cytotoxicity toward malignant cells has been augmented by treatment with biological compounds outside of the body. Thus autologous interleukin-2–activated lymphocytes, especially when administered concomitantly with recombinant interleukin-2, have resulted in tumor regression or remission in a number of advanced cancers (*68*).

Gamma interferon administered in vivo generally lacks antitumor activity although it can be used successfully against certain leukemias and lymphomas (*69*). Some success has been achieved, however, in patients with metastatic colorectal carcinoma by adoptive immunotherapy (*70*). The patient's leukocytes are harvested. The monocytes are then separated and activated by culturing with clinical grade human gamma interferon. The readministration of these activated killer monocytes can be supplemented by the daily administration of recombinant gamma interferon to maintain the activity of the monocytes (*71*). This therapeutic modality is acting essentially like an artificial lymph gland (*72*).

## Conclusions and Future Directions

There is no question that the interaction of materials scientists with biomedical, bioengineering, biotechnological, and clinical scientists in the last decade has resulted in a large number of advances in therapeutic modalities that are life-facilitating (or supporting) for hundreds of thousands of individuals. All of us know, for example, people who have benefited in the last few years from some type of artificial organ such as porous-coated implants for total hip or total knee replacement, or artificial kidney, or blood oxygenator procedures. Even cancer adoptive immunotherapy has resulted in a new artificial organ—the artificial lymph gland. It is anticipated that adoptive immunotherapy alone will soon become standard therapy for a number of problems other than malignancy. All of us will receive help in the near future by devices that will permit us to get our insulin, contraceptive, or heart pill once each month instead of daily. New bioengineering methods and devices for the continuous removal of toxins or pathologic products present in arthritis, atherosclerosis, and malignancy will also be available.

Implants to take the place of therapies currently performed by extracorporeal devices will be possible when further miniaturization of micromechanical and microelectronic devices is achieved.


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