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Bonding Mechanisms at the Interface of Ceramic Prosthetic Materials

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Summary

The development of a bone-bonding calcia-phosposilicate glass-ceramic is discussed. A theoretical model to explain the interfacial bonding is based upon in-vitro studies of glass-ceramic solubility in interfacial hydroxyapatite crystallization mechanisms, compared with in-vivo rat femur implant histology and ultrastructure results.

INTRODUCTION

Interfacial reactions between foreign materials and the body are critical in a wide variety of bio-engineering problems including: thrombosis in artificial cardio-vascular systems, electrode stability in visual prosthesis, and the fixation of orthopaedic devices. Although this communication is primarily directed towards the more specific problem of orthopedic fixation via ceramic to bone bonding, the general approach that is discussed should be applicable to other materials problem areas such as those mentioned above.

The Interface Between Presently Used Materials and Bone

Historically, many materials and different metals have been used to aid in either prosthetic replacement of bones or in osteosynthesis [1]. Today, the most widely used implants in orthopedics are made from metals because of their relative tissue inertness and strength characteristics. In 1937, Venable, Stuck, and Beach published a paper on "The Effects on Bone of the Presence of Metals; Based Upon Electrolysis [2]." In this paper they concluded that dissimilar metals will produce an electrolytic reaction within the tissues and that the alloy of least reaction was one called Vitallium. In 1955, Bowden, Williamson, and Laing published a paper on "The Significance of Metallic Transfer in Orthopaedic Surgery" [3] in which they concluded the physiologic dangers of electrochemical dissolution were such that only metals having a very high corrosion resistance should be buried in the human body and also

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that different metals should never be inserted in the same patient. They also sampled human tissue taken from sites adjacent to buried metals and measured the concentration of the various components of the metal implants in those tissues.

All orthopedic implants today are made from either surgical stainless steel, or from Vitallium. The surgical stainless steel is more reactive in the body than Vitallium, and indeed at the time of removal of a stainless steel appliance, there is always a thin filmy fibrous sheath surrounding the implant, and there may be what appears as a bursa surrounding the steel itself. In removing Vitallium plates, there is noticeably less fibrous reaction, and bone may overgrow the plate itself and encase it. However, at the interface between bone and the Vitallium, there is again a thin fibrous layer of tissue. Ferguson et al. [4] studied the surrounding tissue and found various concentrations of metal which he concluded came from the implant. Many observers feel that the fibrous reaction is due to the reaction of the body to the metal.

Because of the physical limitations of polymers, few of these have been used as orthopedic implants. Much less is known about the reaction of polymers to body tissues itself and also what effect body tissues have on polymers themselves [5, 6]. Although it is stated that polymer implants are insoluble and are not absorbed by the body, Oppenheimer et al. detected Carbon-14 in the urine of rats after intramuscular implantation of polyethylene and methylmethacrylate. The Carbon-14 had to have been freed from the implants. Although some of the polymer implants seem quite inert, there is still found a capsule of fibrous tissue surrounding the implant after a period of time. Further, the long-term effects of resorption of the implant, even though miniscule, are unknown.

Scale of Interfacial Reactions

The historical behavior of materials in the body indicates that when discussing interfacial reactions, it is important to understand the scale of response that is critical to the problem at hand. For example, stainless steel does not "corrode" in the same macro-engineering sense that low carbon iron does. However, stainless steel does form a tenacious oxide film under nearly all conditions of service. Although this microscopic film successfully prevents larger-scale corrosion attack of the metal, it also apparently affects cellular activity in its vicinity. A fibrous membrane around the stainless steel is clear evidence that at the micron level of cellular activity the stainless steel is not completely inert. The cells respond to the foreign interface, tending to wall it

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off from the body, and differentiation proceeds in an abnormal manner. As mentioned above, the net effect is an extensive fibroblastic response forming a fibrous sheath around the metal. Little is known of the ultrastructural detail of the sheath-stainless steel interface.

Consequently, although the stainless steel material has not been rejected by the body on a gross scale, there has been rejection on a micro-scale and perhaps even significant alteration of function at the interface on an ultra-scale. Most so-called "inert materials" reported appear to exhibit a micro-rejection response at the interface such as described above, although they differ greatly in the degree of rejection.

Toxic materials have been defined as those that induce macro-scale rejection, which can be either an inflammatory or carcinogenic response or both. Most materials screening tests have been developed to identify materials that produce a toxic response. However, the specific features of the materials that are responsible for the toxic behavior have generally not been identified.

No implant has been described in the literature which prevents micro-scale rejection and can be considered to be completely bio-compatible on an ultrastructure scale.

It is the lack of micro-scale and ultra-scale bonding at the material-bone interface that produces the orthopedic fixation problem associated with the loosening of nails, screws, plates, and hip prostheses. If a direct bonding of suitable strength can be achieved at the material-bone interface at locations pre-selected by the surgeon, the fixation problem should be eliminated.

A concern for a strong bond between materials and bone leads quite natrually into two fundamental questions that must be answered:

(1) What are the possible sources of bonding at the interface of devices and bone and the relative strength of each?
(2) Which materials variables must be controlled to elicit a strong, viable bond?

The objective of this paper is to present a partial answer to each of these questions and to outline a theoretical and experimental approach which will, hopefully, achieve complete answers.

Review of General Types of Bonding

The three major types of bonding which can occur across an interface are summarized in Fig. 1. They are mechanical bonds, bonds due to physical forces or chemical bonds. Mechanical bonds result from an inertial resistance to motion and are achieved by an interlocking interfacial structure. This method of bonding is the basis for the interest in porous prosthesis and is also the basis for traditional methods of fixation using screws, nails, and pins.

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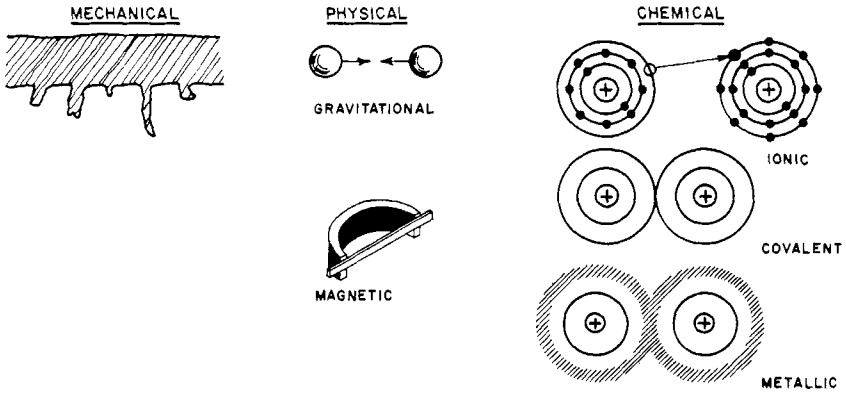

Fig. 1. Schematic of the three major types of bonds that can occur at an interface.

Ingrowth of bone into pores can provide a specific and permanent fixation [7]. However, the strength properties of a mechanical bond to a porous material is an inherent problem. The volume percent of pores occupied by ingrowth is almost never 100% and therefore the strength is reduced by the unoccupied fraction. Mineralization proceeds into the pores only if they are in the range of 150 μ with a low strength cartilage occupying the size fraction less than the critical size [7]. Consequently, the interfacial strength is further reduced by the unmineralized fraction of pores. A further contributor to the decrease in strength of a mechanical interlock bond is that the strength of a porous material decreases proportional to both the size of pores and the volume fraction of pores [8]. Since these strength reduction factors are cumulative, this analysis leads to the conclusion that a mechanical interfacial bond in a porous structure will be 0.1-0.3 times the strength of the solid material, assuming that mineralization does proceed intimately up to and through the material. If mineralization is inhibited at some regions of the interface by the formation of a fibroid layer, the strength of the bone at the interface may also be decreased to a value of 0.1-0.5 times the strength of normal bone.

Traditional orthopedic mechanical fixation techniques involving screws, nails, etc., also have the disadvantages associated with a low cross-sectional area actually carrying the load and the presence of fibroid membranes which decrease the integrity of the bond. For example, the success of an osteosynthesis involving one or more plates spanning a bone fracture and screwed to the bone depends on the location of the plate and quality of the screw-bone junction [9]. For greatest strength and rigidity, the plate should

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be located so that the normal loading pattern causes a tensile load to be placed on the plate. Again the rigidity of the osteosynthesis is a transient phenomenon due to resorption of bone around the screw threads. The use of two plates greatly reduces the anisotropy of the osteosynthesis and in general substantially increases the strength and rigidity of the fixation, but will still not eliminate completely the membrane formation and resorption problem.

As indicated from the above discussion, a non-mechanical bonding mechanism appears desirable for permanent fixation. Physical forces such as magnetic or gravitational offer little promise which leads to the conclusion that direct chemical bonding across the interface of an orthopedic implant and bone may offer the best potential solution.

Schematic representations of several types of chemical bonding that could occur across a biomaterial interface are shown in Fig. 2. Figure 2a illustrates a direct covalent-ionic bond of a PO_4^{3-} group attached both to an organic constituent of bone and the cation or oxygen ion surface of a ceramic. An electrostatic chemical bond between a positively charged amine group and a negatively charged oxygen surface of a ceramic is envisaged in Fig. 2b. Many positively charged amino acids such as lysine, hydroxylysine, histidine, and arginine, could also serve as the basic organic groups in this type of mechanism.

Secondary types of chemical bonding would provide a somewhat weaker interface. For example, hydrogen bonding of a hydroxyalated surface with the carbonyl group of an amino acid may be possible as diagrammed in Fig. 2c. Or, the negatively charged materials surface may attract a rigid hydrosphere which could bond various groups of organic constituents via van der Waals bonding (Figs. 2d and 2e).

A complex combination of ionic, van der Waals, and hydrogen bonding between the material surface and the electrostatic charges at the minor banding sites of collagen, Fig. 2f, may also exist.

Another potentially important type of ionic-covalent bonding at the biomaterial interface is sketched in Fig. 2g. This diagram represents epitaxial crystal growth between hydroxyapatite bone mineral crystals and the biomaterial substrate. An epitaxial interface provides an ionic-covalent bond of a strength equivalent to that of the average of the two materials comprising the interface. It is such a strong epitaxial Al_2O_3 layer on aluminum metal that provides its durability and corrosion resistance.

For each of the above bonds to be formed requires having a specific chemical nature and configuration for each of the interacting species at the interface. However, there is another contribution to bonding due to London dispersion forces which will provide an interfacial attraction regardless of how

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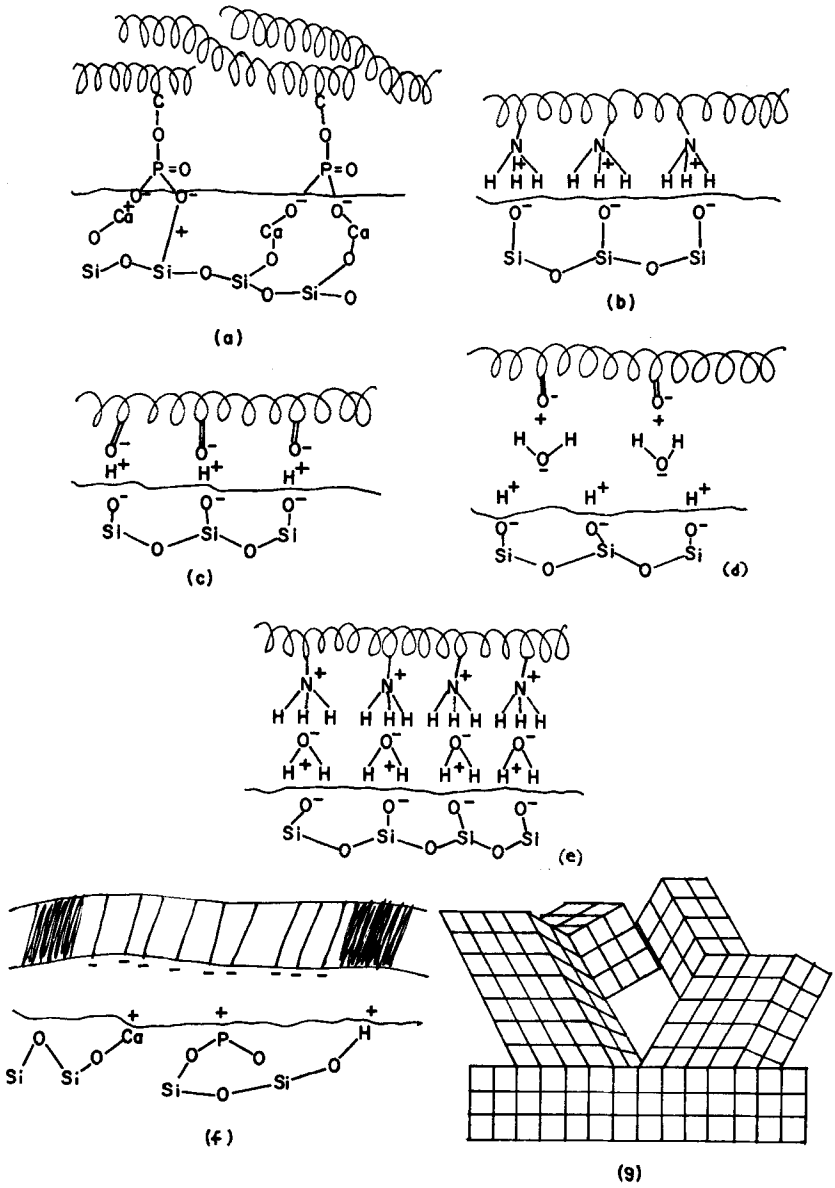

Fig. 2. Various types of chemical bonds which could bond bone to ceramics: (a) direct ionic-covalent bond; (b) electrostatic, ionic bond; (c) hydrogen bond; (d) van der Waals bond; (e) van der Waals bond; (f) complex bonding with charges at collagen bands; (g) epitaxial hydroxyapatite growth on a substrate.

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dissimilar the chemical nature of the materials may be. London dispersion forces arise from the interaction of fluctuating electronic dipoles within a material with induced electronic dipoles in the atoms or molecules comprising a neighboring substance [10].

Dispersion forces operate over longer distances than other intermolecular forces. An important aspect of the dispersion force attraction at an interface is that it occurs independent of and additive to any other type of chemical bonding. Thus even a completely non-polar organic material will have an interfacial interaction with a ceramic or metal due to dispersion forces. The magnitude of the interaction is proportional to the geometric mean of the dispersion force components of the surface energies (γ_s^d) of the two substances [11]. Consequently, even if the organic substance is a low energy solid with a value of γ_s^d of 10-30 ergs/cm^2 there will be a strong dispersion bond established with a high energy surface where γ_s^d is of the order of 80-120 ergs/cm^2. The ultimate tensile strength of such a bond has been calculated to be in the range of 150,000 psi when the organic substance is contiguous with the inorganic material [11].

Structural Factors

The chemical response at the interface of a material is also usually subject to a variety of variables present in the material. A number of materials variables that could be important at a bio-interface are shown in Fig. 3. They include point defects and dislocations which are high energy sites for adsorption or bonding, grain boundaries which provide many energetic sites and a potential force for corrosion or dissolution, the crystal lattice parameter and number of charged ions per unit cell both of which can influence epitaxial bonding, glassy regions and glass-crystal interfaces which can influence chemical solubility, and the local pH. And, of course, a major materials variable is the bulk composition of the crystals and glassy phase in the material. The local composition at the surface, at second phases, or at the surface will also be an important parameter.

Since ground substance, collagen, and hydroxyapatite minerals may all respond differently to each of the above materials factors, the composite interactions that can occur at the interface can be exceedingly complex. There is therefore a considerable need for a materials model that will isolate most of the variables that influence mechanical and chemical bonding so that they can be systematically studied singly and in controlled combinations.

Materials Model

The requirements for a materials model are given in the following table.

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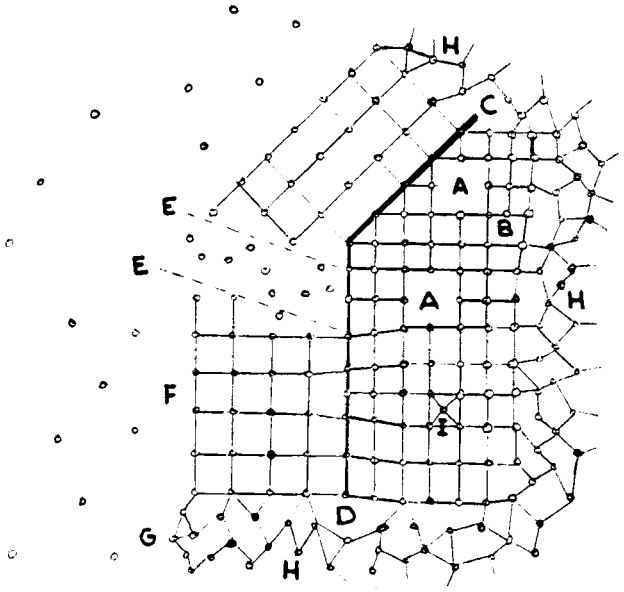

Fig. 3. Materials variables that could influence the interfacial bonding of bone.

TABLE I
Requirements for a Biomaterials Model

Chemical	Crystallographic	Microstructural
Vary type, concentration, and rate of soluble ion(s) and pH	Provide variable substrate for protein and mineral epitaxy	Vary percentage and size distribution of porosity, interfacial area, and type of interfaces

In the authors' judgement one class of materials, glass-ceramics, offer the best potential to satisfy each of the above model requirements and still possess physical properties suitable for bio-engineering applications. Glass-ceramics are prepared by thermally treating a glass in a manner which produces a polycrystalline microstructure in which the crystals are randomly oriented and of a volume fraction and size controlled by the thermal treatment [12].

Chemical requirements of the materials model are easily satisfied since it is possible to incorporate into the glass nearly every element in the periodic

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table in variable percentages [13]. The acidity or alkalinity of the glass can also be varied over wide limits. Rates of solution of glasses can also be altered appreciably by varying the network former ion concentration [14].

Variations in composition and thermal treatment control the type of crystal structure present in the glass-ceramic which satisfies the crystallographic requirement of the model. Since the parent glass has no periodic structure it provides an important basis for evaluating the relative importance of crystallographic features in the model.

Altering the composition and/or thermal treatment of the glass-ceramic will also produce extreme variations in the micro-structure of the material. Size distribution of crystals, average size, and volume fraction of crystals can be varied independently. If a porous structure is desired to investigate surface mechanical bonding the residual glassy phase can be leached out producing a controlled pore size material [15]. The depth of the penetration of the surface pores, pore size, and continuity of pores can be altered in the glass-ceramic model as desired.

It is also highly desirable that a materials model have potential application in actual bio-engineering problems as well as provide fundamental information on interfacial bonding. It serves little purpose to understand the variables required to fix bone to a material if the material is too weak to support a load. Glass-ceramics also offer considerable promise in this regard. Tensile strengths of 30,000-50,000 psi have been reported [12]. The impact strengths of at least certain compositions of glass-ceramics have been reported to be superior to any other sintered ceramics [12]. The elastic modulus of glass ceramics has been shown to be variable over a range from 7×10^6 to 20×10^6 psi, thus making it possible to somewhat approximate the modulus of bone or achieve more stiffness as desired.

An additional attractive feature of glass-ceramics as bio-engineering materials is that they can be applied as a coating, either through flame spraying or enameling, to high strength metals. A glass-ceramic coated metal thus may have a designed biological response without any sacrifice of mechanical strength or reliability.

Glass-Ceramic Model Selected

Glass compositions from the SiO_2-P_2O_5-CaO-Na_2O system shown in Fig. 4 have been selected for the materials model. The compositions indicated on the diagram can be produced as glasses on a laboratory or commercial scale employing the melting and annealing schedules given in Table II. CaO and P_2O_5 contents were chosen to yield Ca/P molar ratios of 5.0, 1.8, and 0.5. The Ca/P ratios were selected to yield a wide variation of Ca and P ions in

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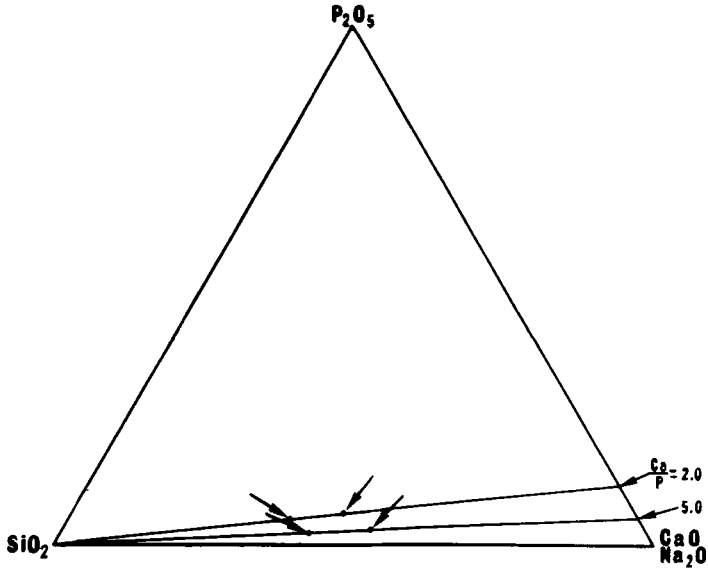

Fig. 4. Glass-ceramic compositions presently used in in-vitro and in-vivo studies of interfacial bonding.

TABLE II

	Melting temperature (°C)	Homogenization time (hr)	Annealing temperature (°C)	Annealing time (hr)
45S5.0	1450	18-24	450	1-4
45S2.0	1450	18-24	450	1-4
55S5.0	1475	18-24	450	1-4
55S2.0	1475	18-24	450	1-4

solution and to bracket the 1.67 Ca/P ratio found in in-vivo hydroxyapatite minerals.

Na ions were added to the glass composition for two purposes. Na_2O is an effective flux, making it easier to melt, homogenize, cast and flame spray the glasses. Second, Na ions dissolve from the glass and can thus aid in maintaining a physiological balance of sodium at the glass-ceramic interface and also modify the local pH.

The role of SiO_2 in the composition is that of a network former which

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maintains the three-dimensional non-periodic glass structure. SiO_2 in the glass strongly decreases the solubility rate of the other ions and thus provides stability to the materials system. The variations in SiO_2 content of the glasses shown in Fig. 4 serve to alter both the solubility rate of the glasses and the total percentage of available "active" ions.

The nomenclature used to denote the glass-ceramic compositions in this paper is a short-hand which includes the above compositional variables. For example, a 45S5.0A glass-ceramic denotes: 45% of the network former which is S = SiO_2 or B = B_2O_3; the Ca/P molar ratio is 5.0. The microstructure of the glass-ceramic is denoted by either an A, B, or C designation with A = as cast, B = partially crystallized, and C = fully crystallized.

Thermal Treatments

In order to develop a uniform polycrystalline microstructure in a glass-ceramic it is necessary to give the glass a two-step thermal treatment. The first step is a nucleation treatment, usually 500-700°C, which causes small regions (100-500 Å) of crystalline order to form randomly throughout the glass structure. At a slightly higher temperature (600-1000°C) equilibrium crystals grow from the nuclei. The volume fraction and size of the crystals depend upon how long the glass is left in this crystal growth stage.

The nucleation and crystal growth treatment of two of the glass-ceramics studied in this program is shown in Fig. 5. In order to obtain complete crystallization in the 45S5.0 glass, two nucleation and growth steps are required. This complication is due to the as-cast glass being phase separated. Liquid in liquid and glass in glass separations are common when two high valence ions such as Si^{4+} and P^{5+} are present simultaneously in a glass [12, 16]. Each ion type will tend to concentrate in a separate phase. Evidence for phase separation in the 45S5.0 glass is shown in Fig. 6. The second phase, probably rich in P^{5+}, appears as droplets in the matrix which is probably SiO_2 rich. The sample shown is a fracture surface of the glass obtained by a quench into liquid N_2. Sharp protuberances in the scanning electron micrograph are due to the typical conchoidal fracture of the glass. An amorphous x-ray diffraction pattern of the as-cast 45S5.0 sample shown in Fig. 7 is evidence of the glassy structure of the material.

Crystals grow during the first nucleation and growth treatment apparently from the phase separated regions, to produce the polycrystalline microstructure of Fig. 8. A second nucleation and growth treatment produces crystallization of the matrix as shown in Fig. 9. The crystal phase which appears in the microstructure resembles hydroxyapatite mineral in its x-ray diffraction profile, although it does not contain hydroxyl groups.

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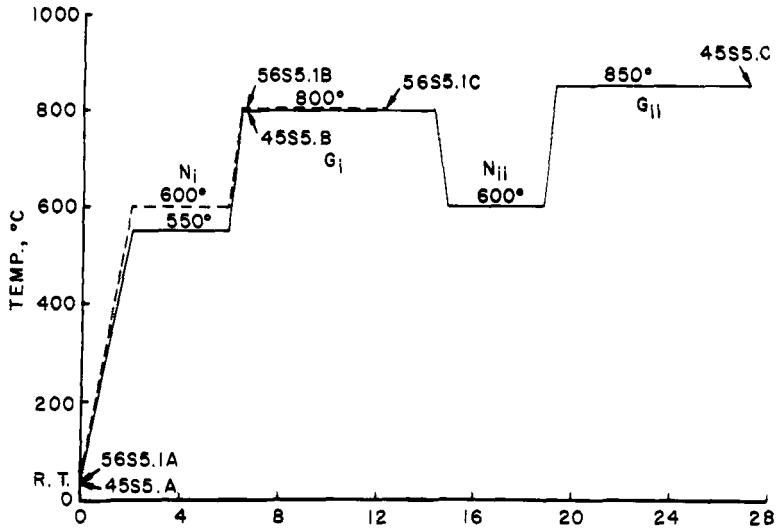

Fig. 5. Nucleation and crystallization treatments used to produce partially crystallized and fully crystallized glass-ceramics.

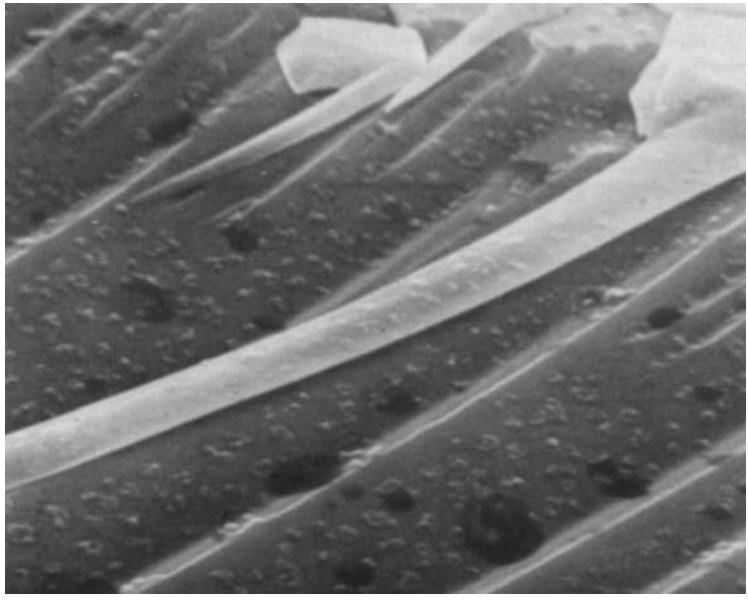

Fig. 6. Phase separated microstructure of the as-cast 45S5.0A glass.

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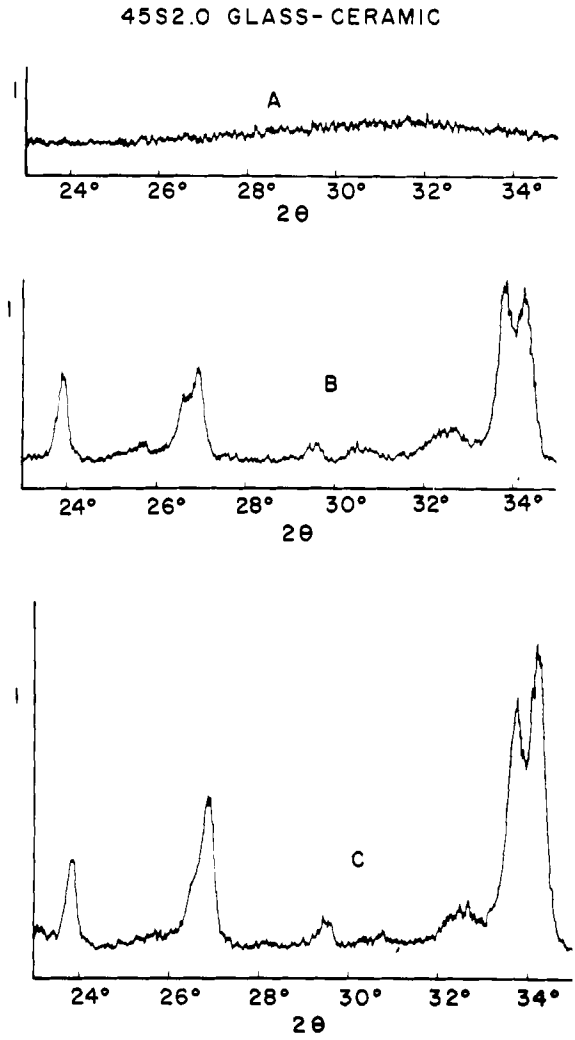

Fig. 7. X-ray diffraction profiles of the amorphous 45S5.0 glass, the partially crystallized glass-ceramic, and the fully crystallized glass-ceramic.

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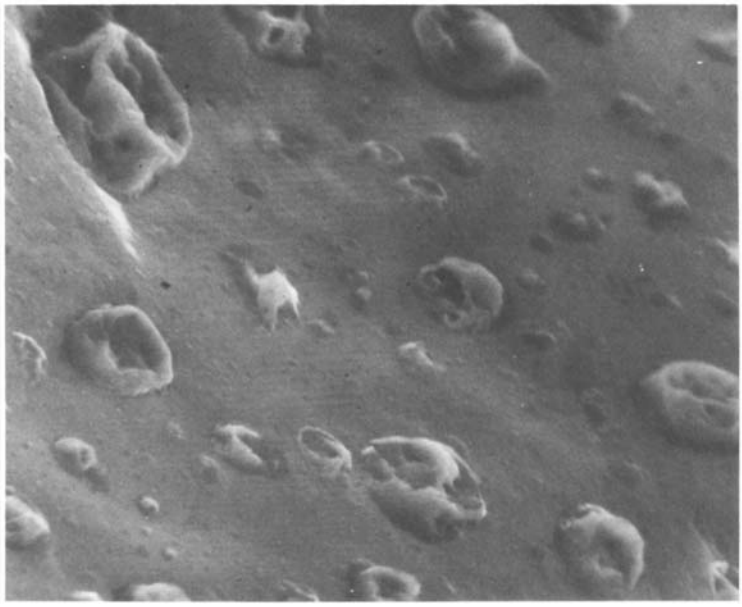

Fig. 8. Microstructure of the partially crystallized 45S5.0B glass-ceramic.

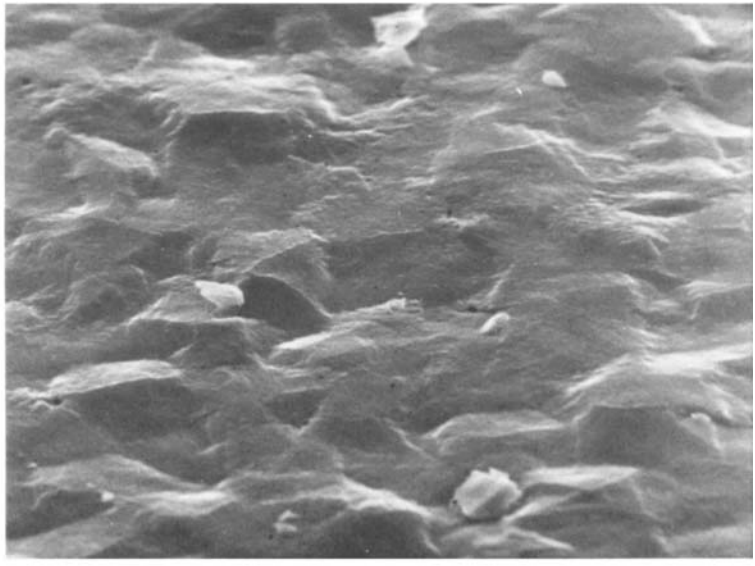

Fig. 9. Microstructure of the fully crystallized 45S5.0C glass-ceramic.

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In-Vitro Solubility Results

The influence of glass-ceramic composition and microstructure on in-vitro ion solubility and hydroxyapatite crystallization from solution has been established for several of the glass-ceramics cited above. The purpose of these studies has been to evaluate variables which may influence the in-vivo response of the glass-ceramics discussed in a following section.

Although many familiar glass and glass-ceramic articles appear to be unreactive in normal environments, other compositions range in chemical durability from rapid and complete dispersion in aqueous solutions to complete inertness [14]. pH is well established as an important variable in controlling the solubility of a glass. Dilute acidic solutions primarily extract monovalent ions such as Na^+ which are replaced in the glass by H^+ (or H_3O^+) ions from the solutions. On the other hand, alkali attack occurs by breaking silicon-oxygen bonds, thus destroying the glass network. Alkali attack is generally more severe and occurs at a linear rate until an equilibrium pH is reached. Acid attack, however, is diffusion controlled so it slows down with time as ions must proceed through the reaction layer.

The degradation of 45S5.0 A, B and C glass-ceramics has been studied as a function of time for periods up to several months. A two-gram sample of each material consisting of −200 +325 mesh powder was placed in a beaker at a pH of 5.4, buffered with succinic acid and NaOH [17], and the temperature controlled at 37°C. One-millileter samples were taken from the solution after various periods of time. The samples were evaporated and the weights measured and corrected for buffer residue. The total weight loss of the sample per gram of initial sample is plotted for the 45S5.0A material in Fig. 10. Chemical analysis of the decomposition product after a 3-month period shows the presence of all of the ions incorporated in the glass-ceramics including significant concentrations of Ca and P ions.

A marked change in pH with time is also experienced for the glass-ceramics. The hydroxyl ion content changes sharply enough with the glass-ceramic dissolution to override the buffer and increase the pH to an "equilibrium value" of 10.0 (Fig. 10). This "equilibrium pH" value is comparable to that observed for other soda-lime-alumina-silica glasses placed in alkaline solutions [18]. As shown in Fig. 10, the large increase in pH occurs around 30 hr after a very show rise to a value of 6.8. The large pH change is accompanied by an appreciable increase in the weight loss of the sample, also at 30 hr. The increased dissolution rate was preceded by a slowly increasing loss of weight following an immediate small surface dissolution when the sample was immersed.

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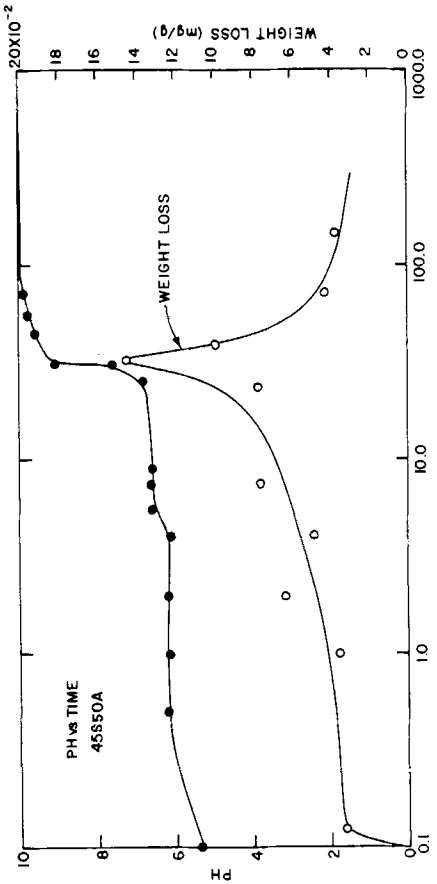

Fig. 10. Solubility and pH changes with time for a 45S5.0A glass in a buffered solution at an initial pH of 5.4.

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The above combination of results suggests the following model for the solubility behavior of the phase separated glass. Upon exposure to an acidic environment there is an immediate attack of alkali ions in one of the two glass phases by the H^+ ions, gradually increasing the alkalinity of the solution. The increasing alkalinity apparently reaches a critical value for alkali attack of the glass network producing a rapid weight loss and rapid increase in pH until equilibrium is achieved. The equilibrium pH has been observed for up to 9 months in time with no change from a value of 10.0 and no change in the sample after the equilibrium value has been reached. Consequently, the solubility behavior of the glass-ceramic is self-protecting in this system.

The influence of various microstructures and sequential pH changes will be reported in the near future.

In-Vitro Hydroxyapatite Results

A series of studies has been performed to investigate the influence of the glass-ceramic substrates on the crystallization of hydroxyapatite from supersaturated and saturated calcium phosphate solutions. The objectives of these studies have been (1) to compare the kinetics of hydroxyapatite crystallization on the substrates with the solution kinetics reported by Eanes, Gillensen, and Posner [19, 20], (2) to evaluate the morphology of the surface crystallized hydroxyapatite, and (3) to evaluate the strength of the hydroxyapatite to glass-ceramic bond.

Amorphous calcium orthophosphates were prepared by rapid precipitation from solutions at a pH of 9.4. The 9.4 pH was chosen for the initial experiments because Eanes and Posner showed that the reaction was slow enough that it could be carefully monitored [20]; the glass-ceramics tend to produce a high pH with time, and a similar pH range may be present locally in-vivo at regions of high osteoblast activity.

The experimental procedure employed to produce the precipitates with a Ca/P ratio of 1.67 was equivalent to that reported by Eanes and Posner [20]. Slurries of the amorphous calcium orthophosphate precipitates were spread in a 0.01-in. layer on glass-ceramic wafers 9/16 in. in diameter and 1/8 in. thick. Quantitative x-ray analyses [21] of the volume fraction of crystalline hydroxyapatite were made for 45S5.0A and 45S1.8A substrates. A sample series of x-ray data is given in Fig. 11 and the results are summarized in Fig. 12, where they are compared with those achieved by Eanes and Posner. Eanes and Posner observed a rapid crystallization when the precipitate was vigorously stirred and concluded that crystals broken during stirring self-nucleated new crystals producing very rapid autocatalytic crystallization.

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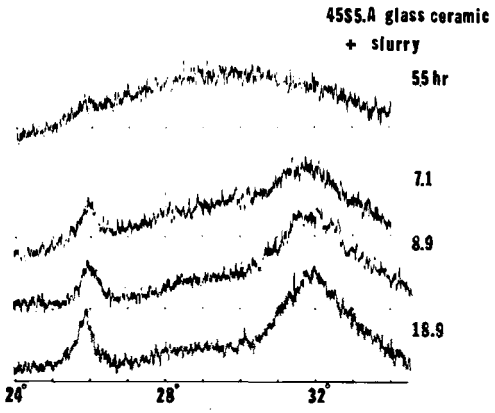

Fig. 11. X-ray diffraction analysis of the crystallization of hydroxyapatite on the surface of a 45S5.0A glass.

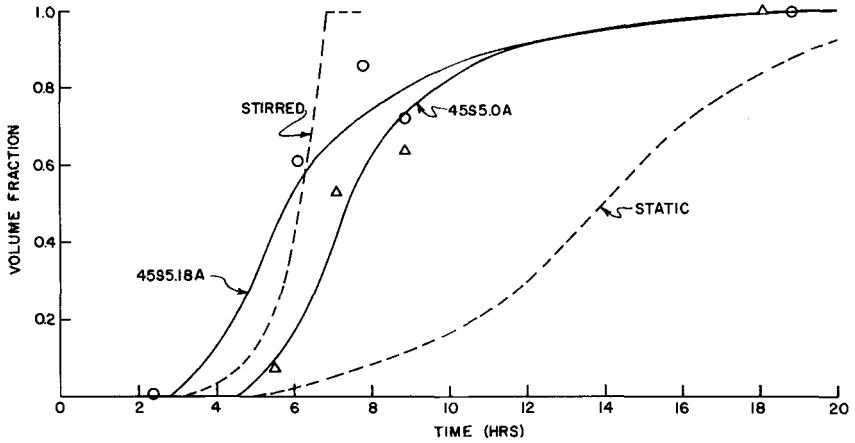

Fig. 12. Comparison of the kinetics of crystallization of hydroxyapatite on glass-ceramic surfaces with results from supersaturated solutions.

When the precipitate remained stagnant, crystallization was much slower, requiring a diffusion of species to the crystal interface.

It can be seen from Fig. 12 that the surface of the glass-ceramic samples apparently heterogeneously nucleate the hydroxyapatite crystals since the rate of crystallization is equivalent to that of Eanes and Posner's stirred precipitate. When the crystallization proceeds to a sufficient thickness the substrate effect disappears and the conversion rate becomes equivalent to that

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of the static precipitate. The net effect is for the glass-ceramic substrate to rapidly accelerate the rate of crystallization at the interface.

Although detailed studies of the microstructural effects on the crystallization kinetics are still in progress, several observations can be made. The presence of a crystalline phase at the interface appears to increase the strength of the chemical bond at the interface. Interfacial bonding of hydroxyapatite crystals with the partially crystallized glass-ceramics is sufficiently strong that an abrasive grinding with SiC paper is required to remove the hydroxyapatite crystals from the surface. This behavior tends to suggest that epitaxial growth may be occurring at the interface although this is especially difficult to prove because of the extremely small size of the hydroxyapatite crystals. Line broadening analysis of the (002) peak using the Scherrer equations [21] yields an average crystal size of approximately 200 Å. The 200 Å size is in the same range as observed for in-vivo mineral crystals and that reported by Eanes and Posner [20].

An examination of the interfacial morphology of the hydroxyapatite crystals grown on the glass-ceramic is presented in Fig. 13. This figure is a

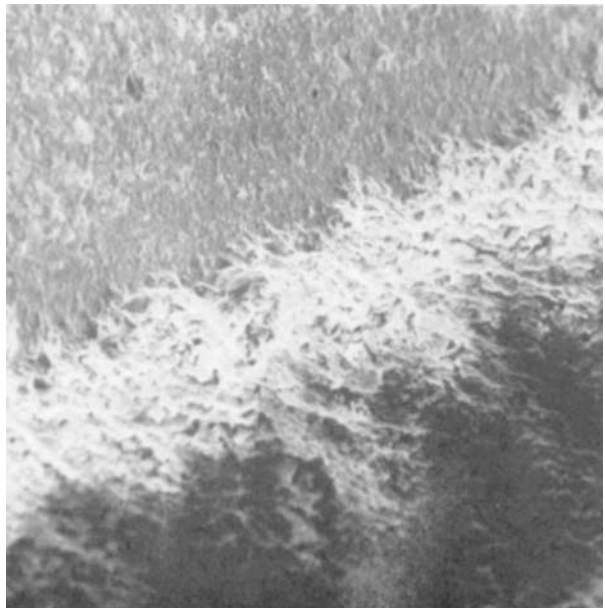

Fig. 13. Morphology of the hydroxyapatite crystallized on a 45S5.0B glass-ceramic substrate.

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scanning electron micrograph of the corner of a fracture section of a 45S5.0B glass-ceramic upon which hydroxyapatite crystals have been grown. The dendrite habit of the crystals is apparent, as is their contiguity with the glass-ceramic. It can be noted that fracturing the specimen did not dislodge the tightly bonded crystals at the fracture surface.

Glass-ceramic substrates of the 45S5.0A, B, C series have also been placed in a saturated calcium-phosphate solution and observed over a 3-week period. Precipitation in the bulk of the solution did not occur but a precipitate did form on the surface of the glass-ceramic. This result indicates that the interfacial solubility of the glass-ceramics can heterogeneously induce surface precipitation of inorganic compounds from solutions not too dissimilar from body serum.

In-Vivo Results

A rat femur model was used to evaluate the in-vivo interfacial response of growing bone to glass-ceramics [23]. Ceramic implants of approximately 1 × 2 × 2 mm were placed into one cortical defect in rat femurs. These animals were sacrificed at 6 weeks and evaluated. The major goal of the initial in-vivo studies was to obtain a morphologic means of evaluating the interface. This goal has been reasonably well obtained.

Whole femur specimens, including the implant, were evaluated by scanning electron microscopy after removal of the unmineralized organic material by ethylene diamine. This technique permits identification of bone by scanning microscopy because of its characteristic morphologic pattern. The glass-ceramic implant can be identified by characteristic fracture patterns at the surface where the bone and ceramic were divided by a saw.

These studies demonstrate an intimate bonding between the 45S5.0A and 45S5.0B glass-ceramics and bone. The glass-ceramic remains bonded within the femur even after sectioning with a milling machine, saw, or diamond microtome. In contrast to the strength of the bond developed with the glass-ceramics, single component oxide control samples tend to simply fall out of the bone defect either during preparation or sectioning. The implants of 99% SiO_2, 99.5% Al_2O_3, and 99.9% MgO consequently were not able to be examined by electron microscopy.

Transmission electron microscopy of the bone-ceramic interface of the 45S5.0A glass-ceramic reveals a dramatic response. Figure 14 shows that there is a seam of partially ossified osteoid between obvious bone and the ceramic. Collagen fibrils, identified by their characteristic banding pattern, are juxtaposed to the ceramic and are parallel to its surface. In some areas, crystals can be seen in these fibrils that are contiguous with the ceramic. This

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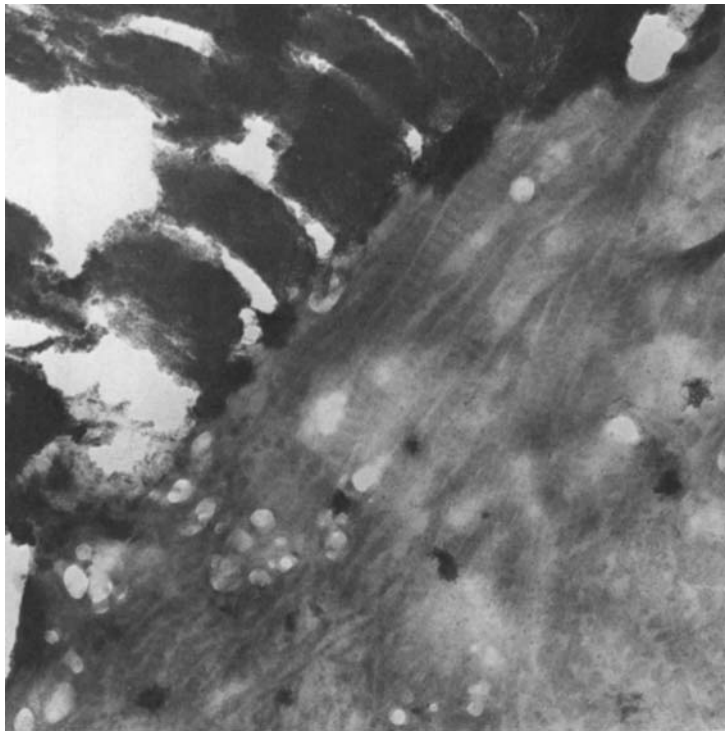

Fig. 14. Transmission electron micrograph of the interface between a rat femur and a 45S5.0A glass-ceramic after 6 weeks.

is interpreted as ossification occurring at the ceramic interface, possibly representing epitaxial crystallization at the surface similar to the in-vitro results.

Electron diffraction of the dark, fractured region in the micrograph shows the characteristic amorphous diffraction pattern of a glass. Selected area diffraction of the region contiguous to the glass shows crystallization, but positive identification of hydroxyapatite crystals has not been achieved as yet. The size of these areas and the size of the precipitated crystals hinders analysis. Investigation of interfaces from femur implants of up to twelve weeks should aid in alleviating this difficulty.

Figure 15 illustrates the completely homogeneous character of the interface obtained after a 6-week implantation of the partially crystallized 45S5.0B sample in a rat femur. It appears in this transmission electron

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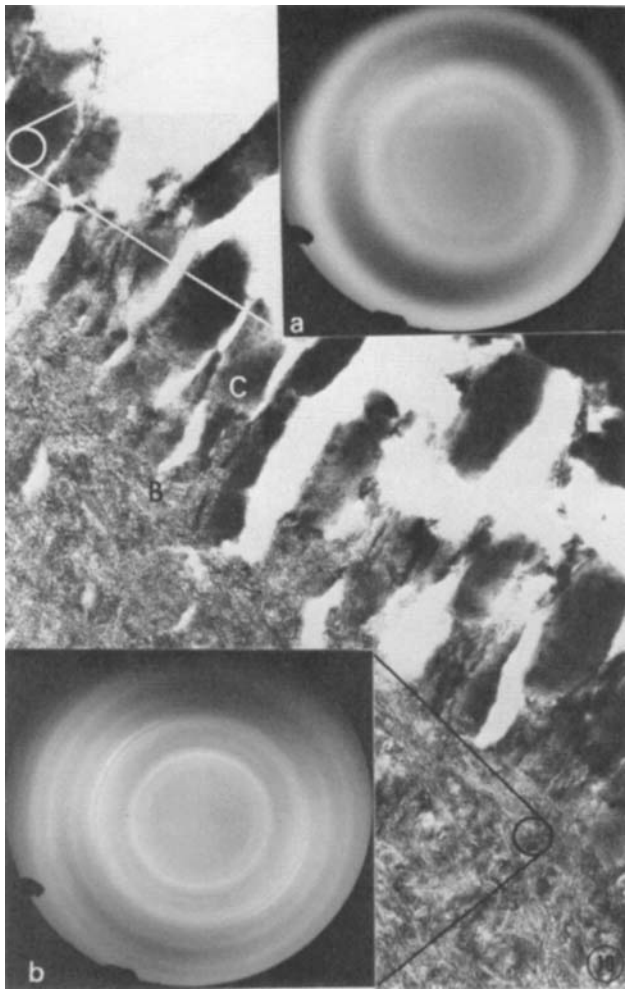

Fig. 15. Transmission electron micrograph of the interface between a rat femur and a partially crystallized 45S5.0B glass-ceramic after 6 weeks.

micrograph that the ossification at the interface has been completed and complete chemical compatibility with the glass-ceramic has been achieved. The contrast in structure of the interface between Figs. 14 and 15 would suggest that the partially crystalline nature of the glass-ceramic interface in Fig. 15 accelerated the ossification process. This conclusion would be

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consistent with the enhanced hydroxyapatite interfacial bonding achieved in-vitro when crystals are present in the glass-ceramic. However, specific conclusions as to details of the bonding mechanism must await the results of a more complete time sequence in both the in-vivo and in-vitro studies.

One-hundred-micron undecalcified sections of bone and the 45S5.0A glass-ceramic, prepared by means of cutting on a milling machine and hand-grinding, were evaluated by microradiography. They demonstrate that some of the ceramic fractures and comes loose during the grinding process, but that a rim of ceramic is left in opposition to newly formed bone. The animal investigated was given intramuscular injections of tetracycline for 3 days prior to sacrifice. When the same sections were viewed by fluorescence microscopy it was noted that tetracycline was localized adjacent to the ceramic at some distance from other areas of bone. This leads to the conclusion that inasmuch as tetracycline appeared to be preferentially deposited in newly formed bone, that bone formation is taking place preferentially at the surface of the implant.

The light microscope observations of decalcified bone in which the ceramic was removed demonstrate at 2 weeks a relatively normal healing process of new bone filling in the area between the femur of the rat and the implant. There did not appear to be any untoward inflammatory response produced by the ceramic in these observations.

DISCUSSION

The preliminary in-vivo studies of glass-ceramic implants in rat femurs lead to the following observations: (1) glass-ceramic implants of the type developed in this program appear to be intimately united to bone at 6 weeks, (2) these implants may enhance ossification of unmineralized tissue at the interface secondary to some chemical characteristic of the implant, and (3) there does not appear to be histologic evidence of early untoward inflammatory response to the implant in the animal. It will be necessary to complete the study now under way in which implants with other combinations of variables are being evaluated at 2-, 4-, 6-, and 12-week intervals to determine if the preliminary observations can be developed into a theory of interfacial response.

However, it is possible to speculate as to several possible reaction mechanisms that may be occurring at the glass-ceramic to bone interface. The preferential alignment of collagen fibrils parallel to the surface of the glass-ceramic as shown in Fig. 14 might suggest that collagen is interacting with the PO_4^{3-} groups in the glass-ceramic as depicted in Fig. 2a. Such an interaction might involve a base catalysed transesterification with the

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glass-ceramic similar to the mechanism discussed by Glimcher [24] for in-vivo mineralization. A high pH was shown to be stabilized at the interface of the glass-ceramic in the in-vitro studies.

Collagen is a unique protein which makes up a large percentage of the connective tissue in the bodies of animals. The amino acid composition and the major characteristics are the same for all types of collagen in the body. However, subtle differences in structure and/or chemistry must be present to account for certain characteristics of different types of collagen. The major consideration would be deposition of mineral hydroxyapatite into and around the structure of collagen in bone and dentine. This type of response normally does not occur in dermal collagen, connective tissue collagen in muscle, or collagen in tendon. In abnormal pathologic conditions ossification indistinguishable from that of normal bone does occur in muscle and tendons or other connective tissue. The differences accounting for this ossifying process in bone and certain pathologic conditions are not known as yet. A recent review by Veis, Spector, and Carmichael discusses the possible implications of bone formation [25]. Ultrastructural observations of early ossification in bone lead one to believe that microscopic apatite crystals might be nucleated in the collagen molecule itself, and it is thought that holes are present in this molecule which might be nucleation sites in the collagen for the hydroxyapatite. There is still some controversy as to this fact.

Because of the present uncertainty underlying the mechanisms of both collagen cross linking and in-vivo nucleation of hydroxyapatite mineral in bone, it is impossible to explain the enhanced ossification at the interface of the glass-ceramics at this time. The in-vitro observations of ionic solubility at the interface and direct chemical bonding of hydroxyapatite crystals does suggest that the glass-ceramic is playing an active role in the in-vivo ossification. The increased rate of mineralization of the partially crystallized glass-ceramics gives further credence to the viewpoint that the implant is directly aiding the physiological processes. It is hoped that the additional studies in progress will lead to identification of the specific mode of interfacial response that is producing the chemical bond.

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References

1. A. A. Zierold, *Arch. Surg.*, 9, 365 (1924).
2. C. S. Venable, W. G. Stuck, and A. Beach, *Ann. Surg.*, 105, 917 (1932).

10974636, 1971, 6, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/jbm.820050611 by Jason Seale - Wiley Online Library on [28/07/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

3. F. P. Bowden, J. B. P. Williamson, and P. G. Laing, *J. Bone Joint Surg.* (British), 37-B, 676 (1955).
4. A. B. Ferguson, P. G. Laing, and E. S. Hodge, *J. Bone Joint Surg.* (American), 42-A, 77 (1960).
5. D. E. Brown, *Arch. Otolaryng.*, 88, 81 (1968).
6. J. P. Nelson and J. C. Ivins, *Minn. Medicine*, 48, 1371 (1965).
7. S. F. Hurlbert, J. J. Klawitter, D. C. Talbert, and C. T. Fitts, in *Research in Dental and Medical Materials*, E. Korostoff, Ed. Plenum Press, New York (1969).
8. W. D. Kingery, "Introduction to Ceramics," Wiley, New York, p. 621 (1960).
9. V. H. Frankel and A. H. Burstein, AAOS Exhibit, January 1968.
10. F. London, *Trans. Farad. Soc.*, 33, 8 (1937).
11. F. M. Fowkes, *Ind. and Engr. Chem.*, 56, 40 (1964).
12. P. W. MacMillan, "Glass-Ceramics," Academic Press, New York (1964).
13. G. W. Morey, "The Properties of Glass," 2nd Ed., Reinhold, New York, pp. 69-101 (1954).
14. F. R. Bacon, *Glass Industry*, 49 (1968).
15. M. B. Volf, "Technical Glasses," Pitman and Sons, Ltd., London, pp. 176-210 (1961).
16. H. Rawson, "Inorganic Glass Forming Systems," Academic Press, New York, pp. 11, 155 (1967).
17. S. P. Colowick and N. O. Kaplan, Eds, "Methods in Enzymology," Vol. I, McCollum-Pratt Institute, The Johns Hopkins University, Baltimore, Maryland, Academic Press, Inc., New York, pp. 138-146 (1955).
18. S. M. Budd and J. Frankiewicz, *Phys. Chem. Glasses*, 2, 111 (1961); 3, 116 (1962).
19. E. D. Eanes, I. H. Gillessen and A. H. Posner, *Nature*, 208, 365 (1965).
20. E. D. Eanes and A. H. Posner, *Trans. N.Y. Acad. Sci.*, 28, 233 (1965).
21. L. L. Hench, A. E. Clark and R. J. Splinter, "Glass and Glass-Ceramic Substrate Effects on Hydroxyapatite Crystallization," to be published.
22. L. V. Azaroff, "Elements of X-Ray Crystallography," McGraw-Hill, New York, p. 552 (1968).
23. C. A. Beckham, T. K. Greenlee, Jr., and A. R. Crebo, "Comparison of Morphological Techniques Used in Evaluating a Ceramic-Bone Implant," to be published.
24. M. J. Glimcher and S. M. Krane, in "Radioisotopes and Bone," Parts I and II. P. Lacroix and A. M. Budy, Eds. Blackwell, Ltd., Oxford, England, pp. 393-434 (1962).
25. Veis, Spector and Carmichael, *Clin. Orthop.*, 66, 188 (1969).

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