Advanced Series in Ceramics – Vol. 1

AN INTRODUCTION TO BIOCERAMICS

Editors

Larry L. Hench

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World Scientific

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AN INTRODUCTION TO BIOCERAMICS

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Vol. 1: An Introduction to Bioceramics
ed. by L L Hench and J Wilson

AN INTRODUCTION TO
BIOCERAMICS

Dedicated to Gerry Merwin (1947-1992) and Bill Hall (1922-1992), clinicians who pioneered the use of new biomaterials.

PREFACE

Since the 1970's, when it was first realized that the special properties of ceramic materials could be exploited to provide better materials for certain implant applications, the field has expanded enormously. Initial applications depended on the fact that smooth ceramic surfaces elicited very little tissue reaction and provided wear characteristics suitable for bearing surfaces (Chapters 2, 11). Resultant orthopaedic use has enjoyed twenty years' clinical success, notably in Europe.

Today, as well as those so-called inert bioceramics, materials have been developed which have properties which allow their use where bonding to soft or hard tissues is needed, where controlled degradation is required, where loads are to be bourne, where tissue is to be augmented, or where the special properties of ceramics can be allied with those of polymers or metals to provide implant materials with advantages over each.

In all of these applications and many others described in this text, the tissue reactions to, and properties of these bioceramics have been increasingly carefully studied so that they can be controlled and more importantly, predicted. This is the information which must be understood before they are applied clinically.

A recent assessment of the growth of the field of bioactive ceramics showed that the number of presentations on that subject at the first World Biomaterials Congress in 1980 formed 6% of the program. By the time of the fourth such congress in 1992 that figure was 23% of the whole (Fig. 1). In 1980 presentations came from 12 centers in 5 countries, in 1992 from 88 centers in 21 countries (Fig. 2). Research is international and clearly still growing.

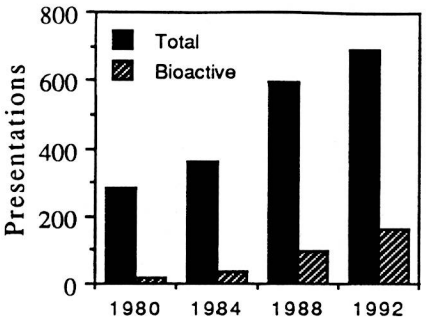

Fig. 1

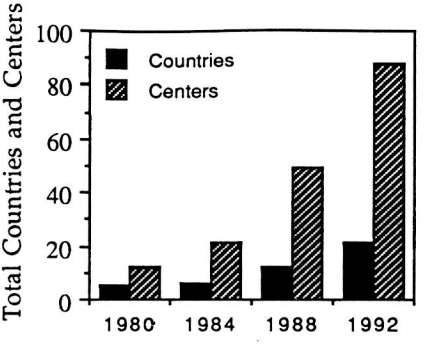

Fig. 2

Bioactive materials can be divided into two major areas, one contains bioactive glasses and glass ceramics (Chapters 3-8 and chapter 13) which develop biological hydroxyapatite at their surfaces after implantation and the other, calcium phosphate ceramics (Chapters 9-12) which are usually developed from chemical precursors. For an exception to this, see Chapter 10.

Materials from both groups have been used as powders and sometimes as solids in applications where mechanical requirements are low and as composites and coatings where mechanical requirements are high. Some have been designed specifically for high strength applications. (Chapters 5,6,8)

Coatings are discussed in Chapters 12-14. At the 1980 congress a single paper described the coating of bioactive glass on 'metal' (316L stainless steel). By 1992 a total of 37 presentations was made, 31 of which described coatings of hydroxyapatite on titanium or its alloy. The interest in coating stainless steel was mainly to provide non-cemented fixation in orthopaedics. This has now been supplanted by coatings on titanium, driven by its clinical success as a dental implant. Figure 3 shows changes in emphasis between 1980 and 1992.

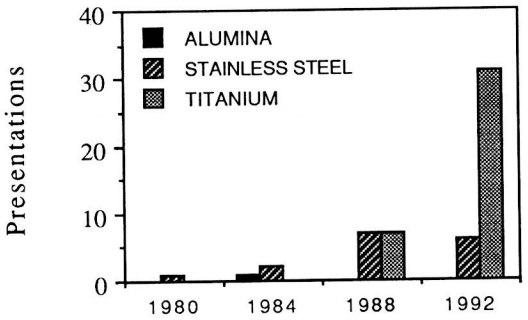

Fig. 3

As the behavior of bioceramics in both short and long-term applications becomes increasingly predictable and essentially reliable, their clinical application will increase as confidence grows. In this text we present the state of research world-wide at this time, with the data which provide the foundations of that research. We hope we have also provided signposts to those areas in which solutions to clinical needs are yet to be found.

Reference:

June Wilson, "World Biomaterials Congresses 1980-1992," *J. Applied Biom.* **4** (1993) 103-105.

June Wilson
Larry L. Hench
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May 6, 1993

CONTENTS

Chapter 1

INTRODUCTION

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OVERVIEW

Thousands of years ago humans discovered that clay could be irreversibly transformed by fire into ceramic pottery. Ceramic pots stored grains for long periods of time with minimal deterioration. Impervious ceramic vessels held water and were resistant to fire, which allowed new forms of cooking. This discovery was a large factor in the transformation of human culture from nomadic hunters to agrarian settlers. This cultural revolution led to a great improvement in the quality and length of life.

During the last forty years another revolution has occurred in the use of ceramics to improve the quality of life of humans. This revolution is the development of specially designed and fabricated ceramics for the repair and reconstruction of diseased, damaged or "worn out" parts of the body. Ceramics used for this purpose are called *bioceramics*. This book describes the principles involved in the use of ceramics in the body. Most clinical applications of bioceramics relate to the repair of the skeletal system, composed of bones, joints and teeth, and to augment both hard and soft tissues. Ceramics are also used to replace parts of the cardiovascular system, especially heart valves. Special formulations of glasses are also used therapeutically for the treatment of tumors.

Bioceramics are produced in a variety of forms and phases and serve many different functions in repair of the body, which are summarized in Fig. 1 and Table 1. In many applications ceramics are used in the form of bulk materials of a specific shape, called *implants, prostheses, or prosthetic devices*. Bioceramics are also used to fill space while the natural repair processes restore function. In other situations the ceramic is used as a coating on a substrate, or as a second phase in a composite, combining the characteristics of both into a new material with enhanced mechanical and biochemical properties.

Bioceramics are made in many different phases. They can be single crystals (sapphire), polycrystalline (alumina or hydroxyapatite), glass (Bioglass®), glass-ceramics (A/W glass-ceramic), or composites (polyethylene-hydroxyapatite). The phase or phases used depend on the properties and function required. For example, single crystal sapphire is used as a dental implant because of its high strength. A/W glass-ceramic is used to replace vertebrae because it has high strength and bonds to bone. Bioactive

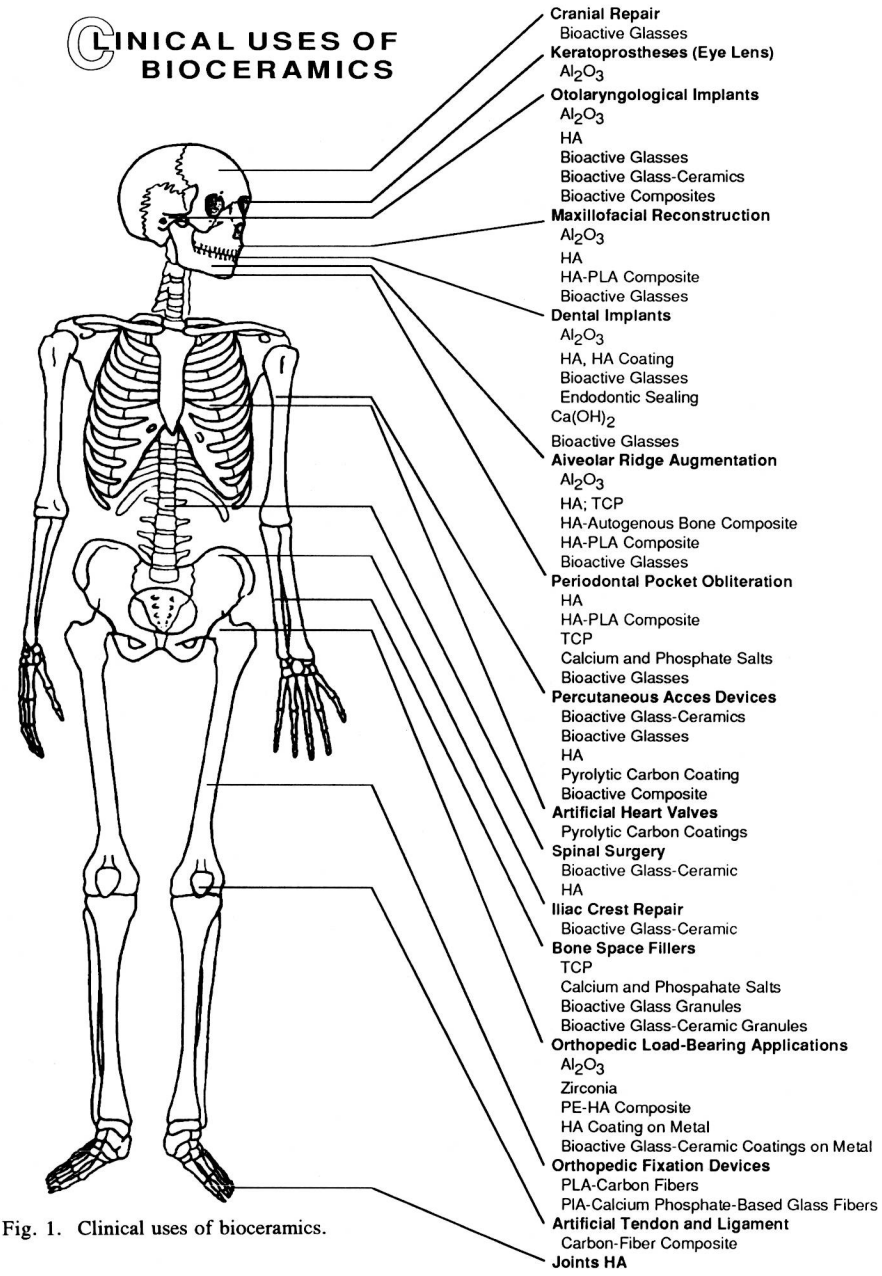

Fig. 1. Clinical uses of bioceramics.

Table 1. Form, Phase and Function of Bioceramics.

Form	Phase	Function
Powder	Polycrystalline Glass	Space-filling, therapeutic treatment, regeneration of tissues
Coating	Polycrystalline Glass Glass-Ceramic	Tissue bonding, thromboresistance, corrosion protection
Bulk	Single Crystal Polycrystalline Glass Glass-Ceramic Composite (Multi-Phase)	Replacement and augmentation of tissue, replace functioning parts

glasses have low strength but bond rapidly to bone so are used to augment the repair of boney defects.

Ceramics and glasses have been used for a long time outside the body for a variety of applications in the health care industry. Eye glasses, diagnostic instruments, chemical ware, thermometers, tissue culture flasks, chromatography columns, lasers and fibre optics for endoscopy are commonplace products in the multi-billion dollar industry. Ceramics are widely used in dentistry as restorative materials, gold porcelain crowns, glass-filled ionomer cements, endodontic treatments, dentures, etc. Such materials, called dental ceramics, are reviewed by Preston, 1988. However, use of ceramics *inside* the body as implants is relatively new; alumina hip implants have been used for just over 20 years. (See Hulbert et al., 1987, for a review of the history of bioceramics.)

This book is devoted to the use of ceramics as implants. Many compositions of ceramics have been tested for potential use in the body but few have reached human clinical application. Clinical success requires the simultaneous achievement of a stable interface with connective tissue and an appropriate, functional match of the mechanical behavior of the implant with the tissue to be replaced. Few materials satisfy this severe dual requirement for clinical use.

TYPES OF BIOCERAMICS-TISSUE INTERFACES

No material implanted in living tissues is inert; all materials elicit a response from the host tissue. The response occurs at the tissue-implant interface and depends upon many factors, listed in Table 2.

There are four general types of implant-tissue response, as summarized in Table 3. It is critical that any implant material avoid a toxic response that kills cells in the surrounding tissues or releases chemicals that can migrate within tissue fluids and cause

Table 2. Factors Affecting Implant-Tissue Interfacial Response.

Tissue Side	Implant Side
-Type of Tissue	-Composition of Implant
-Health of Tissue	-Phases in Implant
-Age of Tissue	-Phase Boundaries
-Blood Circulation in Tissue	-Surface Morphology
-Blood Circulation at Interface	-Surface Porosity
-Motion at Interface	-Chemical Reactions
-Closeness of Fit	-Closeness of Fit
-Mechanical Load	-Mechanical Load

Table 3. Consequences of Implant-Tissue Interactions.

Implant-Tissue Reaction	Consequence
Toxic	Tissue dies
Biologically nearly inert	Tissue forms a non-adherent fibrous capsule around the implant
Bioactive	Tissue forms an interfacial bond with the implant
Dissolution of implant	Tissue replaces implant

systemic damage to the patient (Black, 1984). One of the main reasons for the interest in ceramic implants is their lack of toxicity.

The most common response of tissues to an implant is formation of a non-adherent fibrous capsule. The fibrous tissue is formed in order to "wall off" or isolate the implant from the host. It is a protective mechanism and with time can lead to complete encapsulation of an implant within the fibrous layer. Metals and most polymers produce this type of interfacial response, the cellular mechanisms which influence this response are described in a later section.

Biologically inactive, nearly inert ceramics, such as alumina or zirconia, also develop fibrous capsules at their interface. The thickness of the fibrous layer depends on the factors listed in Table 2. The chemical inertness of alumina and zirconia results in a very thin fibrous layer under optimal conditions (Fig. 2). More chemically reactive metallic implants elicit thicker interfacial layers. However, it is important to remember that the thickness of an interfacial fibrous layer also depends upon motion and fit at the interface, as well as the other factors indicated in Table 2.

The third type of interfacial response, indicated in Table 3, is when a bond forms across the interface between implant and the tissue. This is termed a "bioactive" interface. The interfacial bond prevents motion between the two materials and mimics

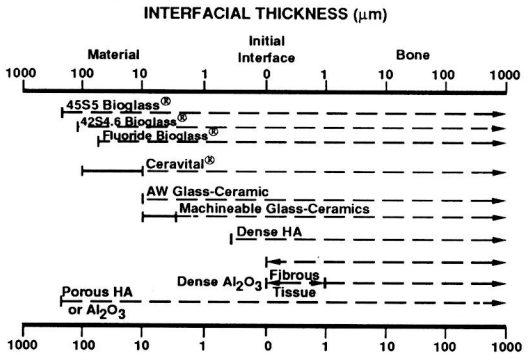

Fig. 2. Comparison of interfacial thickness of reaction layer of bioactive implants or fibrous tissue of inactive bioceramics in bone. (Reprinted from L. L. Hench, "Bioceramics: From Concept to Clinic," *J. Amer. Ceram. Soc.*, **74[7]** (1991) 1487-570, with permission.)

the type of interface that is formed when natural tissues repair themselves. This type of interface requires the material to have a controlled rate of chemical reactivity, as discussed in Chapters 3 and 5. An important characteristic of a bioactive interface is that it changes with time, as do natural tissues, which are in a state of dynamic equilibrium.

When the rate of change of a bioactive interface is sufficiently rapid the material "dissolves" or "resorbs" and is replaced by the surrounding tissues. Thus, a resorbable biomaterial must be of a composition that can be degraded chemically by body fluids or digested easily by macrophages (see below). The degradation products must be chemical compounds that are not toxic and can be easily disposed of without damage to cells.

TYPES OF BIOCERAMIC-TISSUE ATTACHMENTS

The mechanism of attachment of tissues to an implant is directly related to the tissue response at the implant interface. There are four types of bioceramics, each with a different type of tissue attachment, summarized in Table 4 with examples. The factors that influence the implant-tissue interfacial response listed in Table 2 also affect the type and stability of tissue attachment listed in Table 4.

The relative chemical activity of the different types of bioceramics is compared in Fig. 3. The relative reactivity shown in Fig. 3(a) correlates with the rate of formation of an interfacial bond of implants with bone (Fig. 3(b)). A type 1, nearly inert, implant does not form a bond with bone. A type 2, porous, implant forms a mechanical bond via ingrowth of bone into the pores. A type 3, bioactive, implant forms a bond with bone via chemical reactions at the interface. A type 4, resorbable, implant is replaced by bone.

Table 4. Types of Tissue Attachment of Bioceramic Prostheses.

Type of Implant	Type of Attachment	Example
(1) Nearly inert	Mechanical interlock (Morphological Fixation)	Al_2O_3, Zirconia
(2) Porous	Ingrowth of tissues into pores (Biological Fixation)	Hydroxyapatite (HA) HA coated porous metals
(3) Bioactive	Interfacial bonding with tissues (Bioactive Fixation)	Bioactive glasses Bioactive glass-ceramics HA
(4) Resorbable	Replacement with tissues	Tricalcium phosphate Bioactive glasses

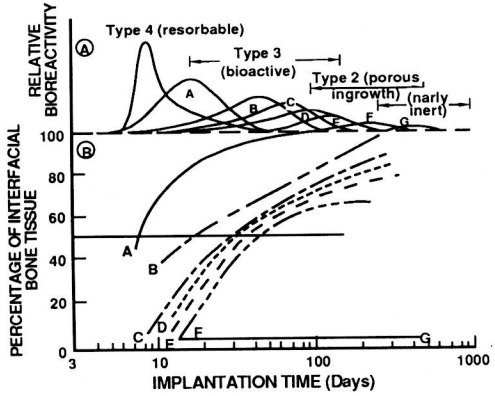

Fig. 3. Bioactivity spectrum for various bioceramic implants: (a) relative rate of bioreactivity and (b) time dependence of formation of bone bonding at an implant interface ((A) 45S5 Bioglass®, (B) KGS Ceravital®, (C) 55S4.3 Bioglass®, (D) A/W glass-ceramic, (E) HA, (F) KGX Ceravital®, and (G) Al_2O_3-Si_3N_4). (Reprinted from L. L. Hench, "Bioceramics: From Concept to Clinic," *J. Amer. Ceram. Soc.*, **74[7]** (1991) 1487-570, with permission.)

The relative level of reactivity of an implant also influences the thickness of the interfacial layer between the material and the tissue (Fig. 2). A type 1, nearly inert, implant forms a non-adherent fibrous layer at the interface. A chemically stable material like alumina elicits a very thin capsule. Consequently, when alumina or zirconia implants are implanted with a tight mechanical fit and movement does not occur at the interface they are clinically successful.

However, if a type 1, nearly inert, implant is loaded such that interfacial movement occurs, the fibrous capsule can become several hundred micrometers thick and

the implant loosens very quickly. Loosening invariably leads to clinical failure for a variety of reasons which includes fracture of the implant or the bone adjacent to the implant.

Type 2 porous ceramics and HA coatings on porous metals were developed to prevent loosening of implants. The growth of bone into surface porosity provides a large interfacial area between the implant and its host. This method of attachment is often called *biological fixation*. It is capable of withstanding more complex stress states than type 1 implants which achieve only "morphological fixation".

A limitation of type 2 porous implants is the necessity for the pores to be at least 100 micrometers in diameter. This large pore size is needed so that capillaries can provide a blood supply to the ingrown connective tissues. Without blood and nutrition the bone will die. Vascular tissue does not appear in pores < 100 μm. If micromovement occurs at the interface of a porous implant the capillaries can be cut off, leading to tissue death, inflammation and destruction of interfacial stability.

When the porous implant is a metal, the large interfacial area can provide a focus for corrosion of the implant and loss of metal ions into the tissues, which may cause a variety of medical problems. Coating a porous metal implant with a bioactive ceramic, such as hydroxyapatite, diminishes some of these limitations. The HA coating also speeds the rate of bone growth into the pores. The coatings often dissolve with time which limits their effectiveness. The large size and volume fraction of porosity required for stable interfacial bone growth degrades the strength of the material. This limits the porous method of fixation to coatings or unloaded space fillers in tissues.

Resorbable implants (type 4 in Table 4) are designed to degrade gradually with time and be replaced with natural tissues. A very thin or non-existent interfacial thickness, Fig. 2, is the final result. This approach is the optimal solution to the problems of interfacial stability. It leads to the regeneration of tissues instead of their replacement. The difficulty is meeting the requirements of strength and short-term mechanical performance of an implant while regeneration of tissues is occurring. The resorption rates must be matched to the repair rates of body tissues (Fig. 3) which vary greatly depending on the factors listed in Table 2. Some materials dissolve too rapidly and some too slowly. Large quantities of material must be handled by cells so the constituents of a resorbable implant must be metabolically acceptable. This is a severe limitation on the compositions that can be used.

Successful examples of resorbable implants include specially formulated polymers. Resorbable sutures composed of poly(lactic acid)-poly(glycolic acid) are metabolized to carbon dioxide and water. Thus, they function for a time to hold tissues together during wound healing then dissolve and disappear. Tricalcium phosphate (TCP) ceramics degrade to calcium and phosphate salts and can be used for space filling of bone.

Bioactive implants (type 3 in Table 4) offer another approach to achieve interfacial attachment. The concept of bioactive fixation is intermediate between resorbable and bioinert behavior. A bioactive material undergoes chemical reactions in the body, but only at its surface. The surface reactions lead to bonding of tissues at the interface. Thus, a bioactive material is defined as: "a material that elicits a specific