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Bioceramics

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Ceramics used for the repair and reconstruction of diseased or damaged parts of the musculo-skeletal system, termed bioceramics, may be bioinert (e.g., alumina and zirconia), resorbable (e.g., tricalcium phosphate), bioactive (e.g., hydroxyapatite, bioactive glasses, and glass-ceramics), or porous for tissue ingrowth (e.g., hydroxyapatite-coated metals). Applications include replacements for hips, knees, teeth, tendons, and ligaments and repair for periodontal disease, maxillofacial reconstruction, augmentation and stabilization of the jaw bone, spinal fusion, and bone repair after tumor surgery. Pyrolytic carbon coatings are thromboresistant and are used for prosthetic heart valves. The mechanisms of tissue bonding to bioactive ceramics have resulted in the molecular design of bioceramics for interfacial bonding with hard and soft tissue. Bioactive composites are being developed with high toughness and elastic modulus that match with bone. Therapeutic treatment of cancer has been achieved by localized delivery of radioactive isotopes via glass beads. Clinical success of bioceramics has led to a remarkable advance in the quality of life for millions of people.

I. Introduction

MANY millennia ago, the discovery that fire would irreversibly transform clay into ceramic pottery led to an agrarian society and an enormous improvement in the quality and length of life. Another revolution has occurred in the use of ceramics during the past four decades to improve the quality of life. This revolution is the innovative use of specially designed ceramics for the repair, reconstruction, and replacement of diseased or damaged parts of the body. Ceramics used for this purpose are termed ''bioceramics.'' Bioceramics can be polycrystalline (alumina or hydroxyapatite), bioactive glass, bioactive glass-ceramic (A/W), or bioactive composite (polyethylene–hydroxyapatite).

Many specialty ceramics and glasses have been developed during this century for use in the health care industry, e.g., eyeglasses, diagnostic instruments, chemical ware, thermometers, tissue culture flasks, fiber optics for endoscopy, and carriers for enzymes and antibodies.[1] Ceramics also are used widely in dentistry as restorative materials, gold porcelain crowns, glass-filled ionomer cements, dentures, etc. The materials used in these applications are called dental ceramics.[2]

This review is devoted to the use of bioceramics as implants to repair parts of the body, usually the hard tissues of the musculo-skeletal system, such as bones, joints, or teeth, although use of carbon coatings for replacement of heart valves also is included. Many ceramic compositions have been tested for use in the body;[1,3] however, few have achieved human clinical application. Clinical success requires the simultaneous achievement of a stable interface with connective tissue and a match of the mechanical behavior of the implant with the tissue to be replaced. Only the few bioceramics that meet these severe requirements for clinical success are emphasized in this review. Historical developments of bioceramics have been presented by Hulbert *et al.*[3]

(1) Need for Bioceramics

Bioceramics are needed to alleviate pain and restore function to diseased or damaged parts of the body. A major contributor to the need for ''spare parts'' for the body is the progressive deterioration of tissue with age. Bone is especially vulnerable to fracture in older people because of a loss of bone density and strength with age.[4] Figure 1 summarizes the effect of time on bone strength and density from the age of 30 years onward. The effect is especially severe in women because of hormonal changes associated with menopause. Bone density decreases because bone-growing cells (osteoblasts) become progressively less productive in making new bone and repairing microfractures. The lower density greatly deteriorates the strength of the porous bone, called trabecular or cancellous bone (Fig. 2), in the ends of long bones and in vertebrae. An unfortunate consequence is that many old people fracture their hips or have collapsed vertebrae and spinal problems.

The great challenge facing the use of ceramics in the body is to replace old, deteriorating bone with a material that can func-

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centennial feature

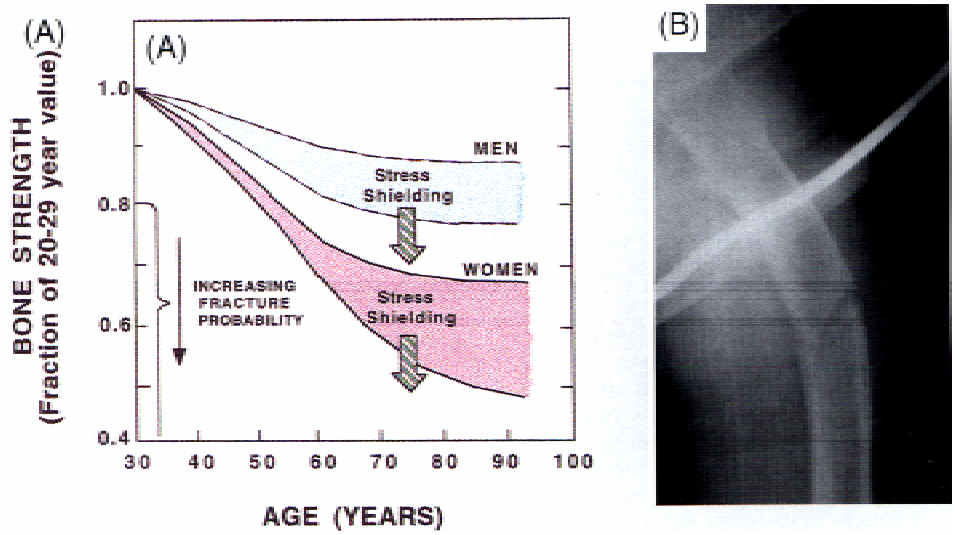


Fig. 1. (A) Effect of age on the strength of bone and probability of fracture. (B) Fractured femoral (thigh) bone caused by osteoporosis, which weakens bone. Stress shielding causes a further decrease in bone density and strength.

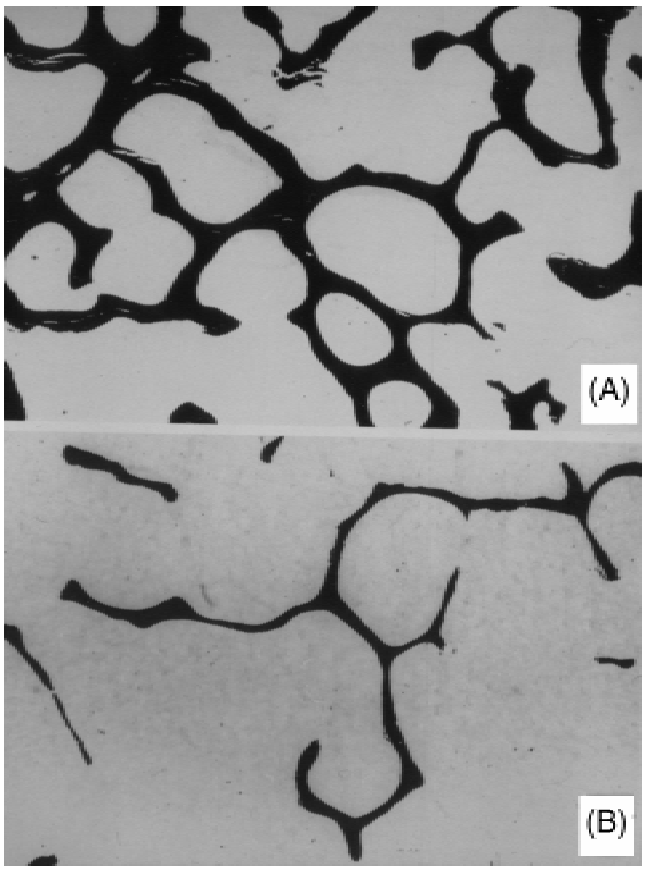


Fig. 2. Trabecular bone structure: (A) normal 30 year old woman and (B) Osteoporotic 60 year old woman. (Photo courtesy of Professor Peter Revell, Royal Free Hospital School of Medicine.)

tion the remaining years of the patient's life. Because the average life span of humans is now 80+ years and the need for spare parts begins at about 60 years of age, bioceramics need to last for 20+ years. This demanding requirement of survivability is under conditions of use that are especially harsh to ceramic materials: corrosive saline solutions at 37°C under variable, multiaxial, cyclical mechanical loads. The excellent performance of the specially designed bioceramics that have survived these clinical conditions represents one of the most remarkable accomplishments of ceramic research, development, production, and quality assurance during this century.

(2) Types of Bioceramic-Tissue Attachments

Survivability of a bioceramic requires formation of a stable interface with living host tissue. The mechanism of tissue attachment is directly related to the type of tissue response at the implant interface.[1,4,5] No material implanted in living tissues is inert; all materials elicit a response from living tissue. The four types of response (Table I) allow different means of achieving attachment of prostheses to the musculo-skeletal system. Table II summarizes the attachment mechanisms, with examples.

A comparison of the relative chemical activity of these different types of bioceramics is given in Fig. 3. The relative reactivity shown in Fig. 3(A) correlates very closely with the rate of formation of an interfacial bond of implants with bone (Fig. 3(B)).[4] Figure 3(B) is discussed in more detail in the section on bioactive ceramics.

The relative level of reactivity of an implant influences the *thickness* of the interfacial zone or layer between the material and tissue. Analysis of failure of implant materials during the past 20 years generally shows failure originating from the biomaterial–tissue interface.[4,5] When biomaterials are almost inert (type 1 in Table II and Fig. 3) and the interface is not chemically or biologically bonded, there is relative movement, and progressive development of a nonadherent fibrous capsule occurs in both soft and hard tissues. Movement at the biomaterial–tissue interface eventually leads to deterioration in function of the implant or of the tissue at the interface or of both. The thickness of the nonadherent capsule varies greatly, depending upon both the material (Fig. 4) and the extent of relative motion.

The fibrous tissue at the interface with dense, medical-grade Al_2O_3 implants can be very thin.[3,6] Consequently, if Al_2O_3 implants are implanted with a very tight mechanical fit and are loaded primarily in compression, they are successful clinically. In contrast, if an almost inert implant is loaded such that in-

Table I. Types of Implant–Tissue Response

If the material is toxic, the surrounding tissue dies.
If the material is nontoxic and biologically inactive (almost inert), a fibrous tissue of variable thickness forms.
If the material is nontoxic and biologically active (bioactive), an interfacial bond forms.
If the material is nontoxic and dissolves, the surrounding tissue replaces it.

Table II. Types of Bioceramic Tissue Attachment and Bioceramic Classification

Type of attachment	Type of bioceramic
Dense, nonporous, almost inert ceramics attach by bone growth into surface irregularities by cementing the device into the tissue, or by press-fitting into a defect (morphological fixation).	Al_2O_3 ZrO_2
For porous implants, bone ingrowth occurs, which mechanically attaches the bone to the material (biological fixation).	Porous hydroxyapatite Hydroxyapatite-coated porous metals
Surface-reactive ceramics, glasses, and glass-ceramics attach directly by chemical bonding with the bone (bioactive fixation).	Bioactive glasses Bioactve glass-ceramics Dense hydroxyapatite
Resorbable ceramics and glasses in bulk or powder form designed to be slowly replaced by bone.	Calcium sulfate (plaster of Paris) Tricalcium phosphate Calcium phosphate salts Bioactive glasses

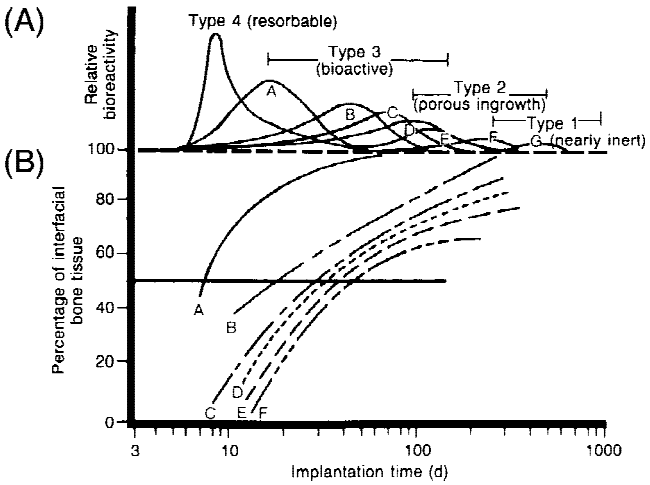


Fig. 3. Bioactivity spectrum for various bioceramic implants: (A) relative rate of bioreactivity and (B) time dependence of formation of bone bonding at an implant interface, where A is 45S5 bioactive glass, B is KGS glass-ceramic, C is S53P4, D is A/W glass-ceramic, E is dense synthetic HA, F is KGX glass-ceramic, and G is Al_2O_3.

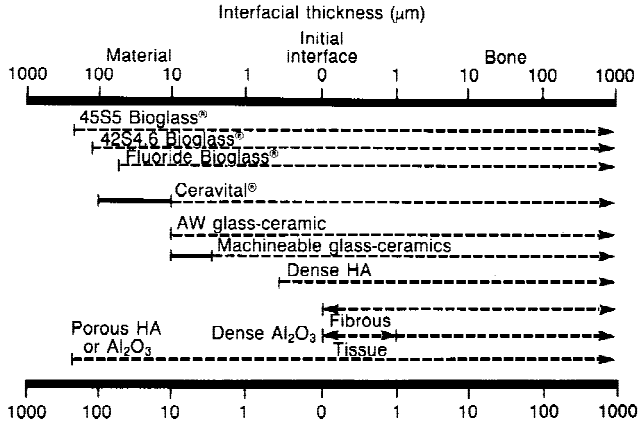


Fig. 4. Comparison of interfacial thickness of reaction layer of bioactive implants bonded to bone or thickness of nonadherant fibrous tissue in contact with inactive bioceramics in bone.

terfacial movement can occur, the fibrous capsule can become several hundred micrometers thick, and the implant loosens quickly. Loosening invariably leads to clinical failure, for a variety of reasons, including fracture of the implant or the bone adjacent to the implant. Bone at an interface with an almost inert implant is very often structurally weak because of disease, localized death of bone (especially if so-called bone cement, polymethylmethacrylate (PMMA), is used), or stress shielding that occurs because the higher elastic modulus of the implant prevents the bone from being loaded properly.

The concept behind microporous bioceramics (type 2 in Table II and Fig. 3) is the ingrowth of tissue into pores on the surface or throughout the implant, originated by Hulbert and co-workers[3] many years ago. The increased interfacial area between the implant and the tissues results in an increased resistance to movement of the device in the tissue. The interface is established by the living tissue in the pores. Figure 5 shows living bone that has grown into the pores of an Al_2O_3 bioceramic. This method of attachment often is termed ''biological fixation.'' Biological fixation is capable of withstanding more-complex stress states than implants that achieve only ''morphological fixation.'' However, the limitation associated with porous implants is that, for the tissue to remain viable and healthy, pores must be >100–150 μm in diameter. The large interfacial area required for the porosity is due to the need to provide a blood supply to the ingrown connective tissue. Vascular tissue does not appear in pores that measure <100 μm. If micromovement occurs at the interface of a porous implant, tissue is damaged, the blood supply may be cut off, the tissue dies, inflammation ensues, and the interfacial stability can be destroyed. When the material is a metal, the large increase in surface area can provide a focus for corrosion of the implant and loss of metal ions into the tissues, which can cause a variety of medical problems.[7,8] These potential problems can be diminished by using a bioactive ceramic material, such as hydroxyapatite (HA), as a coating on the porous metal.[9] The HA coating also speeds up the rate of bone formation in the pores.[9–13] However, the fraction of large porosity required for

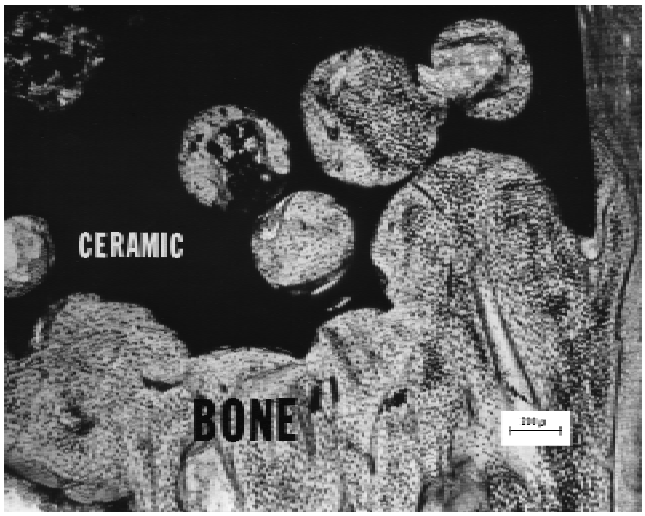


Fig. 5. Ingrowth of bone within >100 μm pores of Al_2O_3 bioceramic, after 8 weeks in rabbit. (Photo courtesy of Professor Sam Hulbert, Rose Hulman Institute of Technology.)

bone growth in any material degrades the strength of the material. Consequently, this approach to solving interfacial stability is best when the material is used as porous coatings on surgical metal alloys or as unloaded space fillers for bone ingrowth.

Resorbable biomaterials (type 4 in Table II and Fig. 3) are designed to degrade gradually over time and be replaced by the natural host tissue.[10–13] This leads to a very thin or nonexistent interfacial thickness (Fig. 4). This is the optimal solution to biomaterial problems if the requirements of strength and short-term performance can be met. Natural tissues can repair themselves and are gradually replaced throughout life by a continual turnover of cell populations. Thus, resorbable biomaterials are based on the same principles of repair that have evolved over millions of years. Complications in the development of resorbable bioceramics are

- Maintenance of strength and stability of the interface during the degradation period and replacement by the natural host tissue;
- Matching resorption rates to the repair rates of body tissues (Fig. 3(A)), which themselves vary enormously, depending upon type of tissue and its age and health.

Some resorbable materials dissolve too rapidly and some too slowly. Because large quantities of material can be replaced, it also is essential that a resorbable biomaterial consists only of metabolically acceptable substances. Otherwise, chronic inflammation and pain occur. This criterion imposes considerable limitations on the compositional design of resorbable biomaterials. Successful examples are resorbable polymers, such as polylactic–polyglycolic acid used for sutures, which are metabolized to CO_2 and H_2O and, therefore, are able to hold a wound together and then dissolve and disappear. Porous or particulate calcium phosphate ceramic materials, such as tricalcium phosphate (TCP), are successful materials for resorbable, hard tissue replacements when only low mechanical strength is required, such as in some repairs of the jaw or head.[10–13] Resorbable bioactive glasses are replaced rapidly with regenerated bone, as discussed below.

Another approach to the solution of the problems of interfacial attachment is the use of bioactive materials (type 3 in Table II and Fig. 3). The concept of bioactive materials is intermediate between resorbable and bioinert materials.[1,4,5] *A bioactive material is one that elicits a specific biological response at the interface of the material, which results in the formation of a bond between the tissues and the material,* shown first by the author and colleagues at the University of Florida in 1969.[14] This concept has been used to produce many bioactive materials with a wide range of bonding rates and thickness of interfacial bonding layers (Figs. 3 and 4). References 1, 3–5, and 15 discuss development of these interesting materials. The bioactive materials available commercially for clinical use are 45S5 bioactive glass, A/W bioactive glass-ceramic, dense synthetic HA, or bioactive composites, such as a polyethylene–HA mixture. All the above bioactive materials form an interfacial bond with adjacent tissue. However, the time dependence of bonding, the strength of the bond, the mechanism of bonding, and the thickness of the bonding zone differ for the various materials.

It is important to recognize that relatively small changes in the composition of a biomaterial can dramatically affect whether it is bioinert, resorbable, or bioactive. These compositional effects on surface reactions are discussed in the section on bioactive ceramics.

(3) Almost-Inert Crystalline Bioceramics

High-density, high-purity (>99.5%) Al_2O_3 (α-alumina) was the first bioceramic widely used clinically. It is used in total hip prostheses and dental implants because of its combination of excellent corrosion resistance, good biocompatibility, low friction, high wear resistance, and high strength.[1,3,6,16–18] Most Al_2O_3 devices are very-fine-grained, polycrystalline α-Al_2O_3. A very small amount of MgO (<0.5%) is used as a sintering aid and to limit grain growth during sintering.

Strength, fatigue resistance, and fracture toughness of polycrystalline α-Al_2O_3 are a function of grain size and concentration of sintering aid, i.e., purity. Al_2O_3 with an average grain size of <4 μm and a purity of >99.7% exhibits good flexural strength and excellent compressive strength. These and other physical properties are summarized in Table III with the International Standards Organization (ISO) requirements for medical-grade Al_2O_3 implants.[6] Extensive testing has shown that Al_2O_3 implants that meet or exceed ISO standards have excellent resistance to dynamic and impact fatigue and also resist subcritical crack growth.[19,20] An increase in average grain size to >7 μm can decrease mechanical properties by ~20%. High concentrations of sintering aids must be avoided, because they remain in the grain boundaries and degrade fatigue resistance, especially in the corrosive physiological environment.[1]

Methods exist for lifetime predictions and statistical design of proof tests for load-bearing ceramics. Applications of these techniques show that specific prosthesis load limits can be set for an Al_2O_3 device based upon the flexural strength of the material and its use environment.[19,21] Load-bearing lifetimes of 30 years at 12 kN loads, similar to those expected in total hip joints, have been predicted.[6] Results from aging and fatigue studies show that it is essential that Al_2O_3 implants be produced at the highest possible standards of quality assurance, especially if they are to be used as orthopedic prostheses in younger patients (<50 years old).

Al_2O_3 has been used in orthopedic surgery for more than 20 years as the articulating surface in total hip prostheses because of its exceptionally low coefficient of friction and minimal wear rates (Fig. 6).[3,6,19] The superb tribiologic properties (friction and wear) of Al_2O_3 occur only when the grains are very small (<4 μm) and have a very narrow size distribution. These conditions lead to very low surface roughness values (R_a = 0.02 μm, Table III). If large grains are present, they can pull out and lead to very rapid wear because of local dry friction and abrasion caused by the Al_2O_3 grains in the joint-bearing surfaces.[6]

Table III. Physical Characteristics of Alumina and Partially Stabilized Zirconia Bioceramics[†]

Physical characteristic	Alumina bioceramics	ISO alumina standard 6474	Partially stabilized zirconia	Cortical bone	Cancellous bone
Content (wt%)	Al_2O_3 > 99.8	Al_2O_3 > 99.50	ZrO_2 > 97		
Density (g/cm^3)	>3.93	>3.90	6.05	1.6–2.1	
Average grain size (μm)	3–6	<7	0.2–0.4		
Surface roughness, R_a (μm)	0.02		0.008		
Vickers hardness (HV)	2300	>2000	1300		
Compressive strength (MPa)	4500		2000	100–230	2–12
Bending strength (in Ringer's solution) (MPa)	595	>400	1000	50–150	
Young's modulus (GPa)	400		150	7–30	0.05–0.5
Fracture toughness, K_{IC} (MPa·m$^{-1/2}$)	5–6		15	2–12	
Slow crack growth (unitless)	30–52		65		

[†]Reference 4, Chs. 1 and 2.

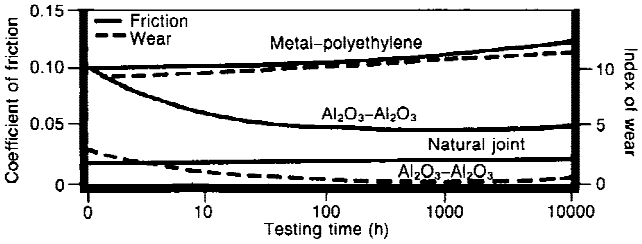


Fig. 6. Time dependence of coefficient of friction and wear of Al_2O_3–Al_2O_3 versus metal–polyethylene total hip joint (*in vitro* testing).

Al_2O_3–Al_2O_3 load-bearing wearing surfaces, such as in hip prostheses, must have a very high degree of sphericity produced by grinding and polishing the two mating surfaces. The Al_2O_3 ball and socket in a hip prosthesis are polished together and used as a pair. The long-term coefficient of friction of an Al_2O_3–Al_2O_3 joint is the closest of any synthetic material to the values of a normal joint. Wear of Al_2O_3–Al_2O_3 articulating surface is 2–10 times lower than metal–polyethylene surfaces (Fig. 6).

Low wear rates have led to use in Europe of Al_2O_3 noncemented cups press-fitted into the acetabulum (socket) of the hip. The cups are stabilized by bone growth into grooves or around pegs. The mating femoral ball surface also is Al_2O_3, which is press-fitted to a metallic stem (Fig. 7). Long-term results, in general, are excellent, especially for younger patients. However, stress shielding of the bone can occur.[6] This is due to the high Young's modulus of Al_2O_3 (Table III), which prevents the bone from being loaded—a requirement for bone to remain healthy and strong. The Young's modulus of cortical bone is 7–25 GPa, which is 10–50 times lower than Al_2O_3. Stress shielding may be responsible for cancellous bone atrophy and loosening of the acetabular cup in older patients with osteoporosis or rheumatoid arthritis.[6] Consequently, it is essential that the age of the patient, nature of the disease of the joint, and biomechanics of the repair be considered carefully before any prosthesis is used, including those made from Al_2O_3 ceramics. The primary use of Al_2O_3 in the United States is for the ball of the hip joint (Fig. 8) with the acetabular (socket) component being ultrahigh-molecular-weight polyethylene.

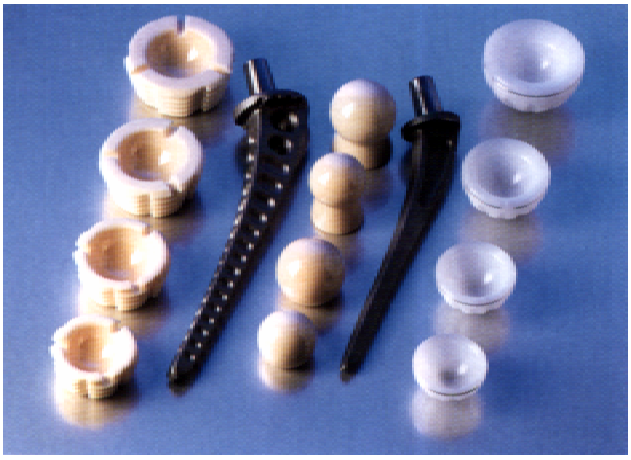


Fig. 7. Medical-grade Al_2O_3 used in total hip replacement: (left) Al_2O_3 acetabular cups mated with Al_2O_3 femoral balls; (center) Al_2O_3 balls also can be used with ultra-high-molecular-weight polyethylene cups; and (right) alternative metallic stem designs for morphological or cement fixation. (Photo courtesy of Dr. Gerd Willmann, CeramTec AG.)

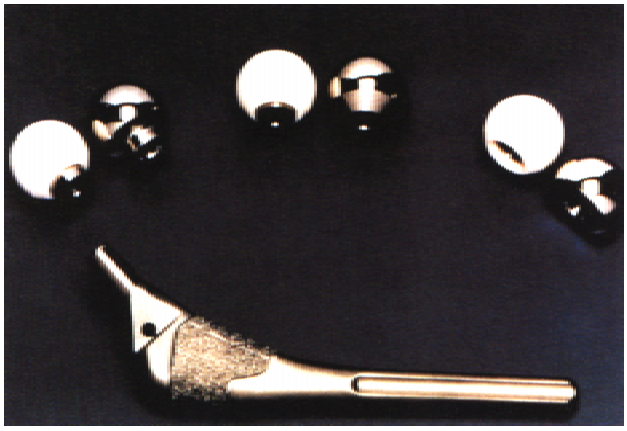


Fig. 8. Medical-grade Al_2O_3 used as femoral balls in total hip replacement. Note the porous coating on the metallic stem used for biological fixation. (Photo courtesy of Dr. Jack Parr.)

Other clinical applications of Al_2O_3 include knee prostheses, bone screws, alveolar ridge (jaw bone) and maxillofacial reconstructions, ossicular (middle ear) bone substitutes, keratoprostheses (corneal replacements), segmental bone replacements, and blade and screw and post-type dental implants.[1,3]

Zirconia (ZrO_2), in tetragonal form, stabilized by either magnesium or yttrium, also has been developed as a medical-grade bioceramic for use in total joint prostheses (Table III). The interest in ZrO_2 derives from its high fracture toughness and tensile strength. These improved properties make it possible to manufacture femoral heads for total hip prostheses that are smaller than the present generation of Al_2O_3 heads. ZrO_2 implants now are used clinically; only implant survivability data over 10 years will establish whether there is a clinical advantage.

II. Porous Ceramics

The potential advantage offered by a porous ceramic implant is the mechanical stability of the highly convoluted interface developed when bone grows into the pores of the ceramic.[22–24] The two primary clinical applications are

- Use of HA coatings on the porous surfaces of total joint prostheses as an alternative to cement fixation and as coatings on dental implants to achieve bioactive fixation;[4]
- Use of porous synthetic calcium phosphate ceramics to fill bone defects.[11–13,22–25]

The mechanical requirements of prostheses severely restrict the use of low-strength porous ceramics to low-load- or nonload-bearing applications.[3,22–25] A porous implant serves as a structural bridge and model or scaffold for bone formation. The microstructures of certain corals make an almost ideal material for forming structures with highly controlled pore sizes. White *et al.*[22,23] developed the replamineform process to duplicate the porous microstructure of corals that have a high degree of uniform pore size and interconnection. The first step is to machine the coral with proper microstructure into the desired shape. The coral genus, *Porites*, has pores with a size range of 140–160 μm pores, with all the pores interconnected.[22] Another coral genus, *Goniopora*, has a larger pore size, 200–1000 μm. The advantages of the replamineform process are that the pore size and microstructure are uniform, and there is complete interconnection of the pores. Clinical applications are reviewed by Schors and Holmes in Ref. 4.

Porous metal surfaces are produced on metallic orthopedic alloys by sintering balls or wires or meshes to the solid metal.[7] Synthetic HA ceramic coatings then are applied to the porous layers, usually by plasma-spray coating.[25,26] The bioactive coatings are applied to relatively small areas of a prosthesis, such as illustrated in Fig. 8. The rate of bone growth into the

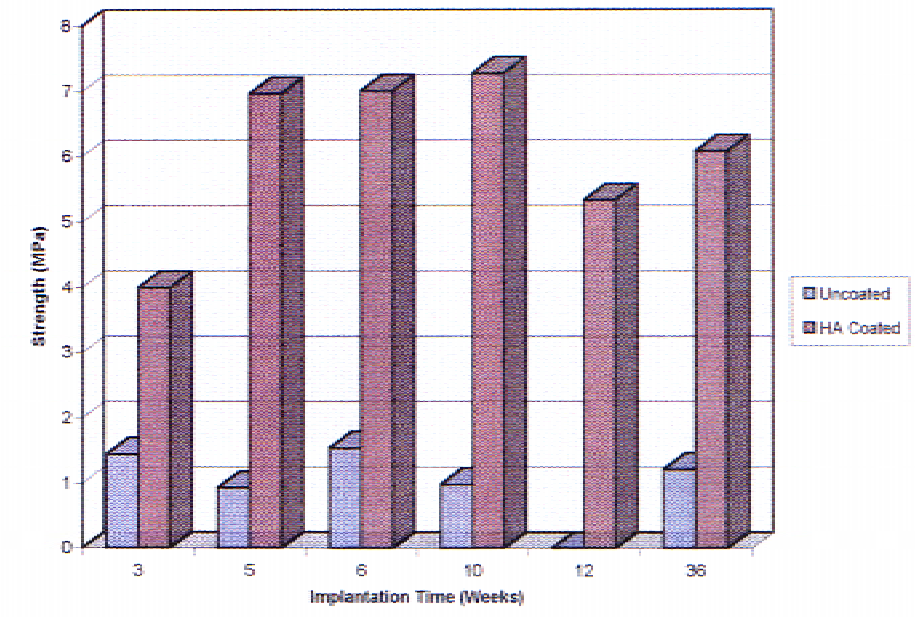


Fig. 9. Comparison of interfacial bond strength of porous titanium with and without plasma-sprayed HA coatings. (Data courtesy of Dr. Steve Cook.)

porous layer is accelerated by the bioactive HA ceramic, and the strength of the bone–implant interface also is enhanced (Fig. 9). Thus, bone bonding and biological fixation are restricted to specific areas, which reduces stress shielding in other areas of bone contact. This merger of the concepts of biological fixation, enhanced bone formation by a bioactive coating, and optimization of biomechanical stress transfer to the host bone is a major accomplishment of the past 20 years of research and development in orthopedic total joint replacement.

III. Bioactive Glasses and Glass-Ceramics

Certain compositions of glasses, ceramics, glass-ceramics, and composites have been shown to form a mechanically strong bond to bone.[4,5,14,27,30–40] These materials have become known as ''bioactive ceramics.''[4,5,25,40,41] Some even more specialized compositions of bioactive glasses bond to soft tissues as well as bone.[35,42] A common characteristic of bioactive glasses and bioactive ceramics is a time-dependent, kinetic modification of the surface that occurs upon implantation.[4,27,41] The surface forms a biologically active hydroxycarbonate apatite (HCA) layer that provides the bonding interface with the tissues. The HCA phase that forms on bioactive implants is equivalent chemically and structurally to the mineral phase in bone. It is that equivalence that is responsible for interfacial bonding.

Materials that are bioactive develop an adherent interface with tissue that resists substantial mechanical forces.[14,38,43,44] In many cases, the interfacial strength of adhesion is equivalent to or greater than the cohesive strength of the implant material or the tissue bonded to the bioactive implant. Figures 10 and 11 show bioactive implants bonded to bone with adherence at the interface sufficient to resist mechanical fracture. Failure occurs either in the implant (Fig. 10) or in the bone (Fig. 11) but not at the interface.

Bonding to bone was first demonstrated for a certain compositional range of bioactive glasses that contained SiO_2, Na_2O, CaO, and P_2O_5 in specific proportions[14] (Table IV). There were three important compositional features to these glasses that distinguished them from traditional soda–lime–

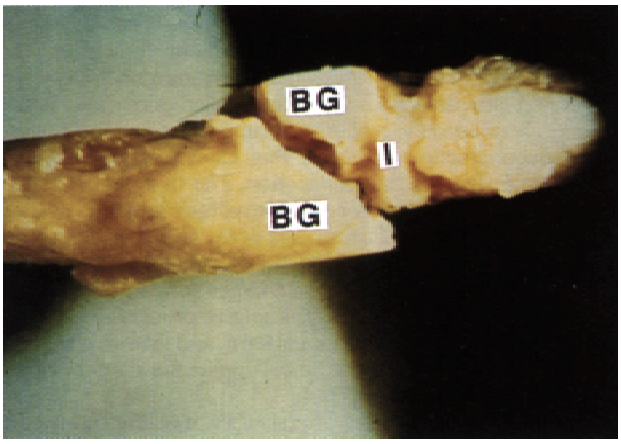


Fig. 10. Fracture of 45S5 bioactive glass [BG] segmental bone replacement in monkey due to torsional loading. Note the bonded interface [I] that survived the load to failure. (Photo courtesy of Professor George Piotrowski, University of Florida.)

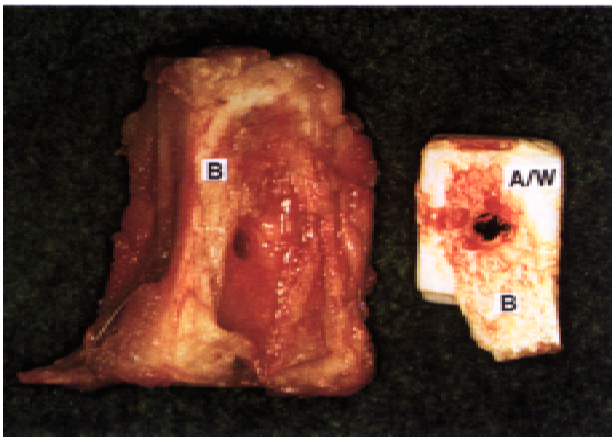


Fig. 11. Interfacial adherence of A/W bioactive glass-ceramic is stronger than either bone [B] or implant [A/W]. (Photo courtesy Professors T. Yamamura and T. Kokubo, Kyoto University.)

silica glasses: <60 mol% SiO_2, high Na_2O and CaO content, and high CaO:P_2O_5 ratio. These compositional features make the surface highly reactive when exposed to an aqueous medium, such as body fluids.

Many bioactive SiO_2 glasses are based upon the formula called ''45S5,'' signifying 45 wt% SiO_2 (S means the network former). Glasses with substantially larger amounts of P_2O_5 do not bond to bone.[43] Substitutions in the 45S5 formula of 5–15 wt% B_2O_3 for SiO_2 or 12.5 wt% CaF_2 for CaO or crystallizing the glass compositions to form glass-ceramics has little effect on the ability of the material to form a bone bond.[43] However, addition of as little as 3 wt% Al_2O_3 to the 45S5 formula prevents bonding.[5,31,43–46]

The compositional dependence (in weight percent) of bone bonding and soft tissue bonding for the Na_2O–CaO–P_2O_5–SiO_2 glasses is illustrated in Fig. 12. All glasses in Fig. 12 contain a constant 6 wt% of P_2O_5. Compositions in the middle of the diagram (region A) form a bond with bone. Consequently, region A defines the bioactive bone-bonding boundary. Silicate glasses within region B, such as window or bottle glass or microscope slides, behave as almost inert materials and elicit formation of a fibrous capsule at the implant–tissue interface. Glasses within region C are resorbable and disappear within 10–30 d of implantation. Glasses within region D are not technically practical and, therefore, have not been tested as implants.

The collagenous constituent of soft tissues can adhere strongly to the bioactive silicate glasses that lie within the compositional range shown in Fig. 12 as region E. Figure 13(A) shows collagen from a 10 d *in vitro* test-tube experiment bonded to a 45S5 Bioglass surface by agglomerates of HCA crystallites growing on the surface. The collagen fibrils are woven into the interface by growth of the HCA layer. The dense HCA–collagen agglomerates mimic the nature of bonding between tendons and ligaments, composed entirely of collagen fibrils, and bone or teeth that are composites of HCA crystals and collagen.[47,48] There is similar attachment of a periodontal ligament (PL) to a tooth (Fig. 13(B)) as to the attachment of collagen fibers to a Bioglass sample (Fig. 13(A)).

The test tube collagen-bioactive glass experiment (Fig. 13(A)) produces a similar interfacial bond as that which occurs in living soft connective tissues, as first discovered by Wilson *et al.*[35,42] (Figs. 14 and 15). Figure 14 shows a disk of 45S5 bioactive glass immobilized in soft connective tissue by an adherant layer. There is no inflammation around the implant, because it does not move and abrade the cells or cause degradation products. The adherance of the collagen fibers to the bonding gel layer on the glass, illustrated in Fig. 15, is stronger than the coherance of the collagen fibers to themselves. This discovery is especially important, because many implants require a stable interface with both soft and hard connective tissues.

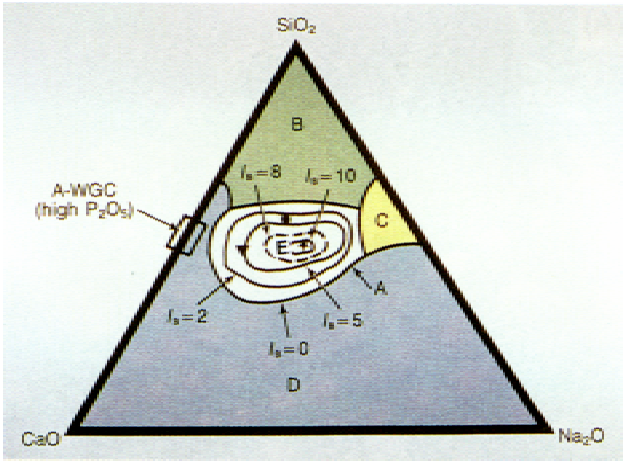
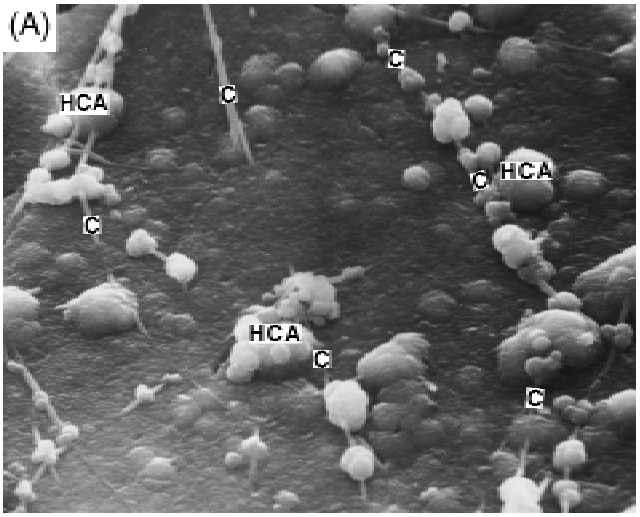


Fig. 12. Compositional dependence (in wt%) of bone bonding and soft tissue bonding of bioactive glasses and glass-ceramics. All compositions in region A are bioactive and bond to bone. They have a constant 6 wt% of P_2O_5. A/W glass-ceramic has higher P_2O_5 content (see Table IV for details). Compositions in region B are bioinert and lead to formation of a nonadherant fibrous capsule. Compositions in region C are resorbable. Region D is restricted by technical factors. Region E (soft tissue bonding) is inside the dashed line where the index of bioactivity, I_B, is >8.

Table IV. Composition and Mechanical Properties of Bioactive Ceramics Used Clinically[†]

Property	Bioglass 45S5	S45PZ	Glass-ceramic Ceravital	Glass-ceramic Cerabone A/W	Glass-ceramic Ilmaplant L1	Glass-ceramic Bioverit	Sintered hydroxyapatite $Ca_{10}(PO_4)_6(OH)_2$ (>99.2%)	Sintered β-$3CaO{\cdot}P_2O_5$ (>99.7%)
Composition (wt%)								
Na_2O	24.5	24	5–10	0	4.6	3–8		
K_2O	0		0.5–3.0	0	0.2	3–8		
MgO	0		2.5–5.0	4.6	2.8	2–21		
CaO	24.5	22	30–35	44.7	31.9	10–34		
Al_2O_3	0		0	0	0	8–15		
SiO_2	45.0	45	40–50	34.0	44.3	19–54		
P_2O_5	6.0	7	10–50	16.2	11.2	2–10		
CaF_2	0			0.5	5.0	3–23		
B_2O_3	0	2						
Phase[‡]	Glass	Glass	Apatite Glass	Apatite β-Wollastonite Glass	Apatite β-Wollastonite Glass	Apatite Phlogopite Glass	Apatite	Whitlockite
Density (g/cm^3)	2.6572			3.07		2.8	3.16	3.07
Vickers hardness (HV)	458 ± 9.4			680		500	600	
Compressive strength (MPa)			500	1080		500	500–1000	460–687
Bending strength (MPa)	42[§]			215	160	100–160	115–200	140–154
Young's modulus (GPa)	35		100–150	218		70–88	80–110	33–90
Fracture toughness, K_{IC} (MPa·m$^{1/2}$)				2.0	2.5	0.5–1.0	1.0	
Slow crack growth, *n* (unitless)				33			12–27	

[†]Reference 15. [‡]Apatite is $Ca_{10}(PO_4)_6(O,F)$, β-wollastonite is $CaO{\cdot}SiO_2$, phlogopite is $(Na,K)Mg_3(AlSiO_{10})F_2$, and whitlockite is β-$3CaO{\cdot}P_2O_5$. [§]Tensile.



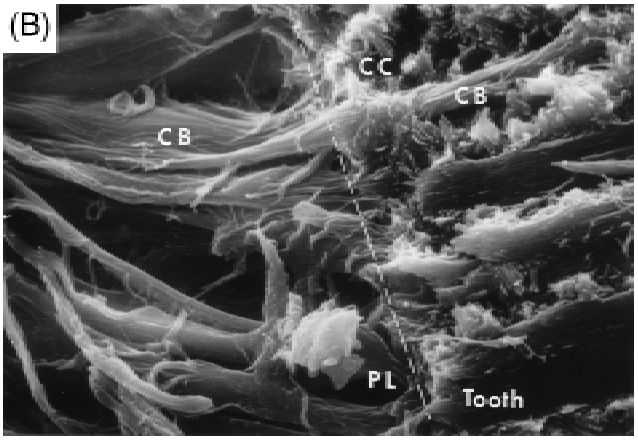


Fig. 13. (A) SEM micrograph of collagen fibrils [C] incorporated within the HCA layer [HCA] growing on a 45S5 bioactive glass substrate *in vitro.* (Photo courtesy of Professor Carlo Pantano, The Pennsylvania State University.) (B) SEM micrograph of tissue attachment to a tooth. Note the collagen bundles [CB] coming from the left in the periodontal ligament [PL] inserted deep into the calcified cementum [CC] on the surface of the tooth. (Photo courtesy of Dr. J. Brady.)

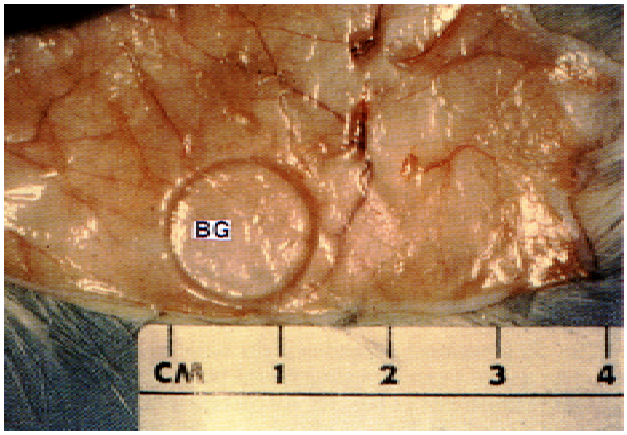


Fig. 14. Adherant soft connective tissue bonding immobilizes a 45S5 bioactive glass [BG] implant. (Photo courtesy of Dr. June Wilson.)

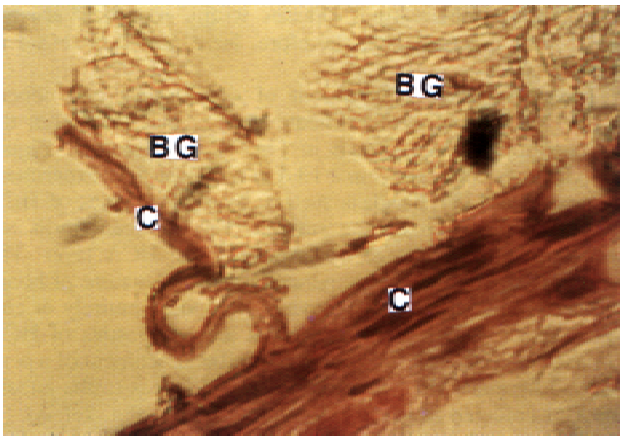


Fig. 15. Adhesion of collagen fibers [C] to bioactive glass bonding gel layer [BG] is stronger than cohesive bonding of collagen to itself. (Photo courtesy of Dr. June Wilson, University of Florida.)

The composite interface composed of HCA collagen on the bioactive glasses is ~30–60 μm of the 100–200 μm total interfacial thickness (Fig. 4). This junction thickness is equivalent to that at naturally occurring interfaces (Fig. 13(B)), where a transition occurs between materials with low Young's elastic moduli (tendons and ligaments) and those with moderately high Young's moduli (bones and teeth). The thicknesses of the hard tissue–bioactive ceramic interfaces are indicated in Fig. 4 for several clinically important bioactive materials. The interfacial thickness of the bonding zone decreases as the compositional boundary shown in Fig. 12 is approached.

Gross *et al.*[5,31,49–52] have shown that a range of low-alkali (0–5 wt%) bioactive SiO_2-based glass-ceramics also bond to bone. Small additions of Al_2O_3, Ta_2O_5, TiO_2, Sb_2O_3, or ZrO_2 inhibit bone bonding (Table IV).

The clinically most important bioactive glass-ceramic is the three-phase silica–phosphate material (Table IV) composed of apatite [$Ca_{10}(PO_4)_6(OH_1F_2)$] and wollastonite ($CaO–SiO_2$) crystals and a residual $CaO–SiO_2$-rich glassy matrix, termed A/W glass-ceramic by Professors Yamamuro and Kokubo, its developers.[34,36–40] A/W glass-ceramic has excellent mechanical properties (Table IV) and forms a bond with bone that has a very high interfacial bond strength (Fig. 11).[37,38] Addition of Al_2O_3 or TiO_2 to the A/W glass-ceramic inhibits bone bonding, whereas incorporation of a second phosphate phase, β-whitlockite ($3CaO·P_2O_5$) does not.

Another multiphase bioactive silica–phosphate, containing phlogopite mica $(Na,K)Mg_3(AlSi_3O_{10})F_2$ and apatite crystals, bonds to bone even though Al_2O_3 is present in the composition.[32] However, the Al^{3+} ions are incorporated within the crystal phase and do not alter the surface reaction kinetics of the material. An advantage of these mica-containing glass-ceramics, developed by Freidrich Schiller University, Jena, Germany, is their easy machinability.[53] Additional compositions of bioactive glasses have been developed at Abo Akademi and the University of Turku, Finland, for dental applications.[45,54,55] Compositions of these various bioactive glasses and glass-ceramics are compared in Table IV.

IV. Interfacial Reaction Kinetics

Bonding of bone to bioactive glasses involves 12 reaction stages summarized in Fig. 16(A). The first five stages occur very rapidly on the surface of most bioactive glasses because of fast ion exchange of alkali ions with hydrogen ions from body fluids (stage 1), network dissolution (stage 2), silica-gel polymerization (stage 3), and chemisorption and crystallization of the HCA layer (stages 4 and 5), as summarized in Table V. The surface reactions lead to the biochemical adsorption of growth factors (stage 6) and the synchronized sequence of cellular

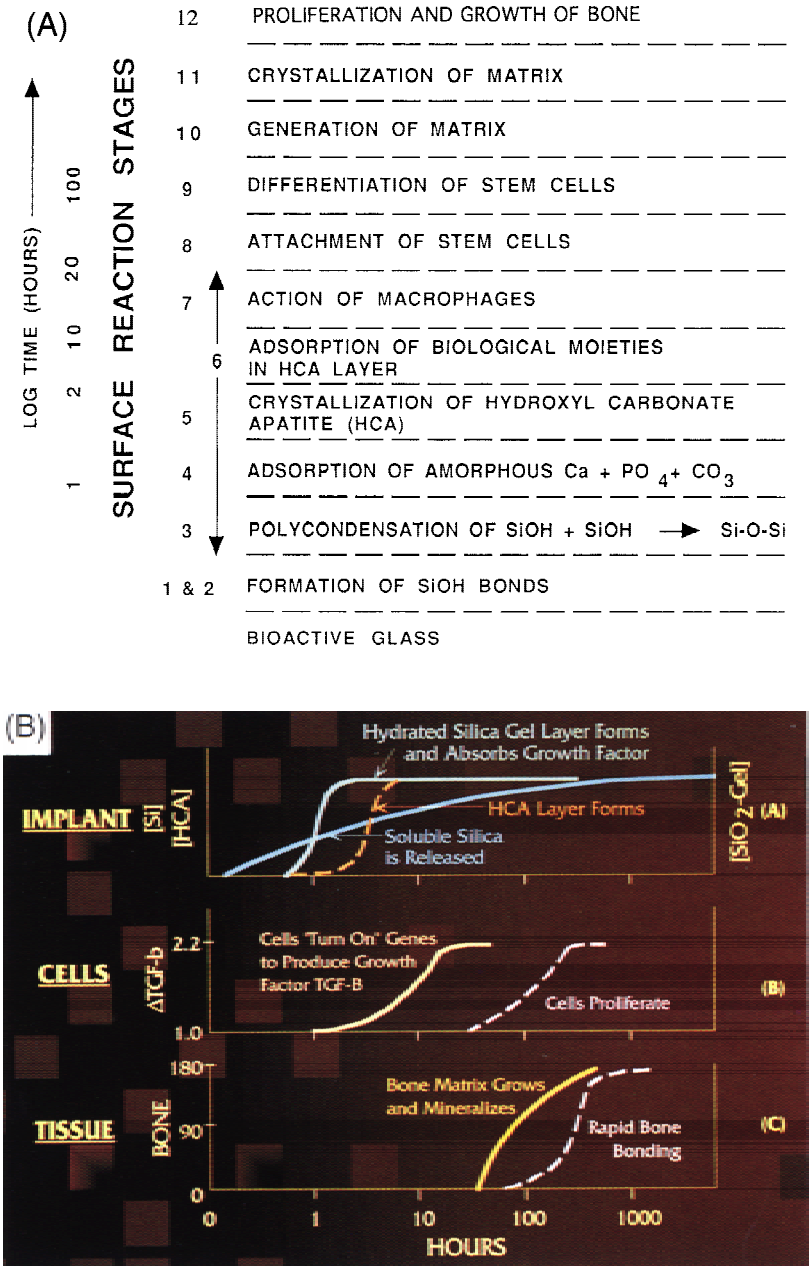


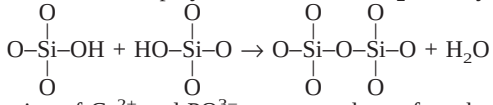
Fig. 16. (A) Sequence of interfacial reactions involved in forming a bond between bone and a bioactive glass. (B) Time dependence of reactions occurring on a bioactive implant surface and the effects on cells that lead to rapid bone bonding and bone proliferation.

events (stages 7–12) that result in rapid formation of new bone. The time dependence of the reaction stages is depicted in Fig. 16(B). Compositions in the center of the bioactive bonding field in Fig. 12 exhibit very rapid rates of stages 1–12. When the concentration of SiO_2 in the glass network exceeds ~55%, the rates of reaction slow greatly, as indicated by the isobioactivity contours in Fig. 12, and bonding to bone is very slow. At a concentration of 60% SiO_2, the rates of reaction are sufficiently slow that the material is biologically inert. Bioactive glass-ceramics, such as A/W glass-ceramic, are intermediate in reactions rates and bioactivity.

Surface compositional profiles resulting from stage 1 through stage 5 reactions have been measured for 45S5 bioactive glasses using Auger electron spectroscopy (AES) combined with argon-ion milling.[56–58] The results (Fig. 17) show that, after only 1 h *in vivo*, there has developed a calcium- and phosphorus-rich reaction layer heterogeneously nucleated and crystallized from the silica-gel layer formed on the glass surface. The calcium- and phosphorus-rich layer is identical in defect composition to biologically grown apatites, because it is grown *in situ.* With time, the interfacial bonding zone between living and nonliving material continues to grow by incorporating calcium and phosphorus ions from body fluids. The final result is a gradient in composition that extends over several hundred micrometers (Fig. 18), similar in dimension to the bonding zone that occurs naturally at bone interfaces. The compositional profiles correlate with electron microscopy of the bioactive glass implant bonding interface in bone[14,43,44,59] and provide the explanation for the high bonding strength of the interface.[60]

Kokubo[61,62] has shown that a calcium- and phosphorus-rich layer also is present at the bonding interface between the polycrystalline apatite- and wollastonite-based A/W glass-ceramic and bone. However, the SiO_2-rich layer was not present, even though a substantial concentration of soluble silicon was lost to solution. CaO–SiO_2-based glasses, without phosphate, form an

Table V. Reaction Stages of a Bioactive Implant†

Stage	Reaction
1	Rapid exchange of Na^+ or K^+ with H^+ or H_3O^+ from solution: $Si–O–Na^+ + H^+ + OH^- \rightarrow Si–OH^+ + Na^+(solution) + OH^-$ This stage is usually controlled by diffusion and exhibits a $t^{-1/2}$ dependence.
2	Loss of soluble SiO_2 in the form of $Si(OH)_4$ to the solution, resulting from breaking of Si–O–Si bonds and formation of Si–OH (silanols) at the glass solution interface: $Si–O–Si + H_2O \rightarrow Si–OH + OH–Si$ This stage usually is controlled by interfacial reaction and exhibits a $t^{1.0}$ dependence.
3	Condensation and repolymerization of a SiO_2-rich layer on the surface depleted in alkalis and alkaline-earth cations: 
4	Migration of Ca^{2+} and PO_4^{3-} groups to the surface through the SiO_2-rich layer, forming a $CaO–P_2O_5$-rich film on top of the SiO_2-rich layer, followed by growth of the amorphous $CaO–P_2O_5$-rich film by incorporation of soluble calcium and phosphates from solution.
5	Crystallization of the amorphous $CaO–P_2O_5$ film by incorporation of OH^-, CO_3^{2-}, or F^- anions from solution to form a mixed hydroxyl, carbonate, fluorapatite layer.

†Reference 15.

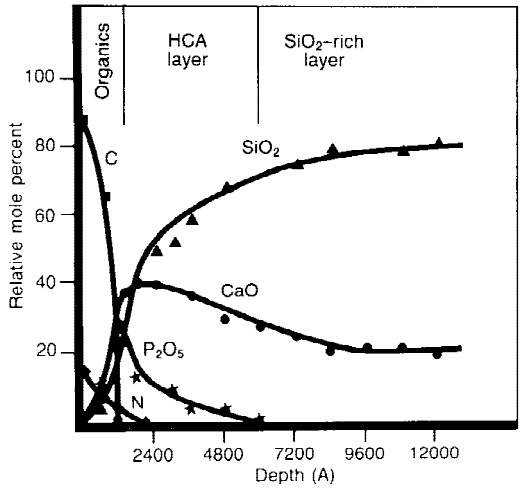


Fig. 17. Bilayer films formed on 45S5 bioactive glass after 1 h in rat bone, as measured by Auger electron spectroscopy and argon-ion beam milling.

apatite layer on their surfaces[62,63] when exposed for 2–30 d in simulated body fluid that contains only 1.0m*M* HPO_4^{2-}. The $CaO–SiO_2$-based glasses were confirmed to bond to living bone by the surface apatite layer.[62] Previously, Ogino *et al.*[57] showed that P_2O_5-free $Na_2O–SiO_2$ glasses form an apatite layer on their surfaces when exposed to an aqueous solution containing calcium and phosphate ions. Li, Clark, and Hench[64] demonstrated that highly porous sol–gel-derived glasses containing primarily SiO_2, with only 10 mol% of CaO and P_2O_5 and no Na_2O, form apatite layers in a *tris*-buffer solution. Earlier, Walker[65] demonstrated that even highly pure SiO_2 eventually forms a bone bond if the surface has a very high surface area, >400 m^2/g. Synthetic HA ceramic implants, which contain no SiO_2 or alkali ions, bond to bone by forming a new epitaxial apatite phase at the interface,[10,66,67] as discussed in a later section.

Consequently, it is concluded that bioactivity occurs only within certain compositional limits and very specific ratios of oxides in the $Na_2O–K_2O–CaO–MgO–P_2O_5–SiO_2$ systems. *A layer of biologically active HCA must form for a bond with tissues to occur. This is the common characteristic of all the known bioactive implant materials.* It is the rate of HCA formation (stage 4) and the time for onset of crystallization (stage 5) that varies greatly. When the rate becomes excessively slow, no bond forms, and the material is no longer bioactive.

The failure strength of a bioactively fixed bond appears to be a nonlinear function of the bonding rate of the implant. Interfacial strength appears to be *inversely* dependent on the *thickness* of the bonding zone. For example, 45S5 Bioglass with a very high bonding rate develops a gel-bonding layer of 100 μm (Fig. 18) that has a relatively low shear strength. In contrast, A/W glass-ceramic, with an intermediate rate of bonding, has an interface of 10–20 μm and a very high resistance to shear (note Fig. 7).[38,62] The interfacial area for bonding is time dependent, as shown in Fig. 3. Therefore, interfacial strength is time dependent and is a function of morphological factors, such as the change in interfacial area with time, progressive mineralization of the interfacial tissues, and resulting increase of elastic modulus of the interfacial bond, as well as a function of shear strength per unit of bonded area and the density and quality of bone bonded to the interface (Figs. 1 and 2). For example, a bioactive implant bonded to osteoporotic bone shears easily through the low-density trabecular bone.

V. Clinical Applications of Bioactive Glasses and Glass-Ceramics

Clinical applications of bioactive glasses and glass-ceramics have been reviewed by Gross *et al.*,[5] Yamamuro *et al.*,[40] and Wilson *et al.*[68,69] (see Table VI). Several of the most important clinical uses are described in this section. Bioactive glass and glass-ceramic implants have been used for more than 10 years to replace the small bones of the middle ear (ossicles) damaged by chronic infection, a clinical problem called ''conductive hearing loss.''[70–73] An example of a 45S5 bioactive glass middle ear implant, used as an ossicular prosthesis, is shown in Fig. 19. Survivability of the bioactive glass implants for middle-ear replacements is considerably longer than occurs when bioinert implants are used for the same purpose (Fig. 20). Bioinert implants do not bond to the eardrum and, therefore, gradually erode through the tissue and are extruded through the eardrum within 2–3 years.[73] In contrast, highly bioactive glasses form a bond with the collagen of the eardrum and also bond firmly to the remaining bone of the stapes footplate and, thereby, are anchored on both ends, which prevents extrusion. Sound conduction is excellent, and there is no fibrous tissue growth to impair sound transmission. Moreover, there is no micromotion at the implant–tissue interface; therefore, the implant remains stable and functions for the lifetime of the patient.[73]

Many patients are ''profoundly deaf'' because of loss of the auditory nerve fibers in the cochlea. Research has shown that such patients can sense electronic impulses applied to the cochlea, although at much lower frequency discrimination. These findings have led to the development of an extracochlear electrical implant that delivers electrical signals in real time en-

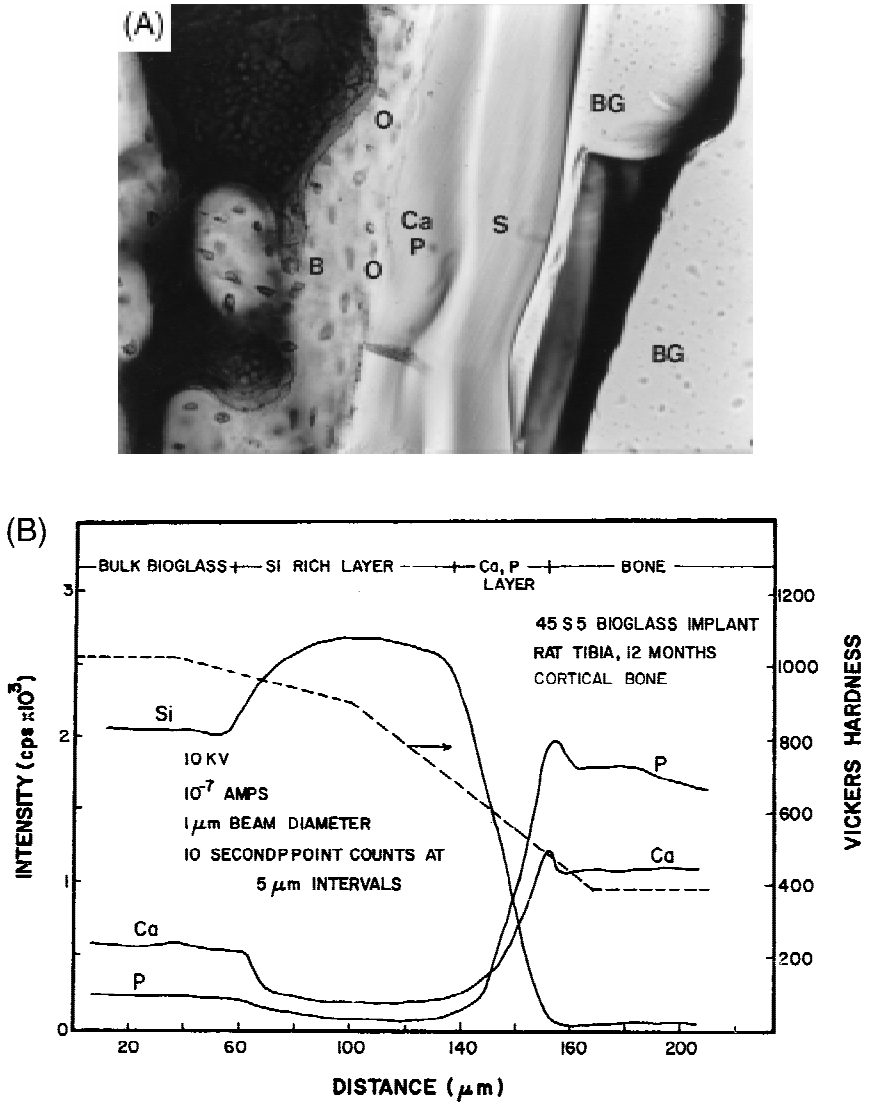


Fig. 18. (A) Optical micrograph of a 45S5 bioactive glass implant [BG] bonded to rat bone [B] after 1 year, showing osteocytes or bone cells [O] in conjunction with the HCA layer [Ca-P] formed on top of the silica gel [S]. (B) Electron microprobe analysis across the implant-bone interface shown in (A).

coded by a computer to match speech patterns.[74] A team led by Professor Fourcin and ENT Surgeon Douek in London reports successful clinical use of an array of four platinum electrodes insulated by medical-grade Al_2O_3 and anchored in the bone with a 45S5 bioactive glass sleeve. The Al_2O_3 provides mechanical and dielectric stability to the device, and the bioactive glass bonds both to the bone and the soft connective tissues as it protrudes through the skin. This hermetic, percutaneous living seal provides both mechanical stability and prevents infection from migrating down the electrodes, thereby protecting the patient who must unplug the electronics at night. Figure 21(A) shows the University of London extracochlear electrode array and its implantation site. Figure 21(B) shows the implant in place in a patient. Patients have used this type of auditory prosthesis for 5 years with success.

Another application of 45S5 Bioglass implants, based upon bonding to both soft tissues and bone, preserves the jawbone of patients who have had their teeth extracted prior to being fitted with dentures. This type of implant, called an Endosseous Ridge Maintenance Implant (ERMI), developed by Stanley *et al.*,[75] is injection molded in the shape of a cone with several sizes to match the size of roots of extracted teeth (Fig. 22). A mating drill bit of equal size is used to prepare the bone for the implant. X-rays (Fig. 23) show that the implants are stable after many years in bone and have prevented resorption (wearing away) of bone under the dentures. Survivability of bioactive glass ERMI implants after 10 years are dramatically greater than other bioactive implants that do not bond to soft tissue (Fig. 24).[75]

The clinical application of bioactive glasses that is most important is in the form of a particulate that is placed around teeth that have had periodontal (gum) disease, a clinical problem that affects tens of millions of people. The 45S5 bioactive glass material rapidly leads to new bone formation around the bioactive glass particles (Fig. 25).[68,69,76,77] The new bone forms by the reaction mechanisms summarized in Fig. 16. Because of the speed of formation of the new bone, the epithelial tissues are stopped from migrating down the tooth, a common problem if nothing is used to fill the space between the tooth and repairing bone. The junction between the tooth and the periodontal membrane is stabilized by use of bioactive glass particulate, and the tooth is saved. Clinical success is quite dramatic, as reported by periodontists[68,69] and oral surgeons.[68] The same particulate bioactive glass material has been used in a wide variety of clinical applications where bone grafting is needed to fill spaces or augment the natural repair process. An example is shown in Fig. 26, which are X-rays of a third molar site prior to surgical extraction (Fig. 26(A)) and 3 months after filling with 45S5 bioactive glass particulate (Fig. 26(B)).[68] An advantage of the rapid bone repair due to the bioactive material

Table VI. Clinical Uses of Bioceramics

Application	Materials†
Orthopedic	Al_2O_3
	Stabilized ZrO_2
	HA powders
	Bioactive glass powders
Coatings for bioactive bonding	HA
	Bioactive glass ceramics
Bone space fillers	Tricalcium phosphate
	Calcium phosphate salts
Dental implants	Al_2O_3
	HA
	Bioactive glasses
Artificial tendon and ligament	PLA–carbon-fiber composite
Periodontal pocket obliteration	HA
	HA–PLA composite
	Tricalcium phosphate
	Calcium phosphate salts
	Bioactive glasses
Alveolar ridge augmentation	HA
	HA–autogenous bone composite
	Bioactive glasses
Maxillofacial reconstruction	Al_2O_3
	HA
	PE–HA composite
	Bioactive glasses
Spinal surgery	Bioactive glass-ceramic
	HA
Therapeutic treatment of tumors	Rare-earth-doped aluminosilicate glasses
Artificial heart valves	Pyrolytic carbon coating
Otolaryngological	Al_2O_3
	HA
	Bioactive glasses
	Bioactive glass ceramics
	PE–HA composite

†HA is hydroxyapatite, PE is polyethylene, and PLA is poly(lactic acid).

is that pain is minimized and the jawbone is rapidly stabilized. Similar procedures can be used to augment the jawbone when necessary to improve the stability of dental implants.[68,77]

Orthopedic applications, using 45S5 bioactive glass particulate, include bone grafting, repair of total hips and knees that have required revision surgery, and spinal fusion. The exciting finding is the hypothesis that bioactive glass is stimulating rapid proliferation of bone by activating a genetically controlled process that leads to production of growth factors.[41] The regenerated trabecular bone from this osteoconductive process is equivalent to normal bone, as shown by comparing the structure of the trabeculae in Fig. 27, created by filling the bone defect with 45S5 bioactive glass particulate with normal trabecular bone, shown in Fig. 2(A).

An especially important clinical application of bioactive implants is the use of A/W bioactive glass-ceramic in the repair of the spine. Professor T. Yamamuro recognized the clinical need of a bioactive ceramic with high strength and fracture toughness suitable for use as a replacement for vertebrae and, with Professor T. Kokubo and colleagues at Kyoto University, developed such a material in 1982.[36–40] The material is made by densifying 5-μm-sized glass powders into the desired shape, then precipitating oxyfluorapatite ($Ca_{10}(PO_4)_6(O,F_2)$) and wollastonite ($CaO–SiO_2$) phases to yield a crack- and pore-free, dense, homogenous glass-ceramic. The physical properties are summarized in Table IV. The high compressive and bend strengths, 1080 MPa and 215 MPa, respectively; high fracture toughness, 2.0 $MPa^{1/2}$; high interfacial bond strength to bone (Fig. 11); and excellent resistance to degradation of properties when exposed to physiological loading conditions (Fig. 28) provide confidence in the use of this material to replace surgically removed vertebrae.[63] In the past, when the vertebral column was extensively damaged by tumors or trauma, its reconstruction had been attempted by use of the patient's own

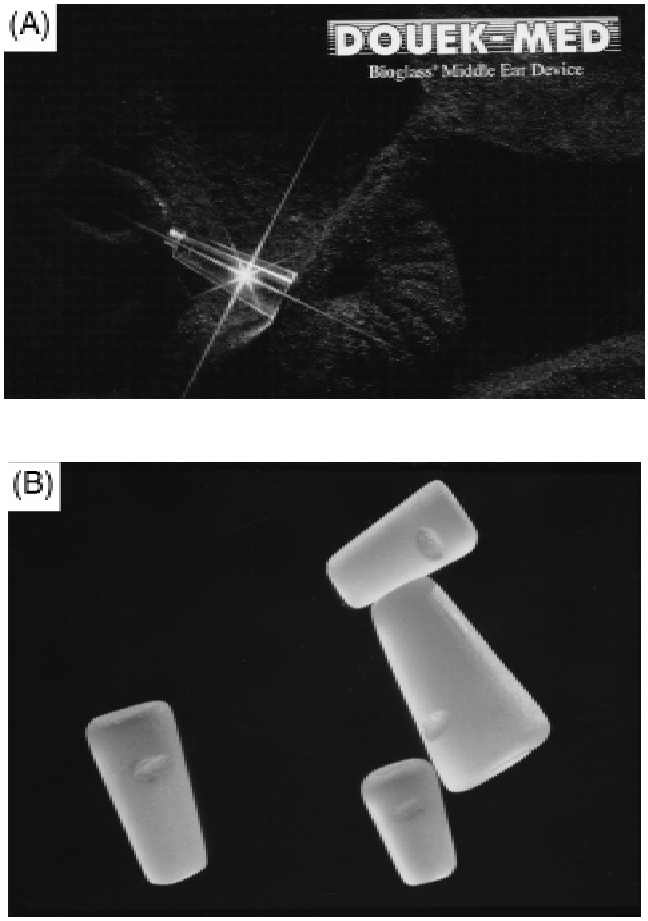


Fig. 19. (A) Schematic of bioactive glass (45S5) ossicular replacement prosthesis bonding to stapes footplate (left) and the eardrum (right). (B) Actual prostheses.

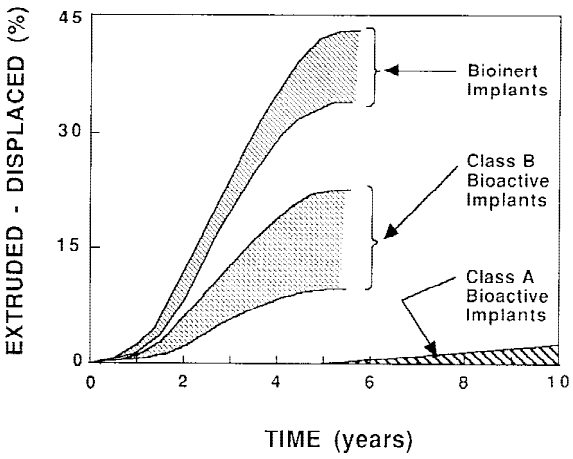


Fig. 20. Survivability comparison of bioinert implants. Class B bioactive implants (synthetic HA) and class A bioactive glass implants (45S5) used to replace middle-ear bones. (Analysis courtesy of Keith Lobel, University of Florida.)

(autogeneous) bone or cadaver (allograft) bone in combination with metals, PMMA bone cement, or Al_2O_3 ceramic. However, autogeneous allograft and bone have limited availability, and the long-term durability of non-bone-bonding implants was often unsatisfactory because of loosening and dislocation.[78,79] Since 1983, A/W glass-ceramic has been used successfully in vertebral replacement. Figure 29 shows four types of A/W prostheses. Use of bioactive glass-ceramic in repair of a burst

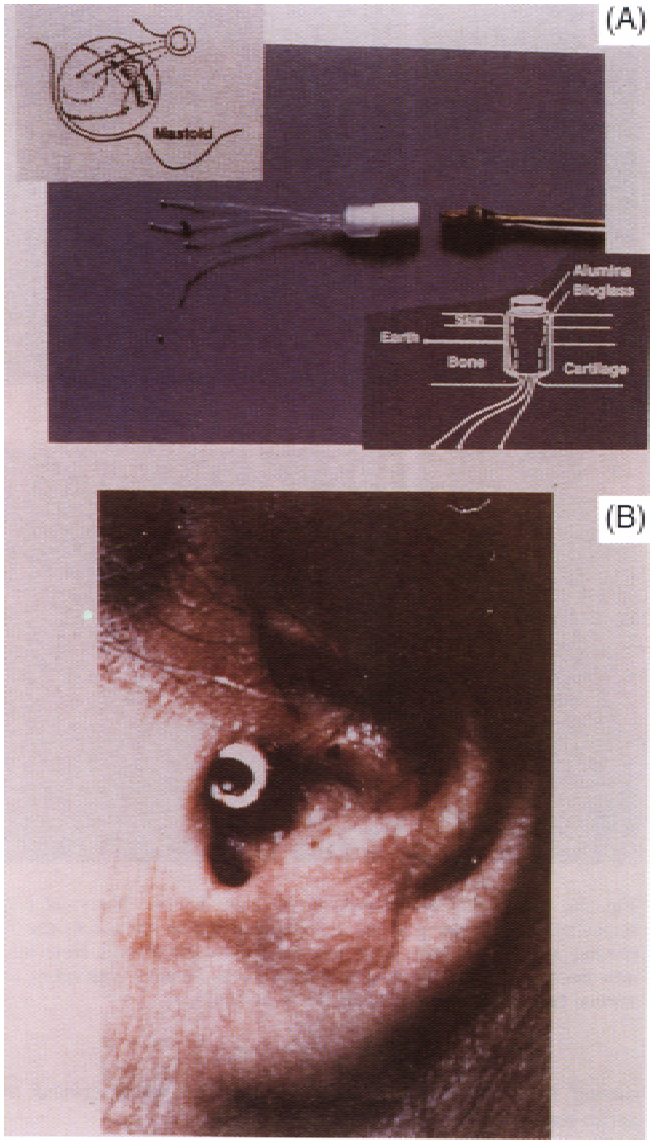


Fig. 21. (A) Extracochlear electric implant for the profound deaf showing electrode array (center), implantation site (upper left), and schematic of the components (lower right). (B) Implant in patient's ear, with electronics disconnected. (Photos courtesy Mr. Ellis Douek, Guy's Hospital, University of London.)

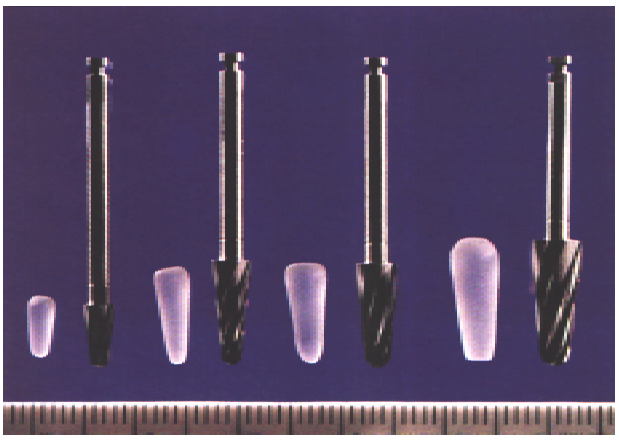


Fig. 22. Bioactive glass implants (45S5) and matching drill bits used to replace the roots of extracted teeth. (Photo courtesy of Dr. David Greenspan, U.S. Biomaterials Corp.)

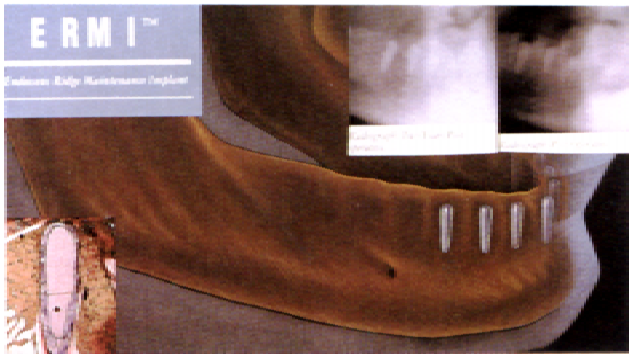


Fig. 23. Use of 45S5 bioactive glass endosseous ridge maintenance implants to maintain the thickness and width of the jawbone of denture wearers. Inserts show (lower left) bonding of alveolar bone to an implant and X-rays (far upper right) after implantation and (near right) after 2 years implantation.

fracture of the L_1 vertebra of a 48 year old man is shown in Fig. 30. Replacement of a L_2 vertebra that had malignant tumor metastasis with a A/W spacer is illustrated in Fig. 31. A case of spondylolisthesis with symptoms of lumbar canal stenosis repaired with bioactive glass-ceramic is shown in Fig. 32. The long-term (>10 years) successful use of A/W bioactive glass-ceramic is due to formation of trabecular bone bonded to all sides of the vertebral implant, as illustrated in Fig. 33, with a stable glass-ceramic–bone interface.

VI. Calcium Phosphate Ceramics

Calcium phosphate-based bioceramics have been in use in medicine and dentistry for 20 years.[3,10–13,25,33,66,67] Applications include coatings of orthopedic and dental implants, al-

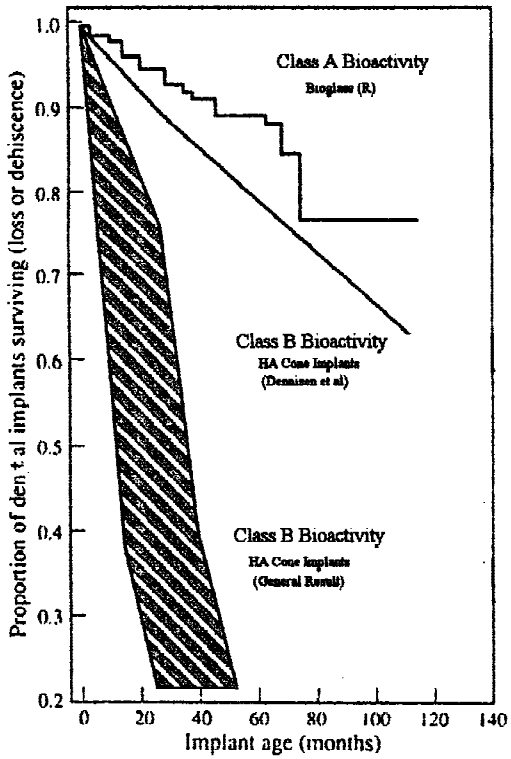


Fig. 24. Survivability for 2–10 years of class A bioactive glass cone implants to maintain endentulous alveolar bone compared with class B (synthetic HA) implants.

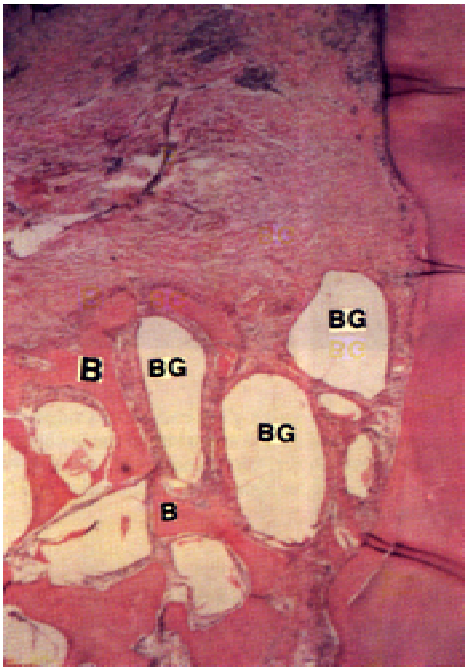


Fig. 25. Bioactive glass [BG] particulate used to enhance bone [B] formation around a tooth [T] and thereby restore its function following treatment of periodontal (gum) disease. (Photo courtesy of Dr. June Wilson.)

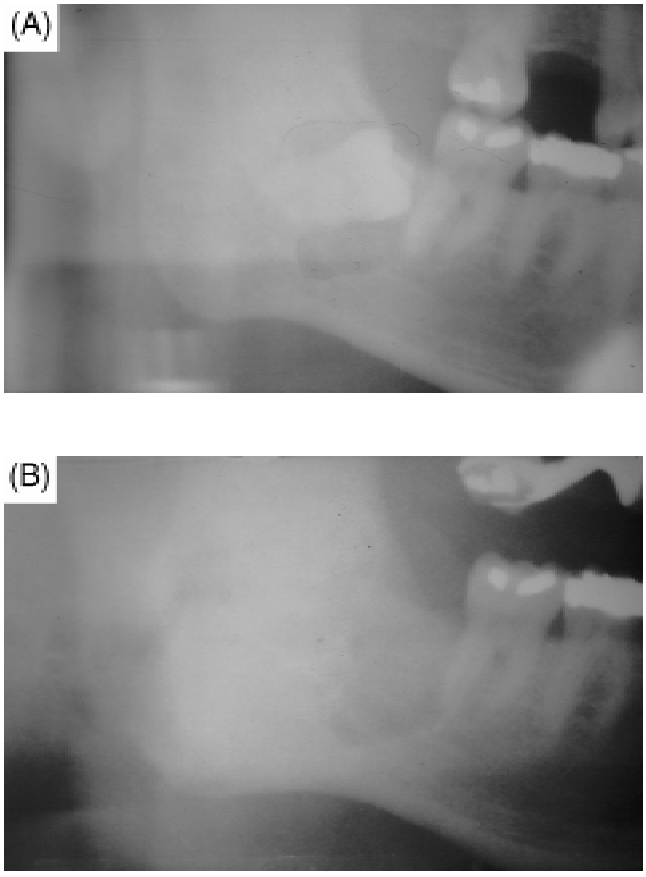


Fig. 26. Use of bioactive glass to fill bone defects: X-rays of (A) impacted third molar prior to extraction and (B) extraction site 3 months after filling with 45S5 bioactive glass particulate. Note that new bone has filled the space with an X-ray density equivalent to normal bone. (Photo courtesy of Dr. King Smith.)

veolar ridge augmentation, maxillofacial surgery, otolaryngology, and scaffolds for bone growth and as powders in total hip and knee surgery (Table VI). Different phases of calcium phosphate ceramics are used depending upon whether a resorbable or bioactive material is desired.

The stable phases of calcium phosphate ceramics depend considerably upon temperature and the presence of water, either during processing or in the use environment.[11] At body temperature, only two calcium phosphates are stable in contact with aqueous media, such as body fluids: at pH <4.2, the stable phase is $CaHPO_4 \cdot 2H_2O$ (dicalcium phosphate, brushite, C_2P), whereas, at pH >4.2, the stable phase is $Ca_{10}(PO_4)_6(OH)_2$ (HA). At higher temperatures, other phases, such as $Ca_3(PO_4)_2$ (β-tricalcium phosphate, C_3P, TCP) and $Ca_4P_2O_9$ (tetracalcium phosphate, C_4P) are present. The unhydrated, high-temperature calcium phosphate phases interact with water, or body fluids, at 37°C to form HA. Thus, the solubility of a TCP surface approaches the solubility of HA and decreases the pH of the solution, which further increases the solubility of TCP and enhances resorption. DeGroot,[10] Williams,[67] and LeGeros and LeGeros[81] have discussed the importance of the Ca:P ratio in determining solubility and tendency for resorbtion in the body. The presence of micropores in the sintered material can increase the solubility of these phases.[10–13,33]

Sintering of calcium phosphate ceramics usually occurs at 1000°–1500°C, following compaction of the powder into a desired shape.[10,33] The phases formed at high temperature depend on temperature and on the partial pressure of water (p_{H_2O}) in the sintering atmosphere. When water is present, HA can be formed and is a stable phase up to 1360°C, as shown in the phase equilibrium diagram for CaO and P_2O_5 with 500 mmHg (66 kPa) p_{H_2O} (Fig. 34). When there is no water, C_4P and C_3P are the stable phases.

The temperature range of HA stability increases with p_{H_2O}, as does the rate of phase transitions of C_3P or C_4P to HA. Because of kinetics barriers that affect the rates of formation of the stable calcium phosphate phases, it often is difficult to predict the volume fraction of high-temperature phases that are formed during sintering and their relative stability when cooled to room temperature.

Starting powders can be made by mixing, in an aqueous solution, the appropriate $CaNO_3$:$(NH_4)_3PO_4$ molar ratio that yields a precipitate of stoichiometric HA. The Ca^{2+}, PO_4^{3-}, and OH^- ions can be replaced by other ions during processing or in physiological surroundings; e.g., fluorapatite ($Ca_{10}(PO_4)_6(OH)_{2-x}F_x$, with $0 < x < 2$) and carbonate apatite ($Ca_{10}(PO_4)_6(OH)_{2-2x}(CO_3)_x$ or $Ca_{10-x+y}(PO_4)_{6-x}(OH)_{2-x-2y}$, where $0 < x < 2$ and $0 < y < x$) can be formed.[80] Fluorapatite is found in dental enamel and HCA is present in bone. Le Geros *et al.*[81] discussed the structure of these complex crystals. The mechanical behavior of calcium phosphate ceramics strongly influences their application as implants.[12] Tensile and compressive strength and fatigue resistance depend on the total volume of porosity. Porosity can be in the form of micropores (<1 μm diameter, due to incomplete sintering) or macropores (>100 μm diameter, created to permit bone growth).[82]

The Weibull modulus (m) of HA implants is low in physiological solutions ($m = 12$), which indicates low reliability under tensile loads. Consequently, in clinical practice, calcium phosphate bioceramics should be used as powders; small, unloaded implants; dental implants (with reinforcing metal posts); coatings on metal implants; low-loaded porous implants (where bone growth acts as a reinforcing phase); or bioactive phase in a polymer–bioactive ceramic composite.

The bonding mechanisms of dense HA implants appear to be very different from those described above for bioactive glasses.[33] A cellular bone matrix from differentiated osteoblasts appears at the surface, producing a narrow amorphous

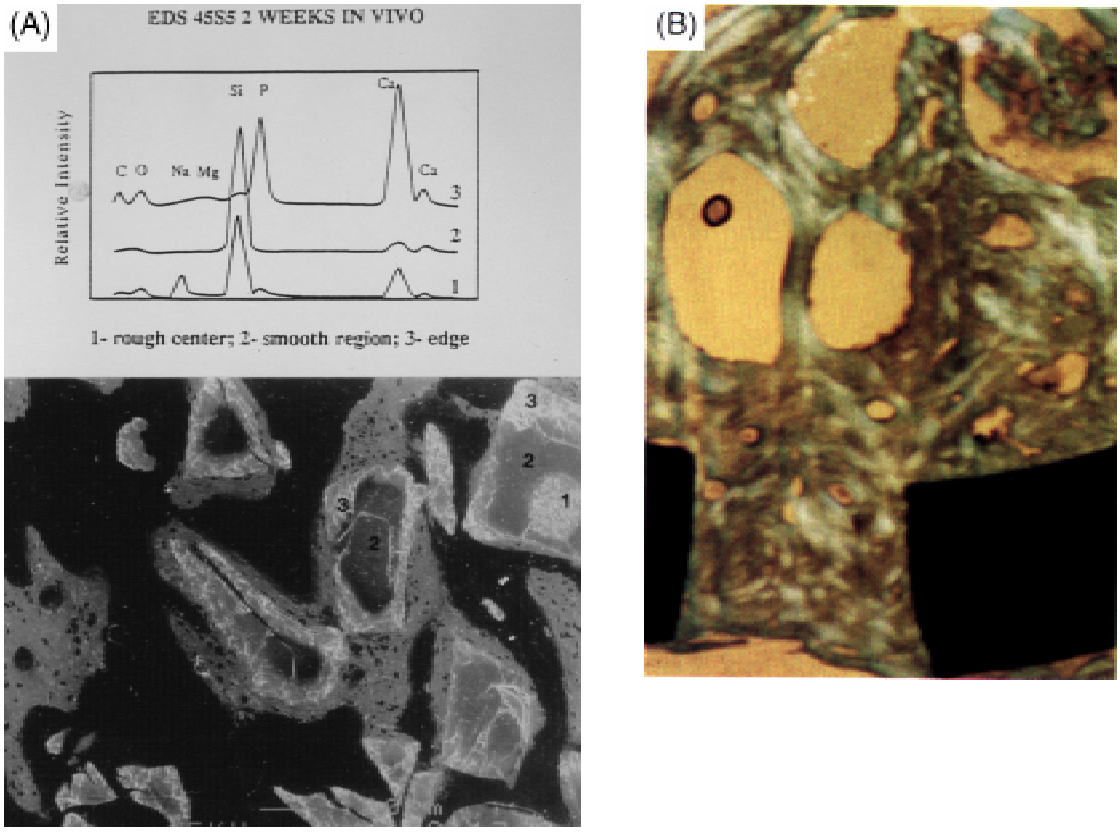


Fig. 27. (A) SEM micrograph of regenerated trabecular bone formed in only 2 weeks in a dog rib using bioactive glass particulate. Energy dispersive spectra of the compositional changes at the glass–bone interface is shown at the top of the figure. (Photo courtesy of Professor Marivalda Periera, Federal University of Minas Gerais, Brazil.) (B) Light microscopy micrograph of regenerated trabecular bone formed by use of bioactive glass (45S5) particulate inside a titanium cage fusing sheep vertebra. (Photo courtesy of Dr. Gary Lowery and Dr. June Wilson.)

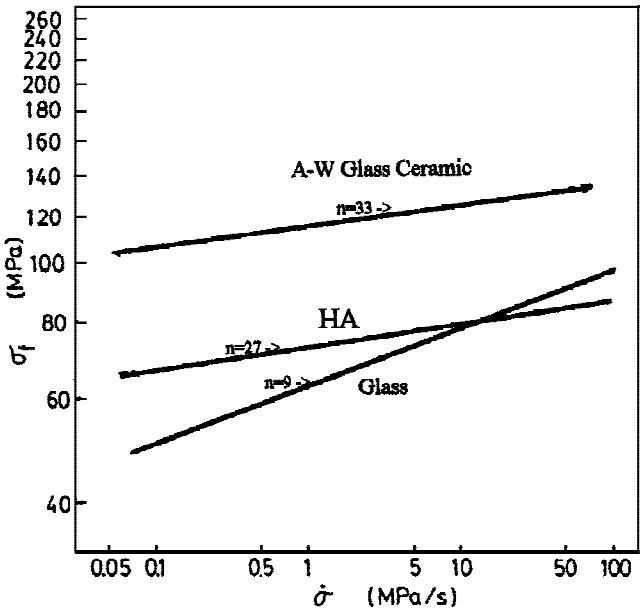


Fig. 28. Lifetime prediction diagrams for high-strength bioactive glass-ceramic A/W compared with dense HA ceramic and a bioactive glass. The A/W glass-ceramic withstands a flexural load of 65 MPa in the body for more than 10 years in contrast with HA, which is predicted to fail in <1 year. (Data courtesy of Professor T. Kokubo.)

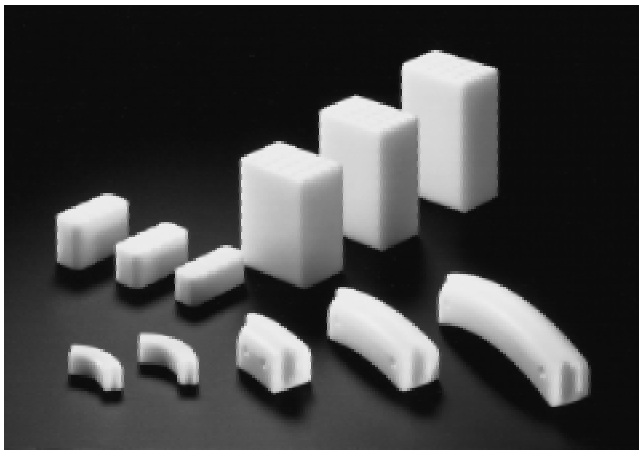


Fig. 29. Four types of bioactive glass-ceramic A/W prostheses for orthopedic applications: vertebral prostheses, iliac crest prostheses, intervertebral spacers, and laminoplasty spacers. (Photo courtesy of Nippon Electric Glass Co. and Professors T. Yamamuro and T. Kokubo, Kyoto University, Japan.)

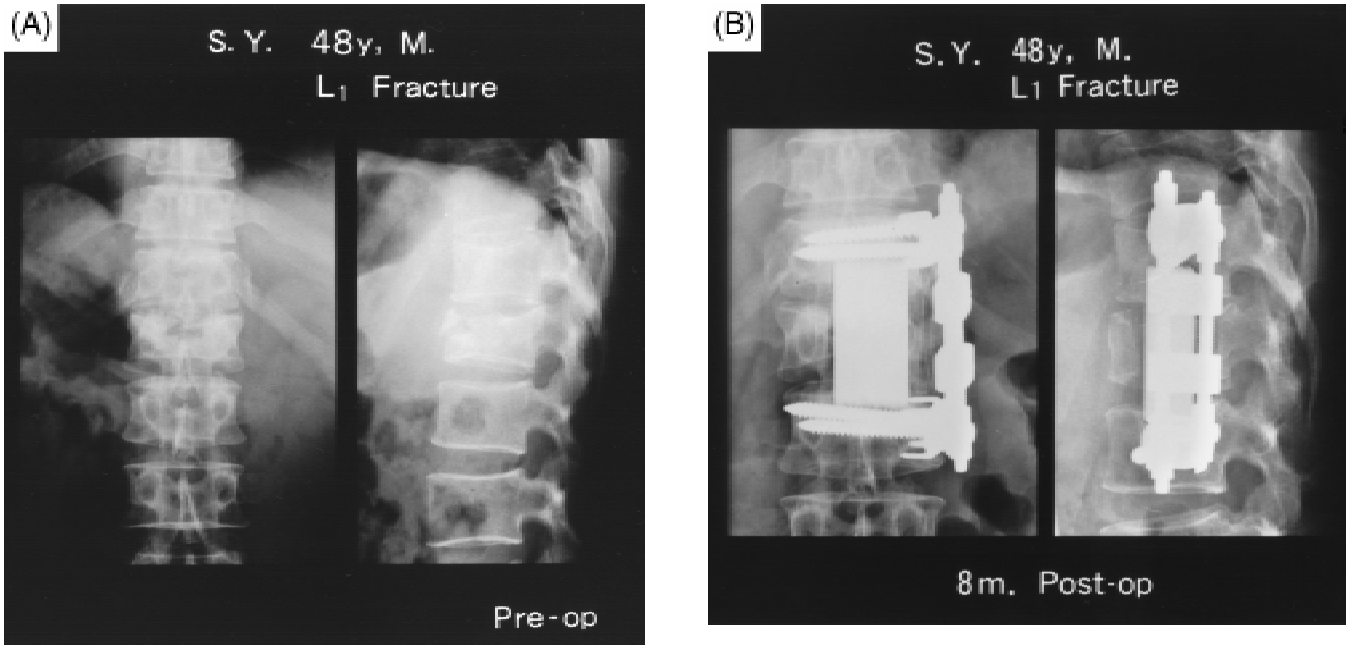


Fig. 30. X-rays of a case of burst fracture of the L_1 vertebra: (A) preoperative anterior–posterior and lateral views and (B) postoperative anterior–posterior and lateral views using bioactive glass-ceramic A/W prosthesis. (Photo courtesy of Professor T. Yamamuro.)

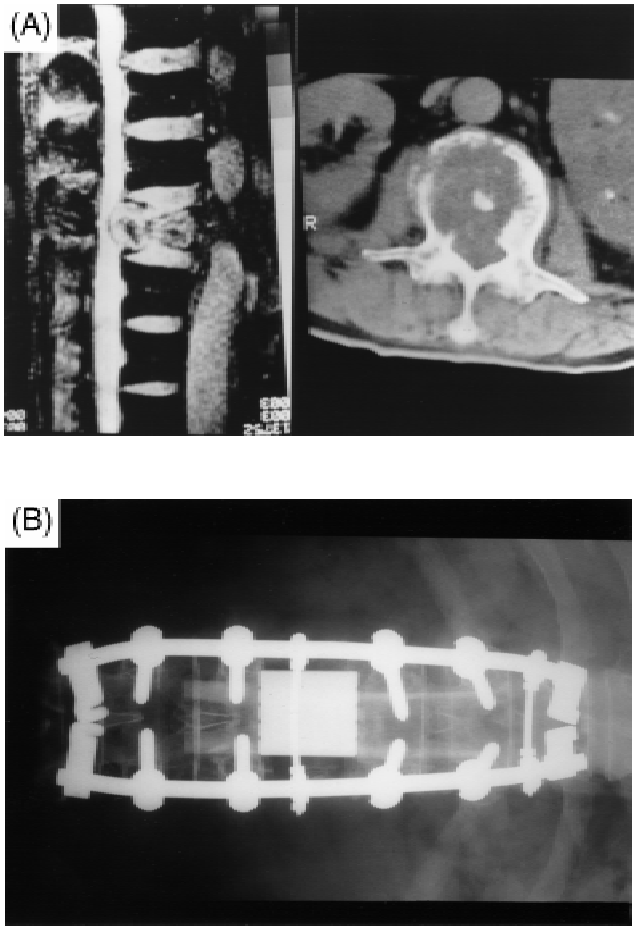


Fig. 31. Case of malignant tumor metastasis to L_2 vertebra: (A) preoperative MRI pictures and (B) postoperative anterior–posterior view using bioactive glass-ceramic A/W prosthesis to replace the vertebra. (Photo courtesy of Professor K. Tomita, Kamazawa University, Japan.)

electron dense band only 3–5 μm wide. Collagen bundles appear between this area and the cells. Bone mineral crystals have been identified in this otherwise amorphous area.[83] As the site matures, the bonding zone shrinks to a depth of only 0.05–0.2 μm. The result is normal bone attached through a thin epitaxial bonding layer to the bulk implant.[83] Ogiso *et al.*[84,85] have shown, through transmission electron microscopy (TEM) lattice image analysis of dense HA bone interfaces, an almost perfect epitaxial alignment of the growing bone crystallites with the apatite crystals in the implant (Fig. 35). A wide range of clinical applications of synthetic HA implants, both solid and porous, are described in Chs. 9–12 of Ref. 4 and in Refs. 3, 9–13, 22–26, 33, 66, 67, 73, 75, 77, 80, and 82.

VII. Composites

One of the primary restrictions on clinical use of bioceramics is the uncertain lifetime under the complex stress states, slow crack growth, and cyclic fatigue that result in many clinical applications. Two creative approaches to these mechanical limitations are use of bioactive ceramics as coatings, discussed above, and the biologically active phase in composites.[86–91] Bonfield argues[89] that analogous implant materials with similar mechanical properties should be the goal when bone is to be replaced. Because of the anisotropic deformation and fracture characteristics of cortical bone, which is itself a composite of compliant collagen fibrils and brittle HCA crystals, the Young's modulus varies ~7–25 GPa, the critical stress intensity ranges ~2–12 $MPa \cdot m^{1/2}$, and the critical strain intensity increases from as low as ~600 $J \cdot m^{-2}$ to as much as 5000 $J \cdot m^{-2}$, depending on orientation, age, and test condition.[103] In contrast, most bioceramics are much stiffer than bone and many exhibit poor fracture toughness (Table III). Figure 36 compares the strength and the elastic modulus of cortical and cancellous bone with various materials used for implants. The only materials that exhibit a range of properties equivalent to bone are composites. The approach used to achieve properties analogous to bone is to stiffen a compliant biocompatible synthetic polymer, such as polyethylene, with a higher-modulus ceramic second phase, such as HA powder.[102] The effect is to increase

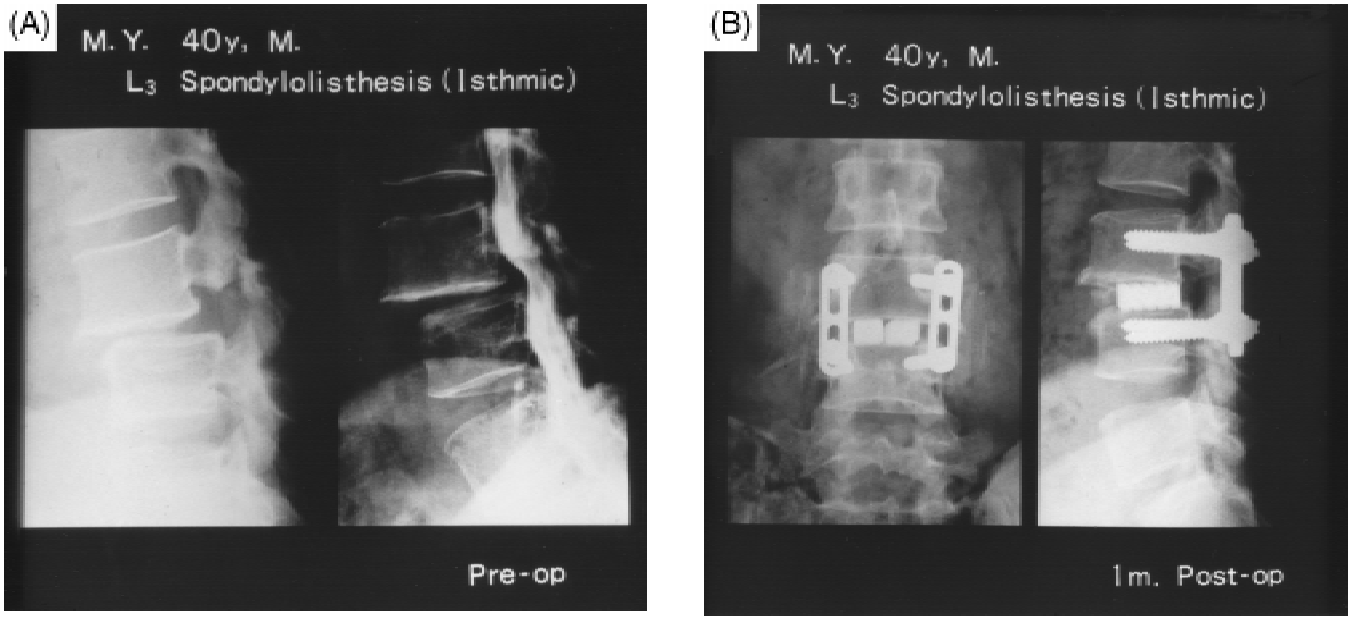


Fig. 32. Case of spondylolithesis with symptoms of lumbar canal stenosis: (A) preoperative lateral X-ray view (left) and lateral myelogram (right) and (B) postoperative anterior–posterior and lateral X-ray views using bioactive glass-ceramic A/W laminoplasty spacer. (Photo courtesy of Professor T. Yamamuro.)

Young's modulus from 1 to 8 GPa and to decrease the strain to failure from >90% to 3% (Fig. 37) as the volume fraction of HA increases to 0.5. The transition from ductile to brittle behavior occurs between 0.4 and 0.45 volume fraction HA. Bonfield reports[102] that the ultimate tensile strength of the composite remained within 22–26 MPa. At 0.45 volume fraction HA, the K_{IC} value was 2.9 ± 0.3 MPa·m$^{1/2}$, whereas, at <0.4 volume fraction HA, the fracture toughness was considerably greater because of the ductile deformation associated with crack propagation. Thus, the mechanical properties of the polyethylene–HA composite are similar to those of bone.

The bioactive phase is exposed by machining the surface of the composite. Bone-growing cells (osteoblasts) anchor onto the HA phase in the composite (Fig. 38) and proliferate.[91] Implant tests of the polyethylene–0.4 volume fraction HA composites demonstrated development of bone bonding between the natural hard tissue and the synthetic implant.[90]

Two clinical applications of the polyethylene–HA composite

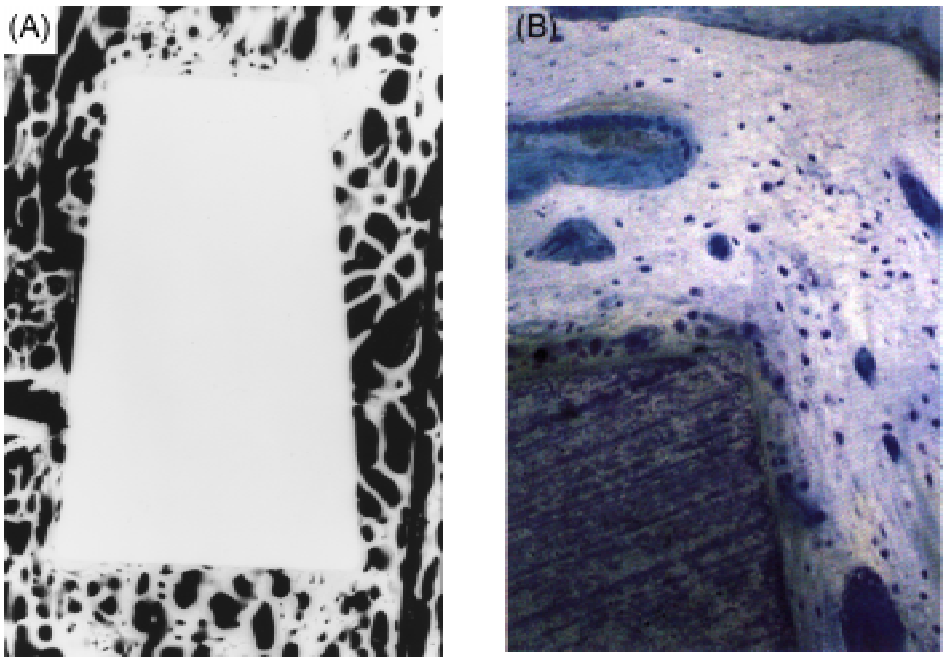


Fig. 33. Vertebral implant of bioactive glass-ceramic A/W in a sheep: (A) microradiograph showing trabecular bone bonding to all sides of the implant, 3 months following surgery and (B) histology of the bone bonding zone of the implant, 8 weeks after surgery. (Photo courtesy Professor T. Yamamuro.)

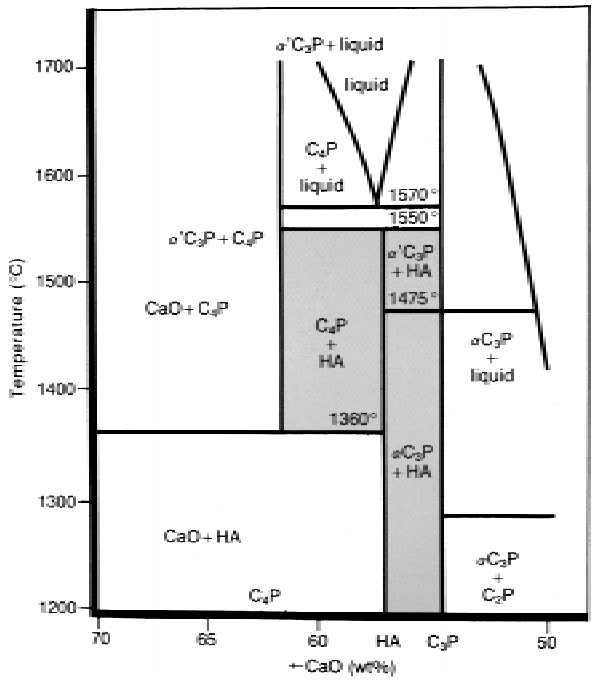


Fig. 34. Calcium phosphate phase equilibrium diagram with 500 mmHg p_{H_2O}. Shaded area is processing range to yield synthetic HA ceramic implants. (Diagram based upon the work[13] of Professor de Groot, University of Leiden.)

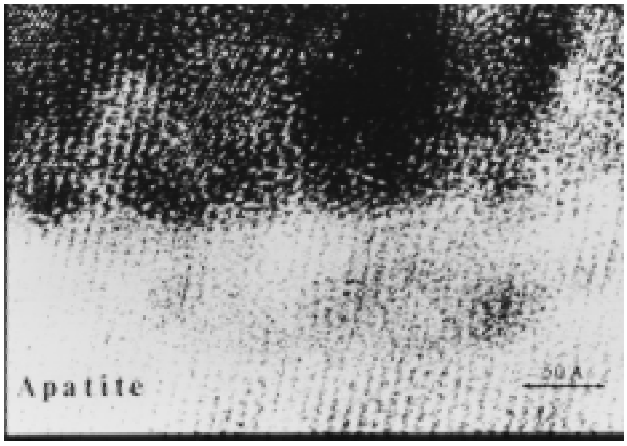


Fig. 35. TEM micrograph using lattice imaging to show epitaxial bonding between HA ceramic implant (bottom) and the biological HA phase of bone (top). (Photo courtesy of Dr. M. Ogiso.[84,85])

are shown in Figs. 39 and 40. It is used as ossicular prostheses (Fig. 39), where the stem of the device is made of the composite and the head is made of synthetic HA ceramic. The composite is very easily trimmed by the surgeon at the time of surgery to the size and configuration required for the patient. Figure 40(A) shows the use of the bioactive composite to repair a fractured orbital floor (eye socket) (Fig. 40(B)). The advantages offered by the composite are ease of shaping of the

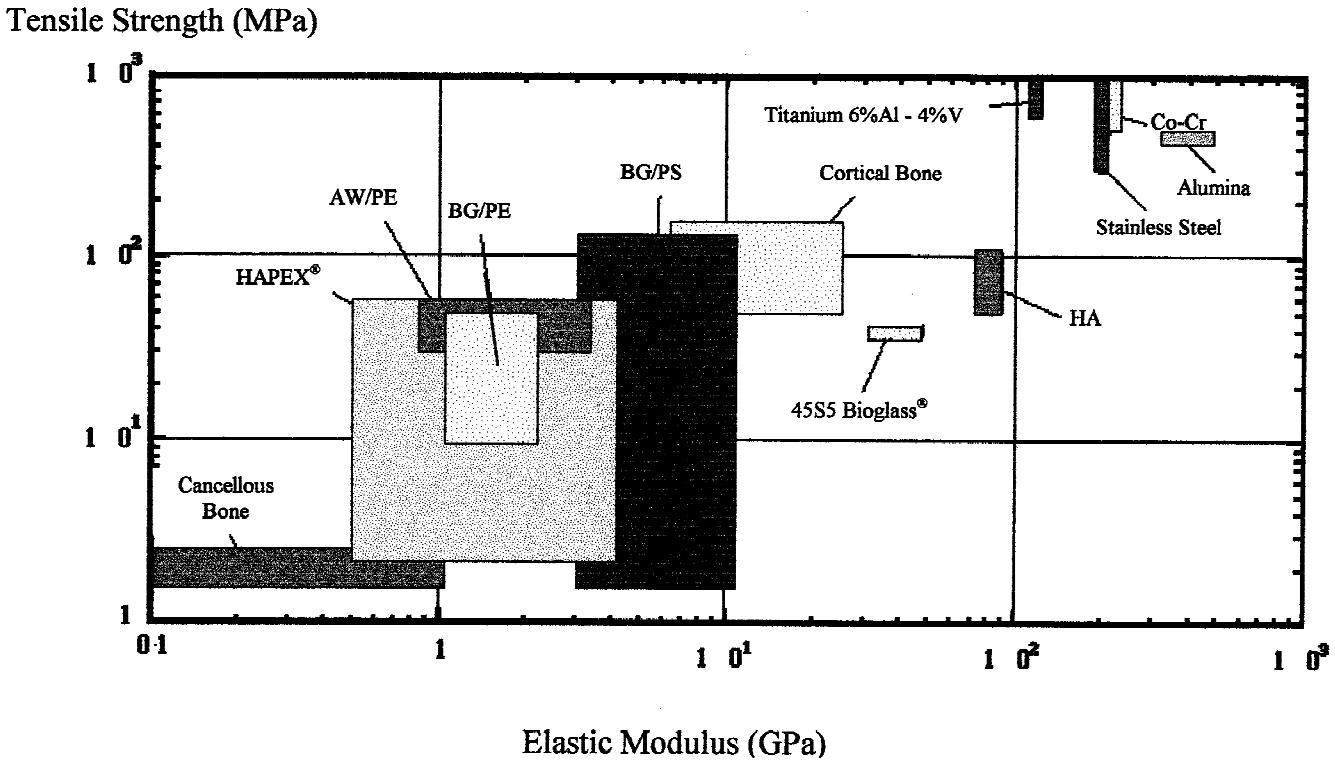


Fig. 36. Comparison of the range of mechanical properties, tensile strength, and elastic modulus of various biomaterials with cancellous, trabecular bone, and cortical bone, including a bioactive composite of HA particles in a polyethylene matrix: AW/PE is a bioactive composite of A/W particles in a polyethylene matrix; BG/PE is a bioactive composite of 45S5 bioactive glass particles in a polyethylene matrix; BG/PS is a bioactive composite of 45S5 bioactive glass or crystallized bioactive glass-ceramic particles in a polysulfone matrix; HA is dense, synthetic HA ceramic; Titanium–6%Al–4%V is an orthopedic alloy; Stainless Steel is 316L medical grade; Co-Cr is medical-grade orthopedic alloys; and Alumina is medical-grade Al_2O_3 (see Table III). (Graphic courtesy of I. Thompson and Y. Fujishiro.)

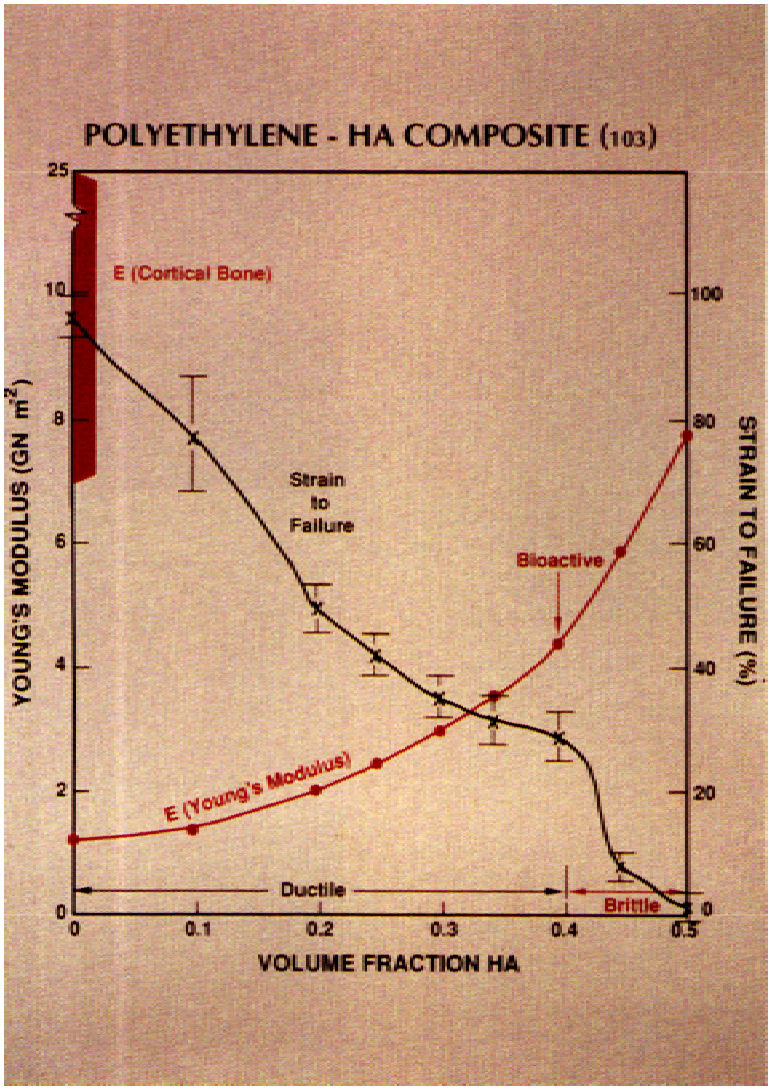


Fig. 37. Effect of HA on Young's Modulus and strain-to-failure of a polyethylene–HA composite. (Based upon data[89] of Professor Bill Bonfield, University of London IRC.)

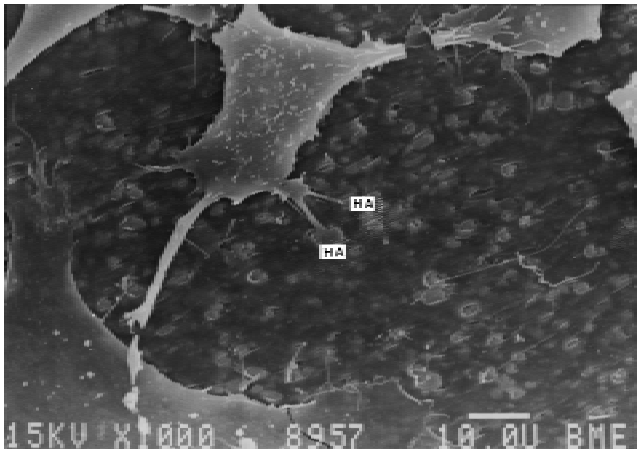


Fig. 38. SEM micrograph showing the anchoring of a bone-growing cell (osteoblast, OB) to HA particles in a bioactive composite of HA in a polyethylene matrix. (Photo courtesy of Professor Bill Bonfield and Dr. Elizabeth Tanner, University of London IRC.[91])

implant to meet the patient's needs at the time of surgery, formation of a bioactive bond to hold the implant in place, and mechanical properties that closely match those of the host tissues.

VIII. Coatings

(1) Carbon

For the ~40 000 patients per year in the United States that require heart valve replacement, the availability of high-performance carbon bioceramics can mean the difference between life and death. There are two classes of replacement heart valves: mechanical and tissue. Mechanical valves are made of synthetic, nonphysiological materials and represent about one-half of the valve replacements done at the present time. Tissue valves, also termed bioprosthetic valves, are usually fabricated from chemically preserved animal tissue, most often pig, mounted on a prosthetic frame, or can be a human aortic valve allograft. All types of replacement valves are a compromise over natural tissues and ''within 10 years postoperatively valve-related complications occur in approximately 50% or more of patients having previously and currently used

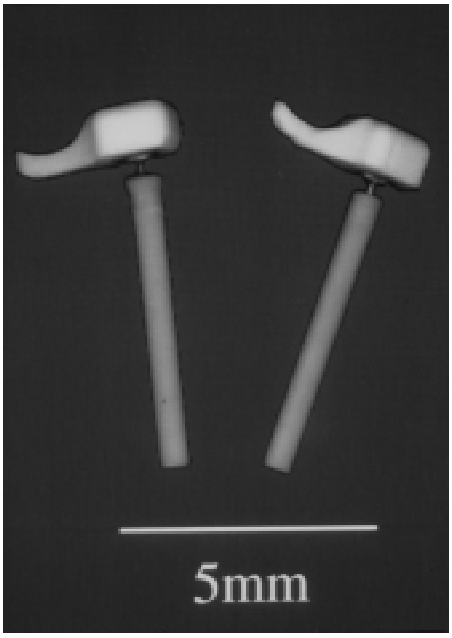


Fig. 39. Ossicular replacement prostheses. Head of the prosthesis is synthetic HA, and the stem is a bioactive composite of HA particles in a polyethylene matrix. (Photo courtesy of Professor Bill Bonfield and Dr. Elizabeth Tanner.)

substitute valves.''[92,93] The relative clinical merits of the two types of heart valves, mechanical versus tissue, are reviewed by Schoen *et al.*[93]

Because of their high mechanical reliability and resistance to blood clot formation, pyrolytic carbon-coated mechanical heart valves are often the valve replacement of choice. Bokros applied for a patent in 1967 describing the medical use of pyrolytic carbon coatings on metal substrates,[94] and the processing and applications in heart surgery were described soon thereafter.[95] The first time the low-temperature isotropic (LTI) carbon coatings were used in humans was as a prosthetic heart valve by DeBakey in 1969.[95] Many current prosthetic heart valves have LTI carbon coatings for the orifice and/or occluder (Fig. 41) because of the excellent resistance to blood clot formation and long fatigue life.[96] Almost a million lives have been prolonged through the use of this bioceramic in heart valves.[98]

Three types of carbon are used in biomedical devices: the LTI variety of pyrolytic carbon, glassy (vitreous) carbon, and the ultra-low-temperature isotropic (ULTI) form of vapor-deposited carbon.[97–99] These carbon materials are integral and monolithic materials (glassy carbon and LTI carbon) or impermeable thin coatings (ULTI carbon). These three forms do not suffer from the integrity problems typical of other available carbon materials. With the exception of the LTI carbons codeposited with silicon, all the carbon materials in clinical use are pure elemental carbon. Up to 20 wt% silicon has been added to LTI carbon without significantly affecting the biocompatibility of the material. The composition, structure, and fabrication of the three clinically relevant carbons are unique when compared with the more-common, naturally occurring form of carbon (i.e., graphite) and other industrial forms produced from pure elemental carbon.

The LTI, ULTI, and glassy carbons are subcrystalline forms and represent a lower degree of crystal perfection. There is no order between the layers such as there is in graphite; therefore, the crystal structure of these carbons is two-dimensional. Such a structure, called turbostratic, has densities of ~1400–2100 $kg \cdot m^{-3}$. High-density LTI carbons are the strongest bulk forms of carbon, and their strength can be increased further by adding

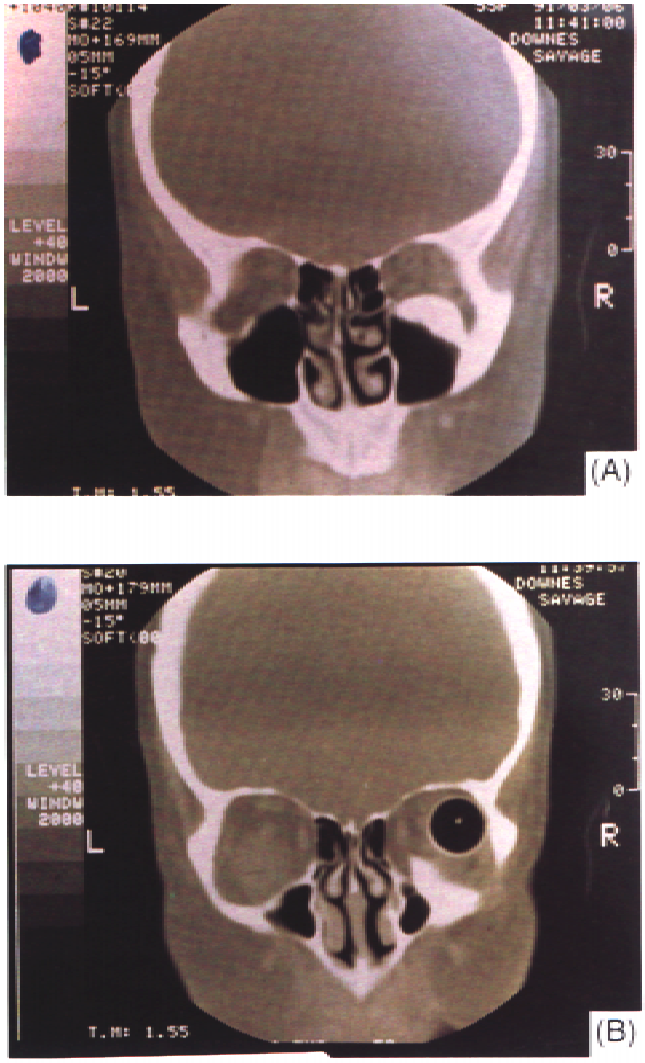


Fig. 40. X-ray of use of bioactive composite of HA particles in a polyethylene matrix in (A) repair of a fracture of the orbit of the eye shown in (B). (Photo courtesy of Professor Bill Bonfield and Dr. Elizabeth Tanner.)

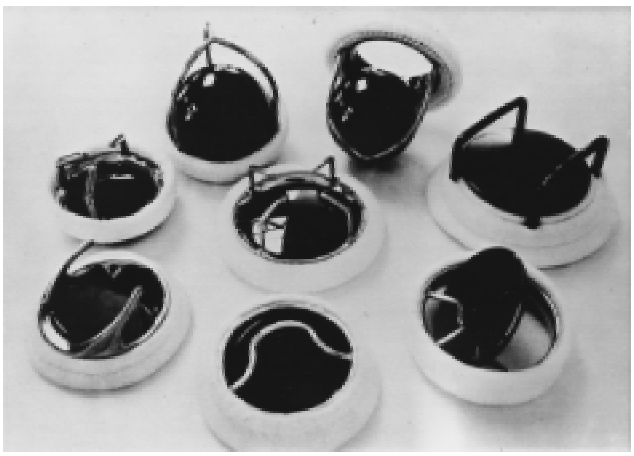


Fig. 41. Low-temperature isotropic (LIT) pyrolitic-carbon-coated heart valves. (Photo courtesy of Dr. Jack Bokros.)

silicon. ULTI carbon also can be produced with high densities and strengths, but it is available only as a thin coating (0.1–1.0 μm) of pure carbon. Glassy carbon is inherently a low-density material and, as such, is weak. Its strength cannot be increased through processing. Processing of all three types of medical carbons are discussed in Haubold *et al.*[98]

The mechanical properties of the various carbons are intimately related to their microstructures. It is possible to generate materials with low elastic moduli (20 GPa) and high flexural strength (275–620 MPa) in an isotropic carbon. There are many benefits as a result of this combination of properties, e.g., large strains (~2%) are possible without fracture. The turbostratic carbons are very tough when compared with ceramics, such as Al_2O_3. The energy to fracture for LTI carbon is ~5.5 $MJ \cdot m^{-3}$, compared with 0.18 $MJ \cdot m^{-3}$ for Al_2O_3; i.e., the carbon is ~25 times as tough.

The turbostratic carbon materials have extremely good wear resistance, part of which can be attributed to their toughness, i.e., their capacity to sustain large local elastic strains under concentrated or point loading without galling or incurring surface damage. The bond strength of the ULTI carbon to stainless steel and to Ti–6Al–4V exceeds 70 MPa, as measured with a thin-film adhesion tester. This excellent bond is achieved, in part, through the formation of interfacial carbides. The ULTI carbon coating generally has a lower bond strength with materials that do not form carbides.

Because of the extremely large number of loading cycles involved in a heart valve, 38 million beats/year,[99] an important characteristic of the turbostratic carbons is their fatigue resistance. In general, cyclic fatigue resistance of LTI carbon coatings on titanium or cobalt–chromium alloys is excellent. It is especially important to eliminate small cracks at the interface of the coating and the metallic substrate during processing and handling to assure long lifetimes under cyclic fatigue conditions, as discussed by Dauskardt and Ritchie.[99] Properties of the turbostratic carbons are listed in Ref. 98 with uses of glassy, LTI, and ULTI carbons in various medical areas.

(2) Hydroxyapatite

Another bioceramic coating that has reached a significant level of clinical application is the use of HA, as a coating on porous metal surfaces for fixation of orthopedic prostheses (Fig. 42). This approach combines types II and III methods of fixation (Table II) and originates from the observations of Ducheyne and colleagues[9] in 1980 that HA powder in the pores of a porous, coated-metal implant would significantly affect the rate and vitality of bone in growth into the pores. Many investigators have explored various means of applying the HA coating,[3,10,13,25,26] with plasma spray coating generally being preferred.[26,100] There is a substantial enhancement of the early stage interfacial bond strength of implants with a plasma-sprayed HA coating when compared with porous metals without the coating, as illustrated in Fig. 9.[101] Long-term animal studies and clinical trials of load-bearing dental and orthopedic prostheses suggest that some HA coatings may degrade or come off with time, depending upon the degree of crystallinity of the HA layer.[25,26] The clinical consequences continue to be debated and will not be conclusive until 10 year survivability statistics from multiple clinical centers have been reported.[102,103] However, early results are encouraging as an alternative to PMMA ''bone cement'' fixation of orthopedic devices.

IX. Therapeutic Applications

A significant problem in the radiation treatment of cancer is the serious systemic side effects. Localization of the radiation at the site of the tumor decreases the radiation dosage required to kill the cancer cells and thereby minimizes side effect toxicities. An innovative approach to the localized delivery of radioactive yttrium-90 (Y^{90}) to treat liver cancer has been developed by Delbert Day at University of Missouri-Rolla using glass microspheres.[104] A yttria aluminosilicate (YAS) glass, containing Y^{89}, is made in the form of 25 μm microspheres. The microspheres, prior to use in hepatic arterial infusion therapy, are bombarded by neutrons that create Y^{90}, a radioactive isotope that is a short-half-life (64 h), short-range (2.5–3 mm in the liver) β-emitter. The microspheres are injected through a catheter placed in an artery, and the blood stream carries them to the liver, where a high proportion goes to the cancerous part because of the approximately 3 times increased blood supply. A localized dosage of up to 15×10^3 rads can be delivered in this manner, whereas a maximum of 3×10^3 rads of external radiation can be tolerated by the patient. The YAS glass microspheres have been safely used for more than 5 years to irradiate, up to 15×10^3 rads, malignant tumors in the liver in more than 100 patients. The rare-earth aluminosilicate glass system provides excellent chemical durability in the body, which is important, because it keeps the radioisotope concentrated in the target organ and prevents dissolution and migration via the circulation of blood. Application of this concept is being explored for treatment of tumors in the kidney and also for treatment of arthritic joints.[104]

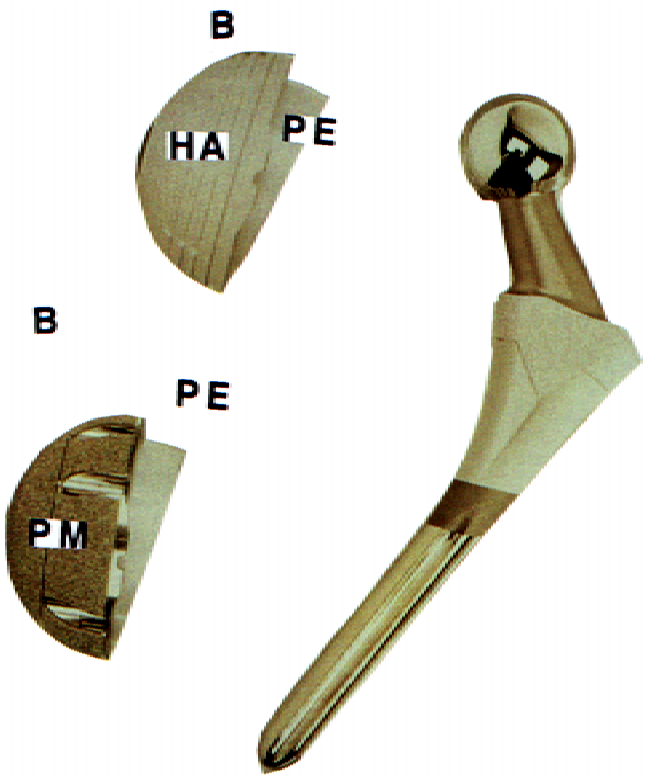


Fig. 42. Synthetic HA coatings on (A) femoral stem and (B) acetabular cup of a total hip prosthesis. Note the porous metal [PM] surface prior to coating and the ultra-high molecular-weight of polyethylene [PE] liner used in the cups to minimize friction. (Photo courtesy of Dr. Bernard Kapp, Stratec Medical.)

X. Summary

Bioceramics has become an integral and vital segment of our modern health care delivery system. The full potential has only begun to be recognized as this century ends. Most of the developments to date have been based upon trial-and-error experiments. However, a theoretical foundation for the development of a new generation of bioceramics now exists. In the next century, the composition, microstructure, and molecular surface chemistry of various types of bioceramics will be tai-

lored to match the specific biological and metabolic requirements of tissues or disease states. This ''molecular-based pharmaceutical'' approach to the design of bioceramics will be coupled with tissue and genetic engineering, sensor technology, and information processing to produce a range of products and applications not imagined presently. This new generation of bioceramics should enhance the quality of life of millions of people as they grow older.

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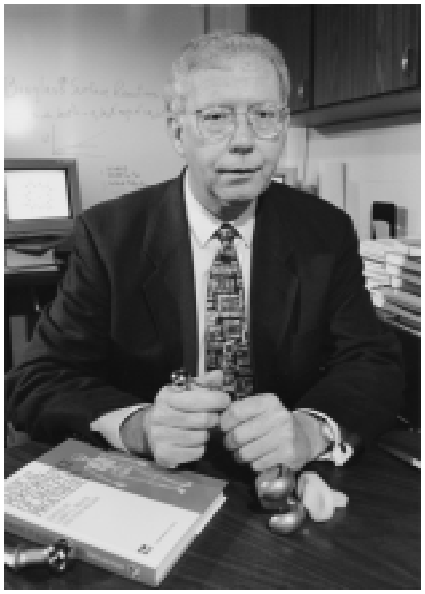

Dr. Larry Hench graduated from The Ohio State University in 1961 and 1964 with B.S. and Ph.D. degrees in ceramic engineering. He went to the University of Florida in 1964 as an Assistant Professor. There, in 1969, he discovered Bioglass, the first synthetic material to bond with living tissue. In recognition of this discovery, Dr. Hench was awarded the 1977 Clemson Award for Basic Research by the Society of Biomaterials and the 1980 George W. Morey Award by the Glass Division of The American Ceramic Society. The technology for manufacturing bioactive glasses was transferred successfully to industry in 1984. Dr. Hench was promoted to Full Professor at the University of Florida in 1972 and to Graduate Research Professor of Materials Science and Engineering in 1986. He also served as Director for the Bioglass Research Center and Co-Director of the Advanced Materials Research Center at the University of Florida. Professor Hench and his students conducted a series of basic science studies during 1978–1985 on glasses to immobilize high-level radioactive wastes, including the first deep geological burial in Sweden. Professor Hench began a study in 1979 of the low-temperature sol–gel processing of glasses, ceramics, and composites, which led to a new class of commercial silica materials for optics and environmental sensors. Professor Hench's studies have resulted in 480 scientific publications, 22 books, and 43 U.S. and foreign patents. He is a member of and has received awards from numerous professional societies. Dr. Hench accepted the University of London Chair at Imperial College of Science, Technology, and Medicine as Professor of Ceramic Materials in 1996. He also serves as Director of the Imperial College Centre for Tissue Regeneration and Repair and as Associate Director of the University of London Interdisciplinary Centre for Biomedical Research. He is actively involved in tissue engineering, artificial organs, and materials for regeneration of diseased, damaged, or aging tissues.