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Review
Bioceramics

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Ceramics, glasses, and glass-ceramics are increasingly being tested for use in the human body. These materials often have excellent chemical properties for biomedical use, but they are brittle and show fatigue. Careful analysis of their mechanical properties is needed to determine appropriate applications. Hydroxylapatite is emerging as the most promising bioceramic because it shows no foreign body reactions and bonds strongly to bone; if properly made without pores or second phases it has excellent fatigue resistance. Glass-ceramics containing hydroxylapatite crystals also show good promise for many applications. Different forms of these materials, such as dense, granular, mixed granular with plaster of Paris, and coatings on metals are being tested and have very good potential as bioceramics.

1. Introduction

Replacement of damaged or diseased body parts is an increasingly important part of medicine. These replacements are made of a wide variety of solid materials: polymers, metals, ceramics, and combinations of these. New materials, forms and parts are being proposed and tested with increasing frequency.

An orthopaedic surgeon described the ideal implant to me as a material that performs its function without toxicity or foreign body reaction, and then is completely resorbed and replaced by new tissue. This ideal is seldom achieved. Often damaged or diseased body parts do not regenerate, so their replacements must have long-term mechanical and chemical stability. Desirable properties of solids for use in the human body are given in Table I.

Ceramics are superior materials for implants except for their mechanical properties. Ceramics and glasses are rigid and brittle; they fail by fracture, and oxide ceramics show fatigue, caused by their reaction with water. The chemical properties of selected ceramics are excellent for implants; they can also be tailored to fit most of the requirements in Table I.

A list of possible applications of ceramics and glasses in medicine are given in Table II, some taken from deGroot [1].

Hydroxylapatite, a calcium phosphate that has similar composition and structure to those of the minerals in bones and teeth, has excellent chemical properties for implantation into the body. A strong bond develops between bone and hydroxylapatite implants, there are no fibrous particles encapsulated at the bone/apatite interface, and the implant induces no foreign body reaction. In the last few years there has been an explosion of interest in hydroxylapatite as a bioceramic, leading to many promising applications; some will be referred to, and more publications on hydroxylapatite appear each week.

In this review of bioceramics, processing of ceramics and glasses is first considered briefly. Then there is an important section on fracture and fatigue of brittle materials. Mechanical stability is often essential in applications of bioceramics. Ceramics have been used or rejected as implants without a thorough understanding of their fracture and fatigue behavior, and of how to relate experimental fatigue properties to their expected stability as implants. Next there is a description of some types of ceramics and glasses that have been used or tested as implants. Finally there is a section on forms of bioceramics. I include in this section my opinions about the most promising materials and forms for applications of bioceramics.

Papers from a symposium on biomaterials are given in [2]; Hanker and Giammara [2, 3] provide extensive background information on implant experiments on many different materials. DeGroot [1] and Ducheyne and Hastings [4] include articles on calcium phosphates and other ceramics and metals as implant materials. A summary of a meeting on bioceramics, including research articles, reviews, and a series of short summaries from workshop groups, is given in [5].

2. Processing of ceramics

Crystalline ceramics are usually made in three steps: forming of a powder to the desired shape, partial drying, and firing at high temperatures to produce dense material. The firing step can include a hold at intermediate temperature to burn out organic binders. In slip casting the powder in a slurry is poured into a mould that absorbs excess water; the resulting ware

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TABLE I Desirable properties of implants

No toxicity.
Mechanically stable: do not fracture, or deform excessively.
No foreign body reaction.
No stimulation of undesirable growths or chemical reactions in body fluids and tissues.
Either: Do not dissolve or corrode.
or: Resorb at a desired rate.

TABLE II Current and proposed applications of bioceramics

Dental restorations: crown, caps, dentures, fillings.
Tooth root replacements.
Rebuilding the alveolar ridge.
Whole tooth replacements.
Reconstructive middle ear surgery.
Fracture healing.
Spine surgery.
Rebuilding of facial and cranial bones.
Filling mastoid defects.
Filling bony defects, for example, in tibial plateau fractures.
Female sterilization.

can be fired directly without further drying. Glasses are made commercially by continuous melting in a large furnace or "tank"; smaller batches of glass are melted for specialty purposes. The discussion of this section is taken mainly from [6]. Processing of crystalline ceramics is described in more detail in [6].

In traditional ceramics such as porcelain, powdered raw materials such as clay (hydrated aluminosilicates), feldspar (alkali aluminosilicates) and silica sand are used directly as-mined. For specialty uses, such as in electronics and most bioceramics, properties are strongly influenced by impurities and particle size of the starting materials, which must therefore be carefully controlled. Precipitation from solution and pyrolysis of organic precursors, including polymers or gels, are methods of producing pure powders.

Powders are usually pressed damp in metal dies or dry in lubricated dies at high enough pressure to form material strong enough to hold together until it is sintered. An organic binder such as polyvinyl alcohol helps to bind the powder together. Drying at about 100 °C is a critical step in preparing damp-formed pieces for firing. Too much or too little water in the pressed powder can lead to blowing apart the ware on heating, or to crumbling, respectively. Binder is removed by heating to a higher temperature in air to oxidize the organic binder to carbon dioxide and water.

When a piece is fired, the powder particles join together to form a solid, porous mass; as firing continues, most of the pores are removed, forming a compact, dense, polycrystalline solid. Sintering together of the particles can occur entirely in the solid state or from a mixture of solid particle and liquid. A liquid phase aids sintering; a small amount of liquid coats grain boundaries in the dense solid, and a larger amount can provide a glassy matrix for solid particles, as in porcelain, and is called vitrification.

Materials that are difficult to sinter to dense enough bodies can sometimes be sintered by a combination of heat and pressure called hot pressing. The main problem in hot pressing is to find materials for dies that will withstand pressure of 30 MPa or higher above 1000 °C. Graphite is widely used, but it is quite expensive and has as short a life as a die, so hot pressing is used only for pieces of high value. Hot pressing is also slow because of the time required to heat and cool the dies for each piece.

A glass composition proposed for implants ("Bioglass") contains 45 wt % SiO_2, 25% Na_2O, 24% CaO and 6% P_2O_5. A typical batch melting temperature for this glass is about 1300 °C. The most difficult step in glass melting and in vitrification is usually the removal of bubbles (fining). Bubbles bigger than about 1 mm diameter rise to the surface in a glass melt of viscosity 100 P, but smaller bubbles must be removed by diffusion of gas in them into the surrounding glass [8]. A number of additives at the level of about 0.5 wt % aid fining. Glass can be formed by drawing, pressing, and blowing [9, 10].

3. Biocompatibility

For solid materials to be useful in the body they must elicit the minimum of adverse reactions. These reactions result from several causes. There are the possibilities of direct toxicity of the implant materials to tissue and organs and toxicity of products from the implant that dissolve and migrate in body fluids and tissues. Heavy metals such as chromium or nickel, fluorine, and certain organic molecules are examples of toxic materials. Any dissolution of these components into body fluids must be avoided.

When a foreign solid material is placed into the body, it can provoke a foreign body reaction. Cells and proteins from the blood and neighbouring tissues try to remove the foreign agent. Giant cells are evidence of a serious reaction. Fibrous tissue forms around the foreign body, encapsulating it. A severe local foreign body reaction can destroy physiological function and cause tissue damage. Examples are thrombus formation in blood vessels, calcification in heart valves, and gross fibrous encapsulation of silica or asbestos particles in the lung, leading eventually to a predisposition to malignant tumors. Immune reactions are also possible, especially from skin, bone or organ replacements from another person or species. After a few hours or days the foreign element stimulates an immune reaction that leads to loss of adherence and production of toxins. If drugs are given to reduce the immune reaction, the patient becomes more susceptible to disease.

4. Fracture and fatigue of ceramics

4.1. Fracture

The strengths of brittle materials such as ceramics and glasses depend mainly on the history of treatment of their surfaces, and on internal defects. Failure usually occurs at much lower tensile than compressive stresses. Examples of tensile strengths in bending of dense, polycrystalline hydroxylapatite [11] are given in Table III.

The fracture and fatigue results reported in Table IV and Fig. 1 were on diametrically loaded samples. In this test a right circular cylinder, about 5 mm diameter and 3 mm thick, was compressed diametrically between two flat plates. The maximum tensile stress is developed normal to the loading diameter, and is therefore present across the diameters of both flat surfaces of the cylinder and also across a plane from one end of the cylinder to another. Thus both surface and volume flaws contribute to failure.

Other test methods include bending with either three or four contact points on a rod or bar specimen, and tensile tests of fibres. The three-point bend results in Table III show that polishing the sample surface increases the measured strength substantially. Many other similar results on brittle materials have led to the hypothesis that fracture results from propagation of flaws or cracks in the sample surface, or from flaws or pores in the sample bulk [17]. The tensile stress, σ, at the tip of a crack of depth, c, and tip radius, ρ, is

$$\sigma/s = 1 + 2(c/\rho)^{1/2} \approx 2(c/\rho)^{1/2} \quad (1)$$

in which s is the applied tensile stress [12]. Thus a crack that is deep and thin concentrates the applied stress to much higher stress at the crack tip, leading to crack propagation when the tip stress exceeds the intrinsic strength of the material. Removing or reducing the depth, c, of the cracks increases the strength.

The samples with 87% apatite contained additional phases, mostly of Whitlockite, $Ca_3(PO_4)_2$, that apparently reduced the strength by increasing the potency of surface flaws. If the apatite contains large pores because of defects or agglomeration in the powders, the cracks can start from these pores, giving lower strength, [13] as is true for ceramics in general.

TABLE III Fracture strength at 25 °C of polycrystalline hydroxylapatite fired at 1100 °C for one hour. Three-point bending, cross-head speed 0.125 cm min^{-1}

Wt % Apatite by X-rays	Average fracture strength, MPa	Remarks
100	112	As cut
100	196	Polished to 1 μm diamond on all four faces
87	79	As cut
87	160	Polished with 600 grit alumina on two faces.

TABLE IV Influence of loading rate on strength of dense hydroxylapatite in diametral tests [18]

Cross-head speed cm min	Mean strength MPa
0.0005	109
0.005	112
0.05	117
0.25	112
1.25	121

When the failure strengths of a number of identical brittle samples are measured under the same conditions of sample preparation and loading, the strengths vary over a wide range, for example by a factor of two. This distribution of strengths can be expressed statistically. A common distribution function is the normal or Gaussian function; the probability density function, P, gives the familiar symmetrical bell-shaped curve as a function of fracture strengths, S_i

$$P = \frac{1}{\sigma(2\pi)^{1/2}} \exp - \frac{(S_i - \bar{S})^2}{2\sigma^2} \quad (2)$$

in which $\bar{S}$ and σ are the mean and standard deviation of the strength distribution. The integral of Equation 2 gives the fraction, F, of samples that breaks below the stress, S_i, or the cumulative distribution

$$F = \tfrac{1}{2}[1 + \mathrm{erf}(S_i - \bar{S})/\sigma 2^{1/2}] \quad (3)$$

where erf is the error function

$$\mathrm{erf}\,u = \frac{2}{\pi^{1/2}} \int_0^u e^{-\lambda^2} d\lambda \quad (4)$$

Another distribution function, the Weibull, is often used for strengths, but there is no intrinsic reason to prefer it, other than certain mathematical convenience [14].

Dense hydroxylapatite was prepared by precipitation from solution, drying, and firing at 1100 °C, as

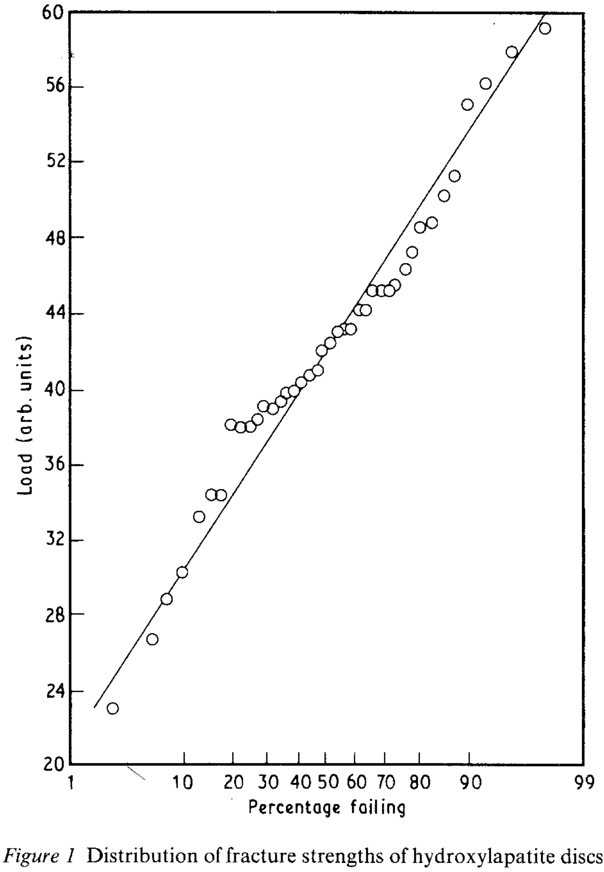

Figure 1 Distribution of fracture strengths of hydroxylapatite discs, by diametral tests, plotted on probability paper. F, fraction failing.

described in [11]. Experimental fracture strengths for hydroxylapatite [15] are plotted in Fig. 1 on probability paper. The abscissa of this plot gives F values from Equation 1 expressed as a percentage, and the ordinate fracture strengths, S_i, so a straight line on the plot shows agreement with Equation 1. Thus the strength data of Fig. 1 fit the normal distribution function; other strength data for hydroxylapatite fit the Type I extreme value distribution function [14].

Because the strengths of brittle materials such as ceramics and glasses depend on surface (and internal) defects that multiply applied tensile stress, these strengths depend strongly upon the processing methods, surface treatment, and handling of these brittle materials. Typical practical tensile strengths are in the range 50–200 MPa. These strengths are far less than the intrinsic strengths of flawless ceramics, which are 10^{10} Pa or higher. There is an indirect relation between practical strengths and intrinsic strengths. A material with higher intrinsic strength usually has better wear and abrasion resistance, so often fewer and less potent flaws are formed during processing and handling of stronger materials. Alumina, because it is hard and has high intrinsic strength, will usually be stronger after a particular treatment than softer materials such as calcium phosphates and glasses. Nevertheless it is possible to make these latter materials with high strengths with proper processing and handling.

4.2. Bone–implant bonding tests

A common way of measuring bone–implant bonding semi-quantitatively is called a push-out test. A cylindrical sample is implanted, for example into the cortex of a femur, and after the bone is recovered the force needed to dislodge (push out) the implant from the bone is judged. Usually a special clamp is made to apply the force.

A quantitative test for measuring the strength of bone–implant adhesion has been described by Nakamura *et al.* [16]. An implant plate $2 \times 10 \times 15\ \text{mm}^3$ in dimension was implanted into a hole in a rabbit tibia such that the plate extended right through the tibia from the medial to the lateral cortex. After sacrifice the bone was cut so that two semicircular bone segments were each bonded to the plate on either side, as shown in Fig. 2. Each bone segment was held by a hook connected to an Instron test machine. In this way the bonding strength of the bone to the implant could be measured directly. A segment of bone without an implant was tested in the same way for comparison.

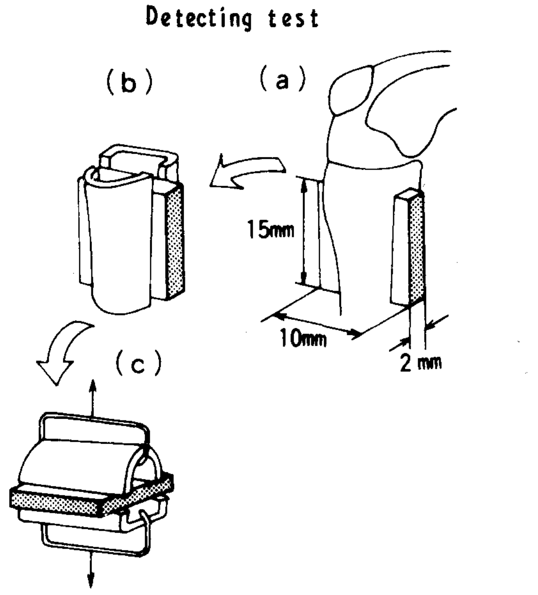

Figure 2 Nakamura test for strength of an adhesive bond between an implanted plate and bone.

4.3. Fatigue

When oxides are held under a tensile stress in aqueous solutions or water vapour, they become weaker. This fatigue can be tested in several ways [17]. In a static fatigue test the samples are held under constant load until they fail. In a second method samples are tested at different constant loading rates in a testing machine. This method requires fewer samples and less time than static tests, but the latter are probably closer to real loading situations. Some experimental diametral measurements of strength of dense hydroxylapatite at different loading rates [18] are given in Table IV. There is a small increase in strength as the loading rate increases.

A variety of functions have been suggested for the dependence of failure time, t, on applied stress, s, in a static test. The most used is a power law dependence

$$\log t/\tau = -n \log(S/S_N) \qquad (5)$$

in which n and τ constant and S_N is the failure strength under conditions for which there is no fatigue, such as at low (liquid nitrogen) temperature. Equation 5 fits experimental data over narrow stress ranges, but is not valid over a large stress range. A better function is treated in [17]. The parameter n in Equation 5 is an approximate measure of the fatigue susceptibility of a material. A large value of n (> 100) means a material is not much subject to fatigue, whereas a low value (< 10) means the material is highly fatigue sensitive. The parameter τ includes factors such as flaw dimensions, the ultimate or theoretical strength of the material, n and S_N [17].

If Equation 5 is valid, Charles [20] found that the constant loading rate β in a fatigue test is related to the fracture stress, S, by

$$\beta^{[1/(1+n)]} = KS \qquad (6)$$

where K is a constant. Thus the slope of a plot of β against log S is $1/(1 + n)$. From a least squares regression analysis of such a plot of the data in Table IV, n is found to be about 80 for pure, pore-free hydroxylapatite [18]. Such a high value of n demonstrates remarkably low fatigue sensitivity for hydroxylapatite in humid air; comparable values for many crystalline and glassy oxides are in the range 10–20, and even for polycrystalline alumina, n is about 30. More fatigue results on hydroxylapatite are discussed below.

Failure times also show a distribution in values, sometimes very wide. If the inert strength is assumed to be normally distributed (Equations 2 and 3), and Equation 5 is valid, the logarithms of failure times, t, in a static test have approximately a normal distribution [21]

$$\log t = \overline{\log t} + 2^{1/2}\sigma' \mathrm{erf}^{-1}(2F - 1) \qquad (7)$$

where $\overline{\log t}$ is the mean of $\log t$ values at a particular applied stress, F is the fraction of samples that fail before time t, and σ' the standard deviation of $\log t$ distributions. The function $\mathrm{erf}^{-1} u$ is the "arc error function", or the number whose error function is u. The standard deviation σ' of the $\log t$ distribution is related to the standard deviation σ of the S_N distribution by [21]

$$\sigma' = n\sigma/\overline{S_N} \qquad (8)$$

in which $\overline{S_N}$ is the mean of the inert (liquid nitrogen) strengths.

Examples of distributions of failure times of implants of hydroxylapatite in dogs are given in Fig. 3, from [21]. There appear to be two different sets of implants in each sample, one much more susceptible to fatigue than the other. More discussion of fatigue of hydroxylapatite is given in the section on this ceramic.

4.4. Toughness

A brittle material such as a ceramic or glass deforms elastically until it fractures; thus if the applied stress is plotted as a function of the relative deformation or strain, a straight line results. A ductile material such as aluminium deforms linearly at very low stresses, but at higher stresses plastic deformation results and the stress–strain curve becomes non-linear; more and more stress is required to increase the strain. Toughness can be defined as the ability of a material to absorb energy during plastic deformation, and an indication of toughness can be obtained from the area under the stress–strain curve for a static test, which represents the work required to fracture the material.

A quantity called the critical stress intensity factor K_c can be measured for a solid material. If there is a crack or notch of depth c in a material and it is subjected to a tensile stress (mode I loading), K_c is defined by

$$K_c = S(\pi c)^{1/2} \qquad (9)$$

in which S is the stress required to cause the crack or notch to propagate to failure. K_c is sometimes considered as a material or intrinsic property of a material, but many experiments show that K_c depends on extraneous factors such as sample microstructure and treatment history. Thus K_c is not an intrinsic property of a material; see also [17] for theoretical reasons for this conclusion.

The critical stress intensity factor, K_c, is sometimes called the toughness of a brittle material.

5. Types of ceramics proposed as implants

Properties of different implant ceramics are given in Table V. Each type is discussed below.

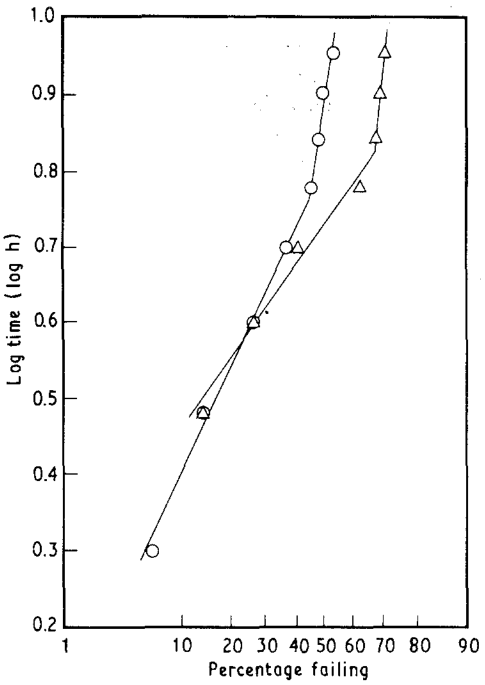

Figure 3 Distributions of failure times of hydroxylapatite plugs implanted in jaws of dogs [22, 23].

5.1. Jade

Jade (base composition $Na_2O \cdot Al_2O_3 \cdot 4SiO_2$) has been found implanted in teeth of Mayan women, of the period 600–800 A.D., perhaps for ornamental and restorative purposes [24]. Natural jade is a quite hard, durable crystalline mineral or ceramic.

5.2. Porcelain

Porcelain has been used for restorative dentistry since the late 18th century. (See [25] for a review of materials in dentistry.) Porcelain inlays and crowns were made by Charles H. Land in the late 19th century by fusing the porcelain on to platinum foil in the form of a model of the tooth. Porcelain can be made with optical properties that match natural teeth with additions of silica or alumina particles; the particles also increase the strength of the porcelain. Porcelain crowns can also be made strong by fusing the porcelain to a metal coping; however, the metal changes the appearance of the crown. Porcelain restorations can also be cast in a mould.

Porcelains contain various mixtures of clay (e.g. kaolin, $Al_2O_3 \cdot 2SiO_2 \cdot 2H_2O$), feldspar ($K_2O \cdot Al_2O_3 \cdot 6SiO_2$) and quartz sand. A typical hard porcelain for whiteware contains 50% clay, 25% feldspar, and 25% sand. Dental porcelains have more feldspar and little or no sand. A typical composition is 95% feldspar, 5% clay. The result is a highly glassy material that is translucent and melts at a lower temperature because of more feldspar. During firing of porcelain the feldspar melts first to provide a molten matrix that speeds formation and gives a glassy matrix on cooling. The clay dehydrates and transforms to fine, elongated crystals of mullite, $3Al_2O_3 \cdot 2SiO_2$, that provide additional strength. Any quartz or alumina particles partially dissolve, and the residual crystals increase strength but reduce translucency.

TABLE V Composition and properties of implant ceramics

Name	Typical composition, wt %	Processing	Fatigue resistance	Remarks
Porcelain	5% clay, 95% feldspar giving: 17% K_2O 19% Al_2O_3 64% SiO_2	Vitrification	Good	Easy to form, fairly hard, good durability
Calcium Aluminate	20% CaO Al_2O_3 80% 3CaO $5Al_2O_3$	Sintering		Made porous
Alumina	Al_2O_3	Sintering	Very good	Hard to form; very hard and durable
Bioglass	45%SiO_2, 24%CaO, 25%Na_2O, 6%P_2O_5	Glass melting	Good	Easy to form, good durability
Glass Ceramic	Spodumene, $2LiO_2$ Al_2O_3 $4SiO_2$	Glass melting, then heating to 600–800 °C	Excellent	Easy to form, but requires heating. Durable
Glass Ceramic	45%CaO, 5%MgO, 34%SiO_2, 16%P_2O_5 crystalline phases: Apatite, CaO SiO_2, $Ca_3(PO_4)_2$	Glass melting, heating	Good	Different amounts of crystalline phases possible
Glass Ceramic "ceravital"	32%CaO, 3%MgO, 45%SiO_2, 12%P_2O_5 crystalline phase: apatite	Glass melting, heating	Good	
Glassy Carbon	100%C	Pyrolyzing organic polymers such as cellulose	Good	Low porosity, highly durable
Whitlokite	$Ca_3(PO_4)_2$	Sintering of precipitated crystals		Resorbs
Hydroxylapatite	$Ca_{10}(PO_4)_6(OH)_2$	Sintering of precipitated crystals	Excellent	Same composition as mineral in bones and teeth

Properties of porcelains are not sensitive to small changes in composition, forming methods or firing temperatures. As the firing temperature or amount of liquid (feldspar) increases, more silica and alumina dissolve in the melt, increasing its viscosity and lowering its reactivity. Porcelains therefore have a glassy matrix, so their chemical properties resemble those of a potassium aluminosilicate glass; they are strong, chemically durable and can be fired at relatively low temperatures and short times. These properties have made porcelains a satisfactory restorative material in dentistry, with the particular advantage of optical matching of teeth, but the disadvantage of brittleness. As implants, porcelains are similar to glasses.

5.3. Alumina

Aluminium oxide is very hard (9 on the Mohr scale), stable to high temperatures, and chemically durable. Polycrystalline sintered alumina is very strong compared to most ceramics, although it is brittle. Its strength, abrasion resistance, and chemical inertness have made it attractive for dental and bone implants.

Polycrystalline alumina is made by sintering the pressed powder, usually with polyvinyl alcohol or other organic material as a binder. The ease of sintering and properties of the dense alumina depend strongly on impurities in the starting material, and a wide range of quality and price is available commercially. Very pure alumina sinters only with difficulty at high temperatures (~ 1900 °C). If the starting material contains a small amount of alkali (sodium or potassium) oxide, liquid forms during sintering, so that densification takes place more rapidly and at lower temperatures. However, the liquid forms a glassy phase at the grain boundaries, making the alumina weaker at high temperatures and less chemically durable. Single-crystal α-alumina (sapphire) attaches to epithelium ([5] p. 4).

5.4. Calcium aluminate

Porous calcium aluminate was made by sintering fine alumina powder with coarse calcium carbonate at 1450 °C for 24 h [26]. Pore sizes from 20–100 μm resulted by using different sizes of the calcium carbonate particles; the pore size was about the same as the particle size. The carbonate decomposes to calcium oxide, which then reacts with alumina to form two calcium aluminate phases, $CaO \cdot Al_2O_3$ and $3CaO \cdot 5Al_2O_3$. With a starting composition of about 27% CaO and 73% Al_2O_3 (by weight), the amounts of the two phases were about those expected at equilibrium (20% $CaO \cdot Al_2O_3$, 80% $3CaO \cdot 5Al_2O_3$). Porous $CaO \cdot TiO_2$ and $CaO \cdot ZrO_2$ were also made by reaction of calcium carbonate with TiO_2 or ZrO_2. Discussion of the use of porous materials in the body is given below.

5.5. Carbon

Glassy carbon is produced by pyrolysing cross-linked organic polymers such as cellulose, phenolformaldehyde, and polyfurfuryl alcohol under carefully controlled conditions [27]. The microstructure consists of random crystallites about 5 nm in size, in contrast to the ordered layer structure of graphite. The density of glassy carbon (1.4–1.5 $g\,cm^{-3}$) is lower than that of graphite, but glassy carbon has low porosity and permeability. The mechanical properties are similar to those of silicate glasses; the strength and modulus are higher than those of graphite. Glassy carbon is chemically inert compared to graphite, probably because of its low porosity. Glassy carbon is quite expensive to manufacture.

There was a flurry of interest in glassy carbon implants in dentistry in the mid-1970s. ([4] Vol. II, p. 135.) Bone does not bond to glassy carbon, so the implants and tooth replacements were made in various shapes, such as blades, with holes for bone to grow into to anchor the implant. Some of these implants were initially successful, but fractured or loosened after a few months to one or two years after implantation. The fatigue resistance of glassy carbon should be high; there do not seem to be any good tests of it, especially in body fluids. There was not much foreign body reaction, except for fibrous encapsulation.

Pyrolytic carbon coatings have been used in a variety of implant applications, such as heart valves and artificial arteries ([4] Vol. II, p. 136). Artificial joints and parts of heart valves have been made of solid carbon. Pyrolytic carbon has good fatigue resistance [28].

5.6. Bioglass

Bone bonds well to the Bioglass composition given in section 2 and to a variety of other silicate glass compositions [29]. Bonding to bone of glass implants apparently involves first leaching of alkali from the glass, forming a hydrated layer on the glass surface. Then a calcium phosphate layer grows on the glass surface, and this layer provides a bond between the glass and new bone [30]. If the glass composition has more than about 60% silica, bonding to bone is not as effective. Fine porosity in the glass surface on a scale of about 10 nm also helps bonding; bone bonds to 'thirsty glass', which is almost pure silica and has porosity of this dimension.

Glass for implants has been reinforced with ductile materials, such as stainless steel wire, which improve its resistance failure [30]. The bonding to bone is not affected by this reinforcement. Some implant studies with glass are summarized in References 2 and 5; glass will probably be most valuable as a coating material.

5.7. Glass-ceramics

Glass-ceramics are glasses in which fine, uniform crystals are grown by controlled heat treatment. They usually have higher strength, chemical durability, and electrical resistivity than the parent glass and can be made with low thermal expansion, giving excellent resistance to thermal shock. To make a glass-ceramic, an article is first formed into a desired shape by conventional methods of fabricating glass, and then it is heated first to nucleate and then grow the crystals throughout the glass. The resultant composite structure of fine crystals held together in a glassy matrix often has improved properties. Glass-ceramics that contain a high density of fine crystals are white and opaque, resembling porcelain, because of light scattered by the crystals. However, it is also possible to make glass-ceramics that are translucent or even transparent.

Two classes of glass compositions are most popular for commercial glass-ceramics, the lithium aluminium and the magnesium aluminium silicates. The crystalline phase in the former can be β-spodumene ($2Li_2O \cdot Al_2O_3 \cdot 4SiO_2$), β-eucrypite ($2LiO_2 \cdot Al_2O_3 \cdot 6SiO_2$), β-quartz or lithium disilicate ($Li_2O \cdot 2SiO_2$), depending on the base composition. Cordierite ($2MgO \cdot 2Al_2O_3 \cdot 5SiO_2$) crystals grow from the second type.

To initiate or "nucleate" uniformly the fine crystals in a glass-ceramic, a special nucleating agent is added to the basic glass composition. Titania (TiO_2) or phosphate (P_2O_5) are effective nucleating agents in many glass-ceramics.

An interesting family of glass-ceramics that forms apatite crystals has been developed [31–37]. Compositions of these materials are given in Table V; they are calcium phosphosilicates containing some magnesium and nucleating agents. In one method [31] the glasses were melted at 1500 °C for 3 h, annealed, and cooled. Then fine crystals of apatite were grown in the glass by heating it at 680 °C for 24 h. The crystallite size was about 40 nm. Bone bonded well to this glass-ceramic containing apatite crystals.

A similar composition of glass was processed to form different crystalline mixtures in glass-ceramics [32–37]. The raw materials were melted at 1450 °C for 2 h and cooled rapidly to form a glass "G" (Table VI). If this glass was heated for 4 h at 870 °C, apatite crystals grew in it to form samples "A". More crystalline materials were made by grinding up the glass and pressing it into pellets with paraffin as a binder. Firing these pellets at 1050 or 1200 °C for 4 h gave samples "A–W" and "A–N–CP" containing apatite, wollastonite, and Whitlokite crystals in a glassy matrix (see Table VI). Good mean strength (178 and 213 MPa, respectively) were found for samples A–W and A–W–CP tested in air. However, these materials cannot be formed in the same way as glasses, because they must be sintered just as crystalline ceramics, so that processing is not as advantageous as for glass-ceramics crystallized directly from glasses.

Implants of these glass-ceramics containing apatite crystals bind well to bone, as shown by the results of adhesion tests given in Table VII. The glass-ceramics A–W and A–W–CP have similar adhesion strength to dense hydroxylapatite; these materials adhere much better than bioglass or alumina. Bone itself was somewhat stronger than the strongest bonds between it and the implants. When bone bonds to these glass-ceramics a very thin layer of hydroxylapatite forms between

TABLE VI Phase contents of glass ceramics containing apatite (ref. 31–34) in wt %

Designation	Apatite $Ca_{10}(PO_4)_6(OH)_2$	Wollastonite $CaO\ SiO_2$	Whitlokite $Ca_3(PO_4)_2$	Glass
G	0	0	0	100
A	35	0	0	65
A-W	35	40	0	25
A-S-CP	20	55	15	10

TABLE VII Failure loads of implanted ceramics by the Nakamura test [16, 42]

Material (see Table 5)	Mean failure load, kg		
	8 weeks	10 weeks	25 weeks
Alumina	0.1		
4555 Bioglass	2.8		
Hydroxylapatite	6.3		7.9
Glass Ceramics			
A-W	7.4	7.1	7.1, 8.2
A-W-CP		7.6	7.2
Bone			12.0

TABLE VIII Fatigue sensitivity of bioceramics

Material	Medium	n (eqn. 5)	Ref.
Hydroxylapatite, $Ca_{10}(PO_4)_6(OH)_2$	Ambient air	80	18
	Ambient air	26	40
	Wet	13	40
	Body fluid	27	34
From Table 6			
G	Simulated body fluid	9	34
A	Simulated body fluid	18	34
A-W	Simulated body fluid	33	34
A-W-CP	Simulated body fluid	22	34
Alumina	Ringer's solution	44	53

the bone and implant [35, 36]; much the same kind of layer forms on implanted micro-porous glasses and other calcium compounds. This layer is sometimes taken as evidence for "bioactivity" of the implant. No such layer forms on well-made hydroxylapatite implants [49–51].

In Table VIII fatigue sensitivities of various bioceramics are compared. Pore-free phase pure hydroxylapatite has by far the least fatigue sensitivity of the materials tested. Some glass-ceramics and alumina show good resistance to fatigue.

Kukobo *et al.* [37] give a highly misleading comparison of fatigue resistance of bioceramics. The authors have compared fatigue lifetimes of samples of different materials of different strengths. Such comparisons must be normalized to inert strengths before they are meaningful. Sample strength is a function of, for example, surface condition, porosity, second phases, and defects; these are not intrinsic properties of a material but depend on how it is processed and treated, thus on sample history. Measured sample strength is therefore not an intrinsic property of a material, but can change over wide limits depending on how the sample is handled, as shown in Table III. Dense hydroxylapatite that is free of pores and second phases can have high strength. The only meaningful comparison to judge fatigue resistance is to compare lifetimes at the same ratio of applied stress to inert strength, or to use a parameter such as n in Equation 5 (see Table VII). On this basis hydroxylapatite has higher intrinsic fatigue resistance than the family of glass-ceramics that contain some apatite crystals [38–41].

Another glass-ceramic system is based on glasses containing SiO_2, K_2O, MgO, and fluoride, with small amounts of alumina and zirconia [42, 43]. The main crystalline phase that grows in this glass is tetrasilicic fluormica [44] $K_2Mg_5Si_8O_{20}F_4$, after heating at 775 °C for 14 h. These crystals are plate-like and related to mica; the microstructure has a network of randomly oriented crystals in a glassy matrix [45]. This material can be cast by the lost-wax process, which allows the material to conform to an irregular surface and is especially valuable for dental restorations [25].

5.8. Hydroxylapatite

Dense hydroxylapatite was first made by pressureless sintering of fine precipitated crystals of exactly the right stoichiometry [11] (Ca/P ratio of 1.67). The resulting ceramic microstructure is remarkable, because it is entirely free of pores, either large or small, and of second phases (see Figs 4 and 5). This microstructure leads to good strength and excellent fatigue resistance, as shown in Tables III and VIII. The absence of pores and second phases is critical in obtaining these properties. Samples with pores and second phases are hard to make strong and have lower fatigue resistance. Thus it is untenable to dismiss hydroxylapatite as an implant material based on results on samples containing these defects [22, 46].

In Reference 22 it is concluded that "fatigue properties of apatite ceramics are insufficient for use as a loaded transmucosal implant under all conditions". Failure results of hydroxylapatite implants on which this conclusion is based are plotted in Fig. 3 as fraction of failed implants as a function of failure time on

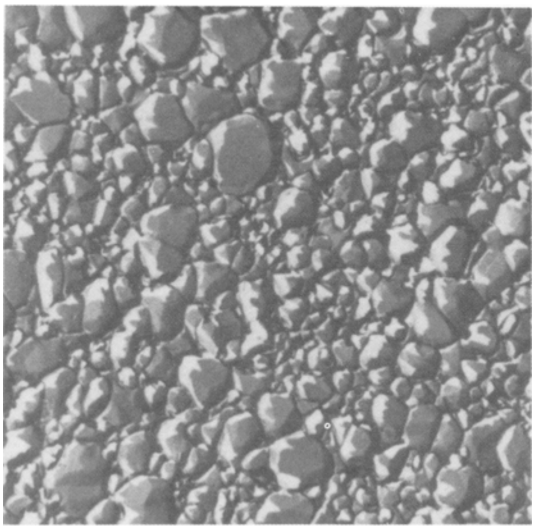

Figure 4 Electron micrograph from a two-stage replica of hydroxylapatite fired 1 h at 1190 °C [11].

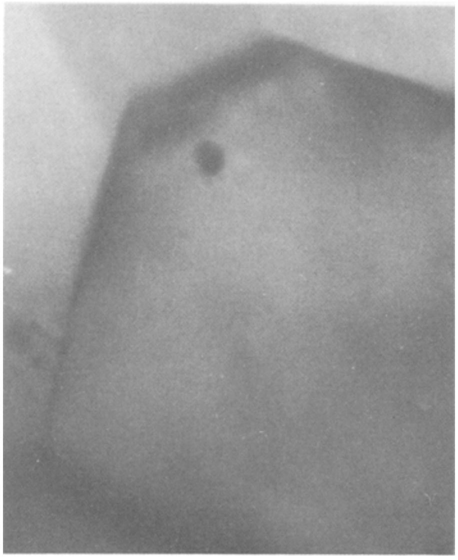

Figure 5 Transmission electron micrograph of ion-thinned hydroxylapatite fired at 1100 °C for 1 h [11].

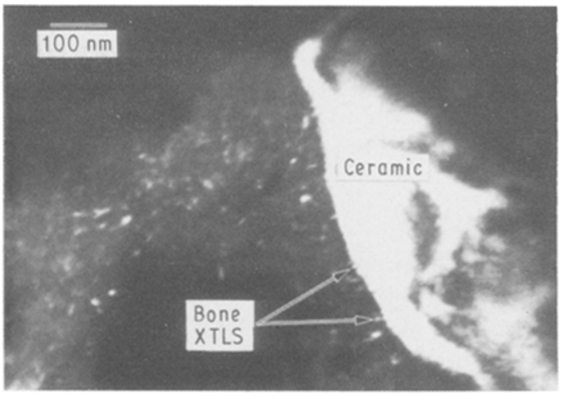

Figure 6 Dark-field image of the thinned interface between a hydroxylapatite implant and bone [51].

probability paper. A straight line on this plot means the data fit a normal distribution (Equation 7). In two different sets of results there are clearly two different populations of samples, one which fails in about the first 6 months of implantation, and another which is much more durable; after 10 months about 30% of the implants in one study and 45% in the other had not failed. The discussions in the section on mechanical properties and the fatigue results on pore-free apatite show that its intrinsic fatigue resistance is high. Thus the problem in the study in Fig. 3 is improper processing or treatment of some or all samples. It is therefore premature to dismiss bulk dense hydroxylapatite as an implant material on the basis of these studies; properly prepared pore-free material should show good fatigue resistance.

One way to ensure good strength of samples especially in a bimodal distribution is a proof test [47], which is a quality control method. All samples are subjected to a stress at a level to cause undesired samples to fail, leaving only stronger samples. A disadvantage of this test is that the proof stress can weaken samples that do not quite fail.

Growing bone bonds strongly to hydroxylapatite, as shown in Table VII. There is no foreign body reaction, no giant cells, and no fibrous encapsulation of the implant. The osteoblasts are "fooled" into treating the apatite as material that belongs physiologically, not surprisingly, because the mineral in bone and tooth enamel is close to hydroxylapatite in composition. In a thinned section of the bone–implant interface, the banded bone collagen grows directly up the implant surface on a scale of 10 nm or less [49, 50]. At even higher magnification bone collagen and mineral are seen to grow directly up to the implant surface [51], as shown in Fig. 6. More recent work confirms these conclusions [52].

In the last few years there has been renewed interest in hydroxylapatite as an implant material in a variety of forms and applications. Some of these applications are described in more detail in subsequent sections. The brittle nature of ceramics limit their impact resistance, so they are not suitable in bulk form for applications requiring impact resistance, such as hip implants. Here coatings of apatite on a metal may prove to be an ideal combination. Other composite and combination forms (e.g. glass-ceramics) to take advantage of the excellent chemical and physiological properties of apatite are promising. Forms motivated by the presumed inadequate fatigue resistance of apatite are less attractive; as discussed above, this effort should better be aimed at improving the quality of the apatite itself, especially eliminating porosity and second phases.

Hydroxylapatite has excellent promise for many implant applications, and should find wide use in the future.

5.9. Calcium phosphate

Dense, pore-free tri-calcium phosphate $Ca_3(PO_4)_2$ or the mineral Whitlokite, can be made by sintering precipitated fine crystals, very similar to the method making hydroxylapatite [54]. The resulting material is strong but probably is less fatigue resistant than hydroxylapatite. Bone bonds well to this material without a foreign body reaction. The only advantage of Whitlokite over hydroxylapatite is that Whitlokite is slowly resorbed by body fluids; it is more soluble in aqueous solutions than apatite. There has been little work exploring applications of calcium phosphate other than apatite. There is more background information on calcium phosphates in [1].

5.10. Calcium carbonate

Various allotropic solid forms (calcite, aragonite) are more soluble in water than the calcium phosphates, but they bond to bone when implanted in it, and resorb slowly [55]. They are reasonably strong, and may have application as implants in unstressed sites.

5.11. Forms of bioceramics

The materials discussed so far were mainly in the form of uniform bulk solids. Other forms, such as coatings, composites, and mixtures have potential applications for special uses. There seems to be a consensus that hydroxylapatite, or apatite-containing materials such as glass-ceramics, are the most promising bioceramics, so this discussion will emphasize these materials. Some workers have concluded that bulk, dense hydroxylapatite is not strong enough or does not have good enough fatigue resistance for applications involving stress; I dispute this conclusion, as described above. Nevertheless there are special applications where different forms are appropriate. In this section, I put forward my own views, even though there is not always much supporting evidence; their confirmation or refutation await further work.

5.11.1. Dense and granular forms

Bulk shapes are appropriate for many of the applications listed in Table II, such as dental restorations, and tooth root and whole tooth replacements. In other applications granular material can be fitted to a desired shape or space, such as for dental restorations. In some of these applications, such as augmenting the alveolar ridge, the granules are difficult to fix; sometimes some of them drift from the desired location. The quality of the result often depends on the surgical techniques. However, a variety of successful applications of different forms of apatite has been reported, and some of them are summarized here.

Hydroxylapatite granules in cranioplasty directly over the dura showed excellent particle control with negligible migration and no meningitis or infection [56]. In a study of granules and blocks of hydroxylapatite as extracranial augmenting material in rhesus monkeys, excellent biocompatibility was reported with no inflammation [57]. There was somewhat better performance with granules than blocks; the granules showed some settling but no gross migration or displacement. In alveolar ridge augmentation granules of hydroxylapatite were prevented from migrating by stabilization with a red rubber urethal catheter [58].

5.11.2. Mixtures with hydroxylapatite

It would be valuable to develop forms of hydroxylapatite that are less sensitive to surgical techniques; one of these is a mixture of hydroxylapatite granules with plaster of Paris [3, 65] (calcium sulphate or gypsum, $CaSO_4 \cdot 2H_2O$). Good results in alveolar ridge augmentation [59] and treatment of periodental defects [60] have been reported for mixtures of hydroxylapatite granules and a matrix of plaster of Paris. This mixture can be shaped to fit a variety of defects and sterilized without changing its form or properties. After implantation the plaster of Paris is gradually replaced by fibro-vascular tissue, and the hydroxylapatite particles remain firmly held in place. It was reported that there was enhanced bone growth in defects with the plaster of Paris mixture than with granular alone or porous hydroxylapatite. No adverse effects were found from the addition of plaster of Paris. This composite material appears to be suitable for a variety of biomedical applications.

Mixtures of fibrillar collagen [61], fibrin glue [62], or alginate [63], or bovine osteogenic factor [64] with granular hydroxylapatite for filling bony defects and augmenting the alveolar ridge have been reported. Although good results were revealed with these composites, they do not appear to have any advantage over the plaster of Paris–apatite combination. The organic material may not be completely resorbed, and there is always a possibility of adverse reactions, although none were reported.

A more complex mixture containing hydroxylapatite, corticocancellous cranial bone, Bacitracin powder and thrombin, was implanted into a variety of bony defects [65]. The autogenous bone is presumed to stimulate subsequent bone growth; however, the osteocytes originally in this bone do not survive the transplantation, so new cells must grow to provide new bone growth. I question whether the autogenous bone is necessary. Osteocytes apparently multiply under a variety of conditions in these bony defects, and there does not seem to be any definitive experiments to trace their origin. This issue is certainly an important one for further experimentation; avoiding the second surgical site is most desirable.

These composites consisted of hydroxylapatite particles in a matrix. An entirely different composite is a hydroxylapatite matrix containing a reinforcing material to provide enhanced mechanical properties. Metal and ceramic wires have been incorporated into a hydroxylapatite matrix [66]. A critical need is to match the thermal expansion coefficients of the wire and matrix. The wires were mixed with hydroxylapatite powder and the mixture hot-pressed at 1000 °C for 15 min up to 1 kbar. Alumina and titanium caused extensive cracking in the matrix. Stainless steel and inconel were heavily oxidized. Hastelloy (51%Ni, 22%Cr, 9%Mo, 18%Fe) of 8 µm diameter, and FeCrally (79%Fe, 16%Cr, and 5% Al) of 20 µm diameter were more successful. Oxide reaction layers on the wire surfaces gave good bonding to the hydroxylapatite. The hardness of the composites was somewhat less than that of dense hydroxylapatite, but the notch fracture strength of both composites was considerably higher than apatite, and the fracture strength of the FeCrally at 20% and 30% wire volume was higher than apatite. These composites are possibly promising for further development.

Another approach is to mix granular hydroxylapatite in an organic matrix such as polyethylene to simulate the structure of bone ([5] p. 173). This composite can show ductile fracture, and bone bonds to it.

There is some indication that incorporation of silver phosphate into hydroxylapatite provides protection against bacterial growth [67].

5.11.3. Coatings

In applications in which an implant is subjected to severe impact stresses, such as a hip joint replacement, ceramics are inadequate because they fail in a brittle manner and do not absorb impact energy. A ductile material such as a metal can absorb an impact by more slowly deforming plastically (see section on mechanical properties). A possibility is therefore to coat a metal with hydroxylapatite to take advantage of the high impact strength of the metal, prevent metal from reacting and migrating into neighbouring tissues, and bind the coating directly to bone. The usual cause of failure of hip implants is loosening of the implant tail in the femur, even if it is cemented, for example by polymethylmethacrylate.

Hydroxylapatite has been coated on to porous titanium metal and alloys [68–70] and cobalt–chromium alloys [70] by plasma spraying. It can also be coated directly on to a dense implant surface [71–75], and I feel this form is preferable to the porous, as discussed below.

In plasma spraying a fine (< 50 μm) ceramic powder is blown through a plasma torch flame on to a substrate. In previous applications of plasma spraying the ceramic powder was usually melted ([7] p. 254); however, melting is not essential. Although the plasma is very hot, if conditions of flow are regulated the powder can have a much lower temperature than the plasma. In spraying hydroxylapatite, the temperature of the powder is critical. If it is too hot (> 1200 °C) the apatite decomposes; if it is not hot enough, the apatite does not adhere to the substrate. In this method the apatite does not melt, because its melting temperature is above 1200 °C; it bonds together and to the substrate by solid-state reaction and diffusion, just as in sintering to a dense solid.

Good bonding to the substrate depends critically upon the thermal expansion match between coating and substrate. The match between titanium and apatite is only fair; the coatings show micro-cracking, probably because of thermally induced strain upon cooling (see Fig. 7). A better match should be possible by judicious alloying to reduce strains and cracking.

Dental implants in dogs, of titanium coated with hydroxylapatite, gave excellent results [71]. There was superior bone bonding directly to the implants as compared to other materials; there was no need for threads, flutes or holes on the implant to fix it. These coated implants had earlier biointegration, a more complex layer of lamellar bone, and better maintenance of crystal bone than other implants such as uncoated titanium. Oxytetracycline fluorescent labels showed no fluorescence 4 and 10 months after implantation, showing that remodelling of bone was finished quite early.

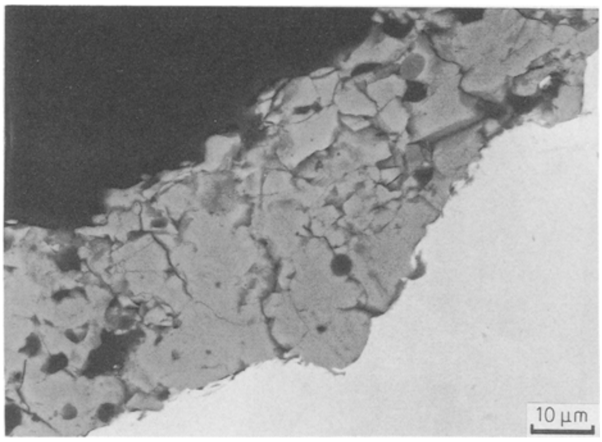

Figure 7 Coating of hydroxylapatite (grey) on a titanium substrate (white). Pores and epoxy potting compound are black.

The coatings also reduce migration of metal away from the implant. Elimination of cracking and holes to the metal surface should further reduce metal corrosion.

Coatings of apatite and other calcium phosphates on steel bond well [72].

Other methods of coating have been tried ([5] p. 19, [81]).

Glass has also been coated on to metal substrates for implants, but problems with glass mentioned above make it less attractive than hydroxylapatite or glass-ceramics containing hydroxylapatite crystals.

Granular coatings of alumina and hydroxylapatite on an alumina substrate in an SiO_2–B_2O_3 binder were tested in implants by the Nakamura detaching test described above [76]. The granular alumina seemed to strengthen the bone–implant bond. My view is that use of a ceramic substrate is curious; why not bond to a metal to take advantage of its ductility?

Controversy about push-out tests of bonding strengths of implants coated with hydroxylapatite has errupted [73, 74, 77, 78], and prompted a stern editorial [79]. My view is that the Nakamura test is superior to these push-out tests, but with care the latter can be.

5.11.4. Porous ceramics

Some of the first bioceramics tested as implants were porous [26], and some interest in porous bioceramics continues. One reason for favouring a porous implant material is to provide a place for bone to grow into the implant and hold it in place mechanically. A pore size of about 100 μm is often used. For nonbonding implant materials such as metals, polymers, and alumina, this reason is perhaps valid; however, for a material that bonds chemically and strongly to bone, such as hydroxylapatite and some other calcium compounds, this kind of porosity is unnecessary. Porosity has serious drawbacks in an implant. It weakens the solid material and increases its surface area, making it more subject to corrosion and dissolution. More ominous is the inevitable residue of spaces in the implant not filled by bone; these spaces are an invitation to bacterial infiltration and infection.

A porous hydroxylapatite derived from coral has been tested in various implant applications, mainly as a substitute for autologous bone [80–82]. In filling defects associated with tibial plateau fractures in humans, porous apatite behaves as well as autografts [82]. It is not clear if other forms of hydroxylapatite, such as dense, granular, and especially granular–plaster of Paris mixture would perform as well.

Macroporous hydroxylapatite has been used to replace part of the auditory canal wall [83]. A small number of these implants developed persistent infections and had to be removed. The results compared well with *in vitro* and animal studies. Incus prostheses of dense hydroxylapatite were developed to replace the second middle ear ossicle. Clinical results with both these implants show that hydroxylapatite had good promise for middle ear implants.

6. Conclusion

Ceramics are attractive as biological implants because bone bonds well to them and they show minimal foreign body reactions. Their main drawback is their brittle nature, and resultant low impact resistance. For applications in which impact resistance is important, the ceramic can be coated on a metal substrate. The strength of a ceramic depends mainly on its processing and surface treatment; practical strengths are one hundred times or more weaker than intrinsic strengths. A ceramic with high intrinsic strength and hardness such as alumina usually has higher practical strength because of higher resistance to wear and abrasion. Solid alumina and alumina coatings have good potential for implant applications in which bonding of bone to the implant is not important.

Bone bonds more strongly to hydroxylapatite than it does to alumina or metals, without any interface layer, fibrous encapsulation, or foreign body reaction. Hydroxylapatite can be made strong and has excellent fatigue resistance. Thus it is the most attractive ceramic for implant purposes, and is being studied intensively.

Other forms than bulk or granular ceramics show value in particular applications. Especially attractive are coatings of ceramic on metal; the metal provides impact resistance and the ceramic good bonding to bone or inertness.

Bone bonds to a glass surface that is microporous, as mentioned in the section on Bioglass. In this case the porosity is on a much finer scale, being about 0.01 μm in size. This porosity can either be present as formed, e.g. in "thirsty" silica glass, or caused by surface leaching, as in Bioglass. The resulting bond is not always as strong as to hydroxylapatite materials, as shown in Table VII.

Although porous materials continue in favour with some research groups, it is uncertain whether they provide any advantages over other forms, and the disadvantages of lowered strength, increased surface area and dissolution, and possible infection means there must be strong advantages to choose them.

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