Surface-Active Biomaterials

Larry L. Hench and June Wilson

Summary. Since the discovery in 1969 of a man-made surface-active material that would bond to bone, a range of materials with the same ability has been developed. These include glass, glass-ceramic, and ceramic materials which have a range of reaction rates and from which it should be possible to select a surface-active material for a specific application. The available materials and their similarities, differences, and current clinical applications are reviewed.

In 1980 an article on biomaterials documented the use of more than 40 different materials in more than 50 different medical and dental devices (*1*). A common characteristic of most of these biomaterials and devices, also discussed in a recent NIH conference (*2*) and a recent book (*3*), is their so-called "bio-inertness." However, it is now well established that no material implanted in living tissues is inert. All materials elicit a response from living tissues. Four types of response are possible: (i) if the material is toxic, the surrounding tissue dies; (ii) if the material is nontoxic and dissolves, the surrounding tissue replaces it; (iii) if the material is nontoxic and biologically inactive, a fibrous tissue capsule of variable thickness forms; and (iv) if the material is nontoxic and biologically active, an interfacial bond forms.

The purpose of this article is to discuss the current state of the science and development for clinical application of this last class of surface-active biomaterials. It is timely to do so for several reasons. First, there is increasing clinical evidence that the useful life of most implants made from inactive biomaterials is much shorter than the patient requires (*2*). Second, failure usually follows movement at the implant-tissue interface. Third, surface-active biomaterials are becoming more widely used in clinical applications, particularly musculoskeletal and dental applications. Fourth, a scientific understanding of the mechanisms of bonding between living and nonliving interfaces is emerging and has major implications for the biological sciences in general as well as for medical and dental surgery. It is essential that this class of biomaterials be understood and used properly if surface-active implants are to realize their potential for long-term stability.

The authors are at the University of Florida, Gainesville 32611. Larry L. Hench is a professor of materials science in the College of Engineering and director of the Bioglass Research Center. June Wilson is a research associate in the Department of Surgery, College of Medicine, and is program manager of the Bioglass Research Center.

Four major categories of surface-active biomaterials have been developed during the past 15 years; dense hydroxylapatite (HA) ceramics, bioactive glasses, bioactive glass-ceramics, and bioactive composites. After many years of animal tests, clinical trials of all four types have begun, and some have been in progress for as long as 5 years.

Hydroxylapatite Ceramics

Hydroxylapatite materials have been used for implants in many forms, especially in dental applications. Denissen (*4*) reported that root-shaped HA implants, buried in contoured, fresh extraction sites in dogs, bonded in place without bone resorption around them. These, however, were not load-bearing implants, but were analogous to the alveolar ridge maintenance devices now in use. In 1983 de Putter *et al.* (*5*) showed that load-bearing, transmucosal implants of dense HA acted as ankylotic elements, similar to bone that is not load-bearing; that is, they did not acquire a periodontal ligament attachment. The gingival tissue response did resemble the natural interface, but chewing forces caused fatigue failure in the implants. The studies of Ogiso *et al.* (*6*), in which hemidesmosomes were identified, support the possibility of normal epithelial attachment to HA surfaces. However, de Putter *et al.* (*5*) concluded that apatite ceramics had no clinical potential in situations where forces other than compression play a role. Recent work by de Putter, de Groot, and others in the Netherlands (*7*) suggests that prestressing the HA implant will prevent fatigue fracture. When HA was implanted in the long bone in experimental animals by Denissen (*4*), the tissue reaction filled an oversized hole and the bone grew as a collar over protruding parts of the implant. This has been noted by other workers who used solid HA in skeletal models (*8*). The ability to fill an oversized implant site might provide a clinical advantage if the overgrowth of bone could be effectively understood and controlled.

In restoration of the bony conduction system and canal wall of the middle ear, HA in a combination of porous and dense forms has been used successfully by Grote (*9*). Where there is no demand for mechanical strength of the device, as in the middle ear, bony ingrowth into porous nonresorbable HA can provide a good functioning structure with integration of implant and host bone.

Hydroxylapatite has been used clinically in particulate form to augment the alveolar ridge (*10*) and in a variety of maxillofacial applications (*11*); it is especially effective when the particulates are mixed with autogenous bone. Data covering periods of 4 and 5 years show continued success with ridge augmentation (*11*). However, particulate HA, when used as a treatment for periodontal disease, has not yet fulfilled its early promise in long-term applications.

Hydroxylapatite has been used as a coating on other, mechanically stronger, materials to provide load-bearing implants. Ducheyne *et al.* (*12*) used an HA coating on porous stainless steel as a tooth replacement. The HA in this application was resorbable and allowed bone to be incorporated within the porous metal. The coating allowed good initial stabilization of the artificial tooth in the critical early weeks after implantation.

In reviewing the uses of hydroxylapatites it becomes clear that the material, which forms the mineral component of bone, is entirely biocompatible in its many forms but can have variable properties related to its method of preparation. It may be solid or particulate, as mentioned here; but it has also been reported in microporous (<5 μm) and macroporous (>100 μm) forms and with major or minimal resorbability. The factors governing resorbability have been

reviewed by Jarcho (*13*), and it is clear that close attention to manufacturing procedures is essential for the production of HA implants that will behave predictably and reliably in vivo.

Surface-Active Glasses

All surface-active glasses under investigation today derive from materials developed at the University of Florida. These Bioglass (*14*) materials were the first man-made materials that formed a chemical bond with bone. Only certain compositions achieve the bone bond, and these are shown in Fig. 1 and discussed in a later section.

Potential clinical applications of implants made from or incorporating surface-active glass components exist in orthopedic, otolaryngological, dental, and maxillofacial surgery. The inherent mechanical weakness of the glass has divided these applications into two groups, those where mechanical strength is unimportant and those where it is critical. Implants in the first group include devices for maintenance of the alveolar ridges in mandible and maxilla and restoration of the ossicular chain in the middle ear. Clinical trials in both of these areas are in progress and to date have been successful. The ridge maintenance devices are cones made from a Bioglass composition, designated 45S5, which are buried in a reamed extraction site. Middle ear prostheses made from the same 45S5 components are used to replace all or part of the ossicular chain in patients who have a history of chronic otitis media and contributing developmental defects. Implants made from Bioglass and those made from other materials now in clinical use have been compared by Merwin *et al.* (*14a*), who showed that a significant determinant of long-term stability of Bioglass devices is the presence of a soft-tissue bond between the implant and the tympanic membrane. This has not been seen with any other material. This bond prevents movement at that critical interface at an early stage and prevents the inflammation and scarring which are associated with loss of transmission and eventual extrusion. If the periosteum of the remaining ossicles can be retained at the interface with the Bioglass implant, a soft-tissue bond is induced there and provides an interface more closely resembling the natural one between undamaged ossicles. If the periosteum is removed, either accidentally or deliberately, the bonded interface will be an ankylotic one resembling that between allogenic ossicular implants, at present considered to be the best available for clinical use. In experiments with mice the soft tissue between Bioglass implants and the remaining ossicular chain and thin collagenous capsule around the implants has persisted apparently unaltered throughout the animals' lifetime. These results and data from other animal experiments reported recently by Merwin *et al.* (*14a*) suggest that modes of failure such as extrusion and scarring associated with other available materials, as reported by various authors (*9*), will not compromise long-term survival of these implants. In addition, the machinability and transparency of these bioactive glass implants allow ease and flexibility of use by the surgeon in the operating room.

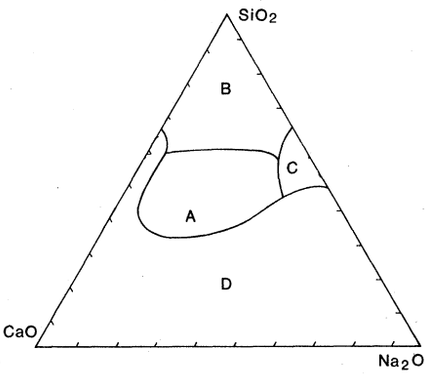


Fig. 1. Behavior of bioactive glass of different compositions. Region A, bone bonding; B, fibrous tissue encapsulation; C, dissolution; D, non–glass-forming. All compositions have a constant 6 percent P_2O_5 by weight.

The second set of applications requires the combination of bone-bonding activity of the bioactive glass with mechanical properties of a substrate. Bioglass coatings have been successfully applied to substrates of stainless steel, Vitallium (*15*), titanium metals, and high-density alumina ceramic. A composite of 45S5 Bioglass and stainless steel fibers has been produced (*16*) which can reproduce the mechanical properties of bone without compromising the integrity of the glass-metal interface. Extensive animal experiments (*3*) have shown that Bioglass coatings on orthopedic devices for noncement fixation should provide a generation of hip prostheses with a longer life than the 20 years available with conventional cement fixation. Load bearing can be achieved with dental implants made from coated alumina or coated metals. Smith (*17*) showed that coated-alumina devices have excellent mechanical behavior. Japanese scientists have used stainless steel implants with Bioglass coatings to hold crowns. T functioned well in dogs (*18*) and currently being used in clinical tria Japan.

Considerable attention has been g to the use of Bioglass-coated implan either alumina or metal in orthodon When a tooth is stressed it may moved in the direction of the load. movement is a consequence of o clastic activity in which bone is rem and osteoblastic activity in which bo laid down under the influence o creased and decreased pressure, res tively. This is the basis of orthod movement of teeth, and there can complication if undesired moveme produced in the teeth which act as chors. It is known that ankylosed t are not moved in this way (*19*).

Smith (*17*) inserted blade-shaped plants of alumina, coated with sur active glass, into the alveolar ridg rhesus monkeys. These animals h rod protruding through the gingiv which, after 9 weeks of healing, pos hold a lingual arch appliance wer tached. The anchors were then subje to forces up to 950 g for several w with no movement of the implant an change in adjacent bone. Smith sug ed that the presence of connective sue, as in the periosteum and period membrane, is essential for the cel involvement that causes teeth to m Absence of this connective tissue i essentially ankylosed pegs, as in a losed teeth, prevented this moven Paige *et al.* (*20*), recognizing that u orthodontic anchors would have t small and simple in shape, showed Smith's findings could apply to cc Vitallium wires as small as 2 m diameter. Turley *et al.* (*21*) put s coated-alumina implants into mon to produce maxillary expansion equally good results, and Grey *et al.* used Bioglass-coated Vitallium impl only 1.6 mm in diameter, with e success in rabbits. When these odontic pegs are removed, as they be by rotational force, the gel shears and only scraps of biocompa material are left in the healing w area.

In all of these applications that re coating of bioactive glass on metal essential to consider the conseque of introduction of other chemicals the glass. Recent experiments showed that accidental introductic aluminum into the glass during co will prevent bonding. It has been gested that the introduction of other al oxides will either alter the rea

rate of the glass or facilitate coating procedures. However, Gross and Strunz (*24*), in the course of numerous comparative evaluations of a wide range of bioactive materials, found that the introduction of other oxides, particularly those of zirconium, titanium, and tantalum, can impair bone development (by disturbance of osteoblast metabolism), matrix vesicles function, and collagen deposition. These oxides should not be used in materials for bone and tooth replacement.

Glass-Ceramics

The surface-active, bone-bonding glass formulations can also be produced as glass-ceramics by nucleation and growth of crystals in the glass. Transparent glasses, which are monophase systems, become opaque glass-ceramics, which contain crystals within a glassy matrix. This transformation produces materials that are often mechanically stronger. However, the grain boundaries in a glass-ceramic may provide sites at which dissolution can occur (*25*).

One such material, Ceravital (*26*), which is based on the Bioglass formulations but has a lower alkali content, has been extensively tested in orthopedic, dental, maxillofacial, and otolaryngological applications. The surface-active glass-ceramic, used as a coating on a metal femoral head endoprosthesis, provided good noncement fixation in dogs for periods up to 20 weeks. Tests to failure of these implants postmortem showed that rupture lines occurred in the bone and not the interface. This provides confirmation that the interface is indeed stronger than the bone.

Good results were obtained when Ceravital as a bulk material was used for jaw augmentation of osteotomies in pigs. More than 60 percent of the surface was bonded to the surrounding bone after 1 year (*27*). Bunte and Strunz (*28*) performed a trial study with 12 implants in humans. Overall the results were very good, and all the implants were incorporated without irritation. However, subperiosteal implants gave poor results, as the thin layer of bone over the implant caused pain during loading, and they were removed.

Ceravital has been used successfully for middle-ear prosthetic devices. Reck and Helms (*29*) used it to restore the ossicular chain and reconstruct the bony posterior wall of the chamber in rabbits. As reported previously (*25*), small areas of lysis at the surface occurred where capillaries in the bone were adjacent to the glass-ceramic. These areas became filled with new bone; which continued to grow over the surface of the implant to a depth of 40 μm. Mucosa covered this bone, and the two layers prevented further lysis of the material for up to 2 years in animals. Where mucosa directly covered the implant the lysis sometimes progressed, and to prevent this bone pâté was required between the implant and soft tissue to ensure the development of bone at the interface. After 5 years of clinical use of Ceravital in patients, Reck and Helms concluded that for total ossicular chain reconstruction prostheses made of this material give better results than preserved allogenic ossicles, previously considered to be the best available. Almost all middle-ear devices must be contoured in the operating room, and it has been shown clinically and experimentally that Ceravital glass-ceramic can be successfully contoured with standard operating room drilling equipment, albeit at a slower rate than bioactive glass. Ceravital devices were contoured by Babighian (*30*), who also confirmed the need for bone pâté to prevent extrusion through the soft tissue of the tympanic membrane. When the pâté was not used extrusion almost invariably occurred within a short time.

A bioactive glass-ceramic has been developed by Vogel and co-workers at the University of Jena in East Germany. Their objective is to produce a material that can be easily machined, and they use variations in composition to produce different properties in the material, including magnetic properties and bioactivity. The bioactive glass-ceramic, which is now undergoing preclinical testing, consists of a mica crystalline phase for machinability and an apatite crystalline phase for bioactivity in a residual glassy phase of unknown composition. Implantations of unloaded samples in guinea pig bone showed satisfactory bonding after 16 weeks (*31*).

At the Kyoto Institute in Japan a new glass-ceramic, known as A/W ceramic, has been developed in a search for bioactive materials with sufficient strength to allow their use in load-bearing conditions. The material contains HA and wollastonite (a form of a calcium silicate) in a glassy phase of undetermined composition. Implantation of unloaded implants in rabbit tibiae showed good bonding at 8 weeks with a bonding strength greater than that of Bioglass, comparable to that of dense HA, but 70 percent of the value for bone. At 25 weeks, when only A/W and dense HA were compared, the relative strengths remained the same (*32*). The material was used clinically to provide spinal fusion in a patient for whom no autologous bone was available (*33*) and has been in place and functioning well for 2 years.

Surface-Active Composites

Many composite materials have been produced since the bone- and tissue-bonding abilities of bioactive materials were recognized. All natural tissues are themselves composites, and the combination of bioactivity and specific mechanical properties should allow the production of materials with properties selected for particular biomedical problems. This is an attractive theory, but in practice most of these composites have not been successful. The principal mode of failure is at the bond between matrix and filler, and many potential materials have failed at this interface under the action of tissue fluid and cellular enzymes. However, success has been achieved in some areas. When particulate HA is mixed with finely ground autologous bone the resulting mixture becomes a composite after implantation as physicochemical bonding takes place in vivo between the components, and this provides a material that is more satisfactory than either component alone in maxillofacial and dental applications (*10*).

A successful composite of 45S5 Bioglass and 316L stainless steel has been made (*16*) by bonding the glass onto a sintered stainless steel fiber matrix. This process results in a composite which has two continuous phases, rather than matrix and filler, but which has only the bioactive phase at the interface with bone. This material can be produced with variable mechanical properties for orthopedic applications.

A novel approach to providing a material that can be used to fix orthopedic prostheses, notably artificial hips, with the convenience of cement fixation allied with the greater long-term reliability of noncement fixation by bioactive materials, has been taken by the Leitz Company in the production of Palavital, a mixture of the conventional bone cement polymethylmethacrylate (PMMA) with Ceravital glass-ceramic particles and a small amount of glass fiber. This cement mixture polymerizes in situ, as does PMMA. After implantation, this bioceramic bone cement, while not strictly a composite, gives a combination of mechanical and physicochemical adhesion,

with junctions of bone to the cement instead of the fibrous capsule usual with bone cements. Preliminary tests (*34*) showed the mechanical strength of Palavital to be comparable to that of other bone cements. Because of its bioactive component, this material may be superior in long-term behavior to other bone cements and may alleviate problems caused by loosening of prosthetic devices. More experimental data are needed to evaluate the contribution of the heat generated on polymerization of PMMA in situ to long-term loosening or long-term stability of the heterogeneous interface.

Interfacial Bonding

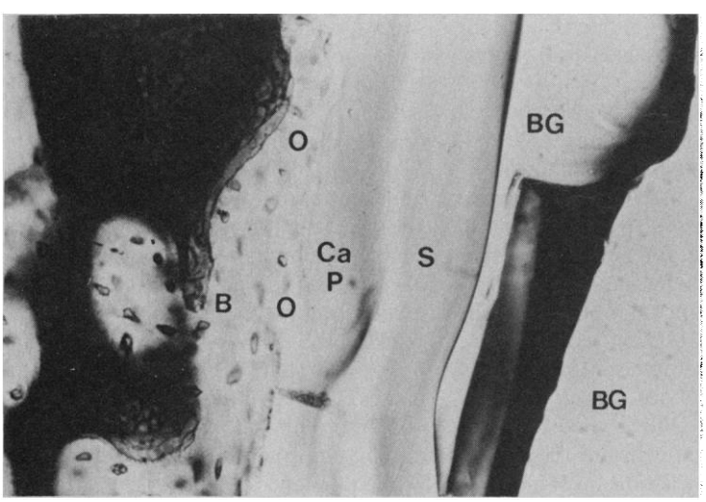
It is a common characteristic of bioactive implants that an interfacial bond forms between the smooth, nonporous surface of the material and adjacent tissue. The idea that chemical bonding could be achieved between a nonliving material and living tissue was first proposed to the U.S. Army Medical R&D Command by Hench in 1967, and evidence for a chemically bonded implant-tissue interface soon followed (*35*). Specially designed bioactive glasses containing Na_2O, CaO, P_2O_5. and SiO_2, termed Bioglasses, were shown to bond to rat femoral bone as early as 10 days postoperatively. The time dependence of hard-tissue bonding, strength of the bond, and proposed bonding mechanisms were soon described. A few years later these findings began to be confirmed with the same bioactive glasses and related compositions of surface-active glass-ceramics (*27, 28, 32, 36*).

Driskell *et al.* (*37*) made the first observation of apparent chemical bonding of bone to tricalcium phosphate ceramics. However, the most convincing evidence of this phenomenon for surface-active ceramics was provided by the studies of Jarcho and co-workers (*8, 13*) on bonding of dense HA implants. Subsequently, numerous investigators, using a variety of materials and animal models, showed that bone bonds to surface-active apatite ceramics (*10, 38*).

A unique feature of surface-active biomaterials is that the interfacial bond with bone is generally stronger than either the bone or the implant. Fracture almost never occurs at the bone-implant interface during mechanical testing (*3*). The strength of the bond therefore has not been measured. However, a series of studies with eight different models has established a lower limit of interfacial bond strength with surface-active glass implants (45S5 Bioglass). The maximum stress level sustained by a load-bearing segmental bone implant loaded in shear, in a torsional test, was calculated as 117 MPa. The femur fractured at this stress, which is 1 standard deviation below the average shear strength of normally healed fractured bone in the same animal (monkey) at 42 weeks. Eventual bone remodeling will increase the stress that the repaired bone can withstand and should lead to a measurable interfacial stress value equivalent to that of natural bone. The average interfacial stress measured for the load-bearing segmental bone model was 83 MPa. This is substantially more than the 3.2-MPa average shear stress calculated for the same 45S5 Bioglass material tested in the form of non–load-bearing cylinders in the cortices of dog femurs, assuming nominal contact area. This wide range of values is associated, in part, with the fact that the interfacial area of mineralized bone bonded to a surface-active implant increases with time and with the loads applied. An unloaded implant develops a bond much more slowly, just as it takes longer for an unloaded fracture to heal. Also, dehydration of the bonding zone can occur during testing and lead to shear failure within the surface gel layer. Other studies of interfacial shear strengths of bioactive glasses and glass-ceramics also show wide ranges of results because of these variables (*32*).

Mechanisms of Bonding

The bonding mechanisms of surface-active glasses and glass-ceramics involve a complex combination of physicochemical and ultrastructural phenomena (*39–41*). At the microscopic level the bond between a surface-active glass and bone appears as a sharp interface, although a compositional gradient is present within the interfacial layer formed on the implant. Figure 2 shows the interface between bone and surface-active glass in a 4-week rat tibial implant. The areas labeled show bulk 45S5 Bioglass, an SiO_2-rich layer, a Ca,P-rich layer, and bone. Electron microprobe analysis and scanning electron microscopy–energy-dispersive x-ray analysis (SEM-EDXA) were used to measure this interfacial compositional sequence, which extended to a thickness of 70 μm at 4 weeks, 75 μm at 12 weeks, 97 μm at 52 weeks, and 268 μm at 128 weeks (the lifetime of a male Sprague-Dawley rat). The thickness of



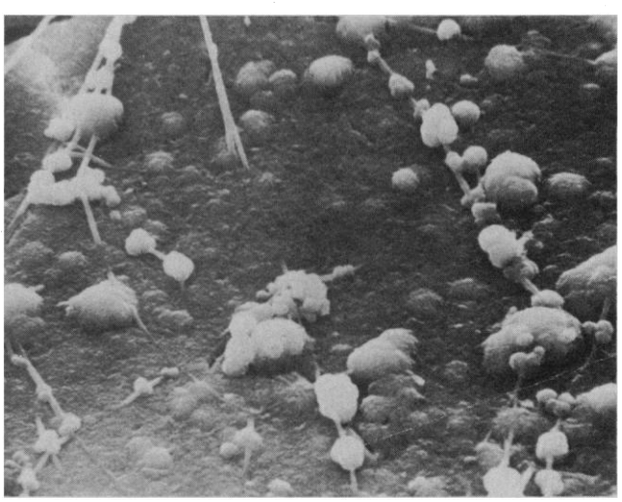
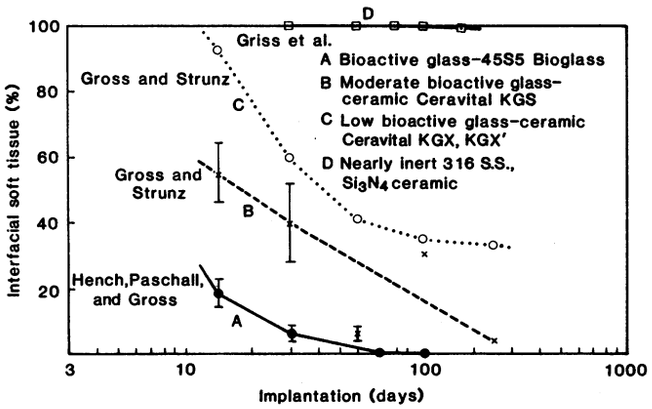


Fig. 2 (left). Bonded interface between rat tibial bone and surface-active glass 30 days after implantation. BG, bulk 45S5 Bioglass; S, SiO_2-rich layer; CaP, Ca,P-rich layer; B, bone; O, osteocyte (×200). Fig. 3 (right). Scanning electron micrograph of collagen fibers attached to a 45S5 Bioglass surface after exposure in vitro at 37°C for 10 days (×5000). [Photo courtesy C. G. Pantano]



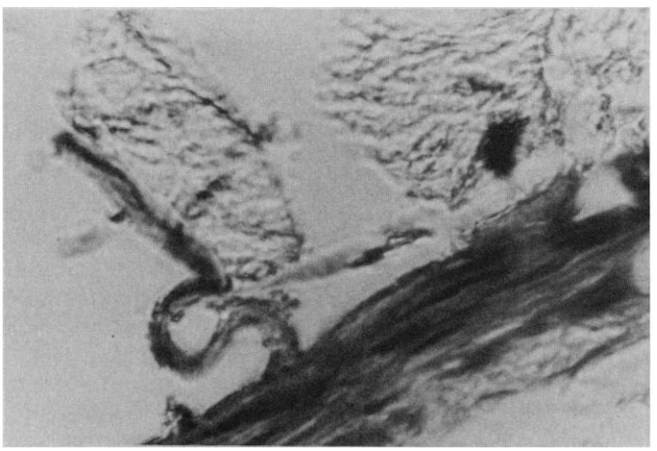


Fig. 4 (left). Time dependence of replacement of soft tissue with bone for various biomaterials (*3*). Fig. 5 (right). Soft tissue attachment to partially decalcified 45S5 Bioglass after 8 weeks subcutis in rat (×250). Note greater adhesion than cohesion.

the Ca,P-rich zone remains relatively constant at 30 to 40 μm during this time period, whereas the silica-rich layer increases at a rate approximately proportional to $t^{1/2}$ due to continued exchange of Na^+ in the glass with H^+ ions from solution.

The Ca,P-rich layer forms instantaneously on the surface-active glasses, as shown by Auger electron spectroscopy of the 45S5 Bioglass composition after 1 hour in vitro (distilled water at 37°C) or in vivo (*40*). Initially the Ca,P-rich layer is amorphous, but it crystallizes into mixed hydroxyl-carbonate apatite agglomerates within 7 to 10 days. When the apatite phase crystallizes in the presence of collagen fibers, in vitro or in vivo, the collagen becomes structurally integrated within the apatite agglomerates and vice versa (Fig. 3). The presence of mucopolysaccharides, such as chondroitin sulfate D, significantly enhances the physicochemical interaction between the crystallizing apatite layer and collagen. Between the collagen fibers and surface-active glass in vivo there is an amorphous zone 80 to 100 nm thick, which can be mineralized. This zone or seam apparently consists of extracellular ground substance which may contain mucopolysaccharides, glycoproteins, and various nectins, and provides a basis for attachment of collagen. Such a seam is present only at the interface of surface-active biomaterials bonded to bone.

After formation of the amorphous cementing zone on the Ca,P-rich layer, further steps in bone development and bonding are governed by osteoblasts in the implant area. Gross and Strunz (*24*) have shown that, at the bonding interface, osteoblasts provide (i) collagen and ground substance and (ii) matrix vesicles for primary mineralization. The sequence of events is consistent with present concepts of primary bone formation. Gross and Strunz summarized their findings: "Within the extracellular matrix and between small bundles of fibrils, matrix vesicles appear and display small, electron-dense, needle-like crystallites assumed to be apatite. After rupture of the vesicle membrane, calcifying fronts are formed. Often this process begins and is therefore more pronounced in the surroundings of the implant and the adjacent osteoblast, but may also start in the area around the osteoblast and then involve the surroundings of the already mineralized seam of amorphous cementing substance at the interface. Later on the whole area is mineralized, the osteocytes being rather evenly distributed and often arranged with their long axis parallel to the surface of the implant. This feature is found in different species—rats, dogs, pigs, chickens and humans—and provides the morphologic basis for the biomechanical quality of the bone bonding."

Systematic studies by Hench *et al.* (*3, 39, 40*) and Gross and Strunz (*24, 25, 41*) have identified many of the compositional factors that can affect bone bonding to surface-active glasses. Substitution of 5 to 15 percent B_2O_3 for SiO_2 in the original 45S5 Bioglass formula (45 SiO_2, 6 P_2O_5, 24.5 CaO, and 24.5 Na_2O, in percent by weight) results in a more reactive composition, whereas replacement of varying proportions of CaO with CaF_2 produces glasses with a wide range of surface activity and resistance to demineralization (*42*). Variations in Na_2O/CaO ratios and $SiO_2/(Na_2O + CaO)$ ratios in the 45S5 Bioglass formula, with a constant 6.0 percent by weight P_2O_5, result in a compositional field (region A in Fig. 1) where bone bonding occurs in the rat within 30 days. Compositions in region B do not bond, those in region C resorb, and those in region D cannot be formed into glasses.

Gross and Strunz (*24*) have shown that a range of low-alkali (0 to 5 percent by weight) surface-active glass-ceramics (Ceravital) bond to bone; however, addition of Al_2O_3, Ta_2O_5, TiO_2, Sb_2O_3, or ZrO_2 tends to inhibit bone-bonding mechanisms at the interface. Addition of as little as 3 percent Al_2O_3 in the 45S5 formula seriously degrades bondability of the material (*23*). A series of commercial vitreous enamels showed similarly negative results (*41*). Often a seam of unmineralized osteoid tissue was present, indicating release of substances that impede steps of the mineralization process. Morphometric measurements also showed persistence of chondroid on the implant interface for these compositions, suggesting inhibition of cellular differentiation into osteoblasts. The inhibited cells did not switch from the production of metachromic ground substance and type II collagen to the production of type I collagen and organelles for mineralization. In contrast, bioactive glasses and glass-ceramics, without such inhibiting elements, do show bonding with osteoblasts, matrix vesicles, and normal mineralization at the bonding interface. Gross and Strunz (*41*) showed that compositions which bond release monophosphates at their interface, whereas nonbonding compositions release tri-, tetra-, or polyphosphates. The altered monophosphate and polyphosphate concentrations may influence local alkaline phosphatase concentrations and the formation or function of matrix vesicles.

Glasses with a high P_2O_5 content also show adverse effects on tissue reactions and bonding; which may also be related to the interfacial monophosphate and polyphosphates developed in vivo (*41*).

These and other studies have identified a number of the surface chemical features essential for a stable interfacial bond with bone. In hard tissues, the central issue seems to be the relative competition between fibrogenesis and osteogenesis at the interface. Many factors, such as movement or infection, favor proliferation of the less highly differentiated fibroblasts with eventual capsule formation, whereas very specific conditions must be satisfied for osteogenesis to occur (*3*). Of course, this is exactly the situation in the repair of natural tissues. Recent studies (*43*) have indicated that attachment of osteogenic stem cells to a precursor acellular structure on an implant is necessary for differentiation to proceed and mineralizable bone matrix to be generated. The tissue culture findings, comparing CHO, NIL, and HeLa fibroblast cell lines with primary bone cell cultures, showed a factor of 3 to 10 decrease in rates of cell spreading and mitosis on the bioactive surfaces for cells with small fibronectin concentrations. In contrast, the time of spreading and division of osteoblast-like primary culture cells was equivalent on active and inert surfaces. These data indicate that a population of fibroblasts, such as that present at an implant interface in the first week of healing, will respond much more slowly on the bioactive surface, allowing attachment and proliferation of osteoblasts to be favored.

A quantitative comparison of the relative percentages of soft tissue, osteoid, chondroid, and bone contact, or bone connection [based on figure 14.35 in (*3*)] shows an extensive amount of soft tissue in contact with "bioinert" implants after 2 weeks (Fig. 4). This soft-tissue capsule remains during the lifetime of the implant and is responsible for eventual movement and failure of the interface. In contrast, by the end of 2 weeks surface-active implants show substantially less soft tissue, with the quantity varying with relative surface activity of the implant. The relative proportions of bonded bone, chondroid, and osteoid tissue at the implant interface are dependent on composition.

Evidence for the bonding process for HA implants was included in a review by Jarcho (*13*). He pointed to the resemblance between the mechanisms of bonding of this material and the Bioglass range of materials. As acellular bone matrix from differentiating osteoblasts at the surface appears, there is a narrow amorphous electron-dense band 3 to 5 μm wide. Between this area and the cells, collagen bundles are seen. Bone mineral crystals have been identified in this "amorphous area." This is the earliest observation; as the site matures the bonding zone shrinks to a depth of only 0.05 to 0.2 μm [which agrees with Denissen's observations (*4*)]. The eventual picture is of normal bone attached through a very thin bonding layer to bulk implant. A consequence of this thin bonding zone is a very high gradient in elastic modulus at the bonding interface (*3*), which is a major difference between surface-active apatites and surface-active glasses.

Soft Tissue Bonding to Surface-Active Materials

The role of collagen in the bonding of surface-active materials to bone has been clearly demonstrated, and a similar effect may be demonstrated with Bioglass in connective tissue if the processing problems associated with relative movement at the interface can be solved. After decalcification of the glass in situ, 8 weeks after subcutaneous implantation in rats, histological sections showed collagen fibers adherent to the remnants of the glass where the fibers in the capsule were pulled apart before the bond between glass and fiber was broken (Fig. 5). A similar effect was observed when fibers of Bioglass were implanted in muscle and then pulled out of the tissue bed (*44*). Although adhesion between a bioactive solid material and soft tissue is not likely to be useful in load-bearing situations or where there is other mechanical stress, there are applications where such a bond is desirable—for example, when surface-active glasses are used for replacement of the ossicular chain and in transmucosal applications. For such implants the bond that attaches the prosthesis to the two remaining ossicles or to the gingiva will be a soft-tissue bond. This interface resembles the natural interface in both form and function.

Conclusions

There is now a wide range of surface-active implants made from glasses, glass-ceramics, ceramics, and composites. All of them develop a bond with tissues that prevents motion at the interface. The implants are used in dental, maxillofacial, otolaryngological, and orthopedic surgery, although their use as load-bearing devices will require improvements in strength and fatigue resistance. The rate of bonding and the strength and stability of the bond vary with the composition and microstructure of the bioactive material. The mechanism of bonding generally involves a bioactive acellular layer rich in calcium phosphate, mucopolysaccharides, and glycoproteins, which provides an acceptable environment for collagen and bone mineral deposition. The biologically active surfaces of these materials uniquely influence the behavior of different cell types, and an understanding of the mechanisms involved has broad implications for the life sciences as well as for the surgical repair of the musculoskeletal system.

References and Notes

1. L. L. Hench, *Science* **208**, 826 (1980).
2. J. Boretos and M. Eden, Eds., *Contemporary Biomaterials, Material and Host Response, Clinical Applications, New Technology, and Legal Aspects* (Noyes Press, Park Ridge, N.J., 1984).
3. L. L. Hench and E. C. Ethridge, *Biomaterials—An Interfacial Approach* (Academic Press, New York, 1982).
4. H. Denissen, thesis, Free University of Amsterdam (1979).
5. C. de Putter, K. de Groot, P. A. E. Sillevis Smitt, in *Clinical Applications of Biomaterials*, A. J. C. Lee, T. Albrektsson, P.-I. Brånemark, Eds. (Wiley, New York, 1982), p. 237.
6. M. Ogiso *et al.*, *J. Dent. Res.* **60A**, 419 (1981).
7. C. de Putter, K. de Groot, P. A. E. Sillevis Smitt, J. M. Van der Zel, *Trans. Soc. Biomater.* **6**, 27 (1983).
8. M. Jarcho *et al.*, *J. Mater. Sci.* **11**, 2027 (1976).
9. J. J. Grote, Ed., *Biomaterials in Otology* (Nijhoff, The Hague, 1984).
10. J. M. Kent, J. H. Quinn, M. F. Zide, M. Jarcho, *Abstracts of the Second Southern Biomedical Engineering Conference* (Southwest Research Institute, San Antonio, Texas, 1983), p. 27.
11. A. N. Cranin, in *Biomaterials '84, Transactions, Second World Congress on Biomaterials*, J. M. Anderson, Ed. (Society for Biomaterials, Washington, D.C., 1984), vol. 7, p. 324.
12. P. Ducheyne *et al.*, *J. Biomed. Mater. Res.* **14**, 225 (1980).
13. M. Jarcho, *Clin. Orthop. Relat. Res.* **157**, 259 (1981).
14. Bioglass is a registered trademark of the University of Florida.
14a. G. E. Merwin, J. Wilson, L. L. Hench, in (*9*), pp. 220–229.
15. Vitallium is a registered trademark of Howmedica, Inc.
16. P. Ducheyne and L. L. Hench, in *Biomaterials '82* (Advances in Biomaterials Series), G. D. Winter, D. Gibbons, H. Plenk, Eds. (Wiley, New York, 1982), p. 21.
17. J. R. Smith, *Am. J. Orthod.* **76**, 618 (1979).
18. N. Inoue *et al.*, *J. Jpn. Orthod. Soc.* **40** (No. 3), 291 (1981).
19. D. L. Mitchel and J. D. West, *Am. J. Orthod.* **68**, 404 (1975).
20. S. F. Paige, A. E. Clark, R. Costa, G. J. King, J. M. Waldron, *J. Dent. Res.* **59A**, 445 (1980).
21. P. Turley, P. A. Shapiro, B. C. Moffett, *Arch. Oral Biol.* **25**, 259 (1980).
22. J. B. Grey, M. E. Steen, G. J. King, A. E. Clark, *Am. J. Orthod.* **83** (No. 4), 311 (1983).
23. R. L. Folger, C. S. Kucheria, R. E. Wells, G. E. Gardiner, in *Biomaterials '84, Transactions, Second World Congress on Biomaterials*, J. M. Anderson, Ed. (Society for Biomaterials, Washington, D.C., 1984), vol. 7, p. 352.
24. U. M. Gross and V. Strunz, in *Clinical Applications of Biomaterials*, A. J. C. Lee, T. Albrektsson, P.-I. Brånemark, Eds. (Wiley, New York, 1982), p. 237.
25. U. M. Gross, J. Brandes, V. Strunz, I. Bab, J. Sela, *J. Biomed. Mater. Res.* **15**, 291 (1981).

26. Ceravital is a trademark of E. Leitz Wetzlar, West Germany.
27. U. M. Gross and V. Strunz, *J. Biomed. Mater. Res.* **2**, 46 (1978).
28. M. Bunte and V. Strunz, *J. Maxillofacial Surg.* **5**, 303 (1977).
29. R. Reck and J. Helms, in (*9*), pp. 230–241.
30. G. Babighian, in (*9*), pp. 242–247.
31. W. Holland, K. Naumann, W. Vogel, J. Gummel, *Wiss. Z. Freidrich Schiller Univ. Jena Math. Naturwiss. Reihe* **32**, 571 (1983).
32. T. Kokubo *et al.*, in *Biomaterials '84, Transactions, Second World Congress on Biomaterials*, J. M. Anderson, Ed. (Society for Biomaterials, Washington, D.C., 1984), vol. 7, p. 351.
33. T. Yamamuro, private communication.
34. F. Hahn, V. Strunz, J. Boese-Landgraf, *Adv. Biomater.* **4**, 95 (1982).
35. L. L. Hench, R. J. Splinter, W. C. Allen, T. K. Greenlee, *J. Biomed. Mater. Res. Symp.* **2**, 117 (1971).
36. B. A. Blencke, H. Bromer, K. K. Deutscher, *J. Biomed. Mater. Res.* **12**, 307 (1978).
37. T. D. Driskell, C. R. Hassler, V. J. Tennery, L. G. McCoy, W. J. Clarke, paper presented at the IADR (International Association for Dental Research) meeting, Chicago, 1973.
38. H. W. Denissen, B. V. Rjeda, K. de Groot, *J. Biomed. Mater. Res. Symp.* **2**, 188 (1978).
39. L. L. Hench, in *Fundamental Aspects of Biocompatibility*, D. F. Williams, Ed. (CRC Press, Boca Raton, Fla., 1981), chapter 4.
40. L. L. Hench and A. E. Clark, in *Biocompatibility of Orthopaedic Implants*, D. F. Williams, Ed. (CRC Press, Boca Raton, Fla., 1982), vol. 2, p. 129.
41. U. Gross and V. Strunz, *J. Biomed. Mater. Res.*, in press.
42. D. Spilman, J. Wilson, L. L. Hench, in *Biomaterials '84, Transactions, Second World Congress on Biomaterials*, J. M. Anderson, Ed. (Society for Biomaterials, Washington, D.C., 1984), vol. 7, p. 287.
43. T. L. Seitz, K. D. Noonan, L. L. Hench, N. E. Noonan, *J. Biomed. Mater. Res.* **16**, 195 (1982).
44. J. Wilson, G. H. Pigott, F. J. Schoen, L. L. Hench, *ibid.* **15**, 805 (1981).

Ductile Ordered Intermetallic Alloys

C. T. Liu and J. O. Stiegler

Summary. Many ordered intermetallic alloys have attractive high-temperature properties; however, low ductility and brittle fracture limit their use for structural applications. The embrittlement in these alloys is mainly caused by an insufficient number of slip systems (bulk brittleness) and poor grain-boundary cohesion. Recent studies have shown that the ductility and fabricability of ordered intermetallics can be substantially improved by alloying processes and control of microstructural features through rapid solidification and thermomechanical treatments. These results demonstrate that the brittleness problem associated with ordered intermetallics can be overcome by using physical metallurgical principles. Application of these principles will be illustrated by results on Ni_3Al and Ni_3V-Co_3V-Fe_3V. The potential for developing these alloys as a new class of high-temperature structural materials is discussed.

Ordered intermetallic alloys constitute a unique class of metallic materials which form long-range ordered crystal structures below their melting points (T_m) or critical ordering temperatures (T_c). The various atomic species in these alloys tend to occupy specific sublattice sites and form superlattice structures. The structures and properties of ordered intermetallics were studied extensively in the 1950's and 1960's, and as a result of these efforts many attractive properties were identified and characterized (*1–4*). In ordered lattices, dislocations travel in pairs or groups, and their motion is thus subject to certain constraints, particularly at elevated temperatures (*5*). In general, the strength of ordered intermetallics does not degrade rapidly with increasing temperature. In many cases, these alloys exhibit yield stresses that increase with test temperature (*5–8*) rather than decrease, as is common for conventional or disordered alloys. Long-range order produces stronger binding and closer packing between atoms. The restricted atom mobility generally leads to slower diffusion processes and better creep resistance in ordered lattices. Ordered intermetallics such as aluminides and silicides are usually resistant to oxidation and corrosion because of their ability to form compact, adherent oxide surface films that protect the base metal from excessive attack (*9*).

The interest in ordered intermetallic alloys subsided in the latter part of the 1960's because of severe embrittlement problems (*1–4, 10–12*). Many intermetallics are so brittle that they simply cannot be fabricated into useful structural components. Even when fabricated, their low fracture toughness severely limits their use in structural applications. The design of ordered intermetallic alloys has been studied at a number of laboratories, and such work (*13–21*) has shown that the ductility and fabricability of several intermetallic systems can be substantially improved through application of physical metallurgical principles. The success of these efforts has renewed the interest in ordered intermetallics, and is expected to encourage their development as a new class of structural materials for high-temperature applications.

This article summarizes current efforts in the design of ductile ordered intermetallic alloys. These materials are often designated as both ordered alloys and intermetallic compounds. The term "ordered alloys" commonly refers to alloys that form long-range ordered crystal structures at relatively low temperatures (say, $T_c < 700°C$) and are disordered at higher temperatures. The term "intermetallic compounds," on the other hand, generally designates strongly ordered alloys with specific alloy formulas and compositions (that is, line compounds). This review focuses on the class of strongly ordered alloys that are ordered over a range of composition and have appreciable solubility of additional elements, allowing us to use alloying principles to design ductile materials.

Brittleness of Ordered Intermetallics

Ordered intermetallic alloys generally exhibit low ductility and brittle fracture, which severely restrict their use as structural materials. The brittleness in a particular alloy can usually be attributed to either of two major causes, namely, an insufficient number of slip systems and grain-boundary weakness. Many ordered alloys that crystallize in low crystal symmetries simply do not offer enough slip systems to permit extensive plastic deformation. Examples of alloys exhibiting limited crystalline deformation include Co_3V (*10*), Ni_3V (*10*), Fe_3Al (*22*), NiAl (*23*), Ti_3Al (*11*), and TiAl (*24*).

C. T. Liu is a group leader and J. O. Stiegler is director of the Metals and Ceramics Division, Oak Ridge National Laboratory, Oak Ridge, Tennessee 37830.