Reprinted from Ceramic Bulletin [illegible] January [illegible]
Copyright [illegible] by The American Ceramic Society, Inc.

Calcium Phosphate Ceramics as Bone Substitutes

CARLOS LAVERNIA
Division of Orthopaedic Surgery, School of Medicine, University of California at San Diego, San Diego, California 92103-9981

and

JULIE M. SCHOENUNG*
Department of Chemical and Materials Engineering, College of Engineering, California State University, Pomona, California 91768-4069

Bone is composed of living cells and matrix. The cells in bone control the remodeling process that regulates the bioavailability of the minerals within the skeleton. Bone matrix has three basic components: inorganic, organic, and water. The inorganic, or mineral, phase consists mostly of hydroxyapatite, and accounts for 69% of the weight of bone. Collagen is the principal component of the organic phase. Other ceramic structures present in bone include dicalcium phosphate, octacalcium phosphate, amorphous calcium phosphate, and tricalcium phosphate. This matrix phase controls the structural properties of the skeleton and is the framework within which cells live.

The ideal material for bone substitution has the following characteristics: chemical compatibility, mechanical suitability, and ease of handling in an operating room environment. The material must also be easily sterilized and be available at a reasonable cost. Calcium phosphate ceramic systems are ideal since their elemental components are present in bone naturally. Hydroxyapatite (HA) and tricalcium phosphate (TCP) are the two calcium phosphate ceramics most commonly used for bone replacement.

To discuss the issue of bone replacement, several terms need to be defined. Osteoinduction refers to the capability of a substance to induce either differentiation or cell replication of inactive bone cells, turning them into active bone "making" cells. Osteoconduction is the ability of a material to provide channels into which bone can grow. The term osteophilia is often used in the literature and literally means "love for bone."

Fig. 1. Autogenous bone obtained and ready to be used to fill a gap.

Alternatives for Replacing Bone

Large gaps within the skeletal system can be caused by trauma or tumors. An orthopedic surgeon faced with filling in a large gap within a bone has several alternatives: autografting, allografting, and biomaterials. Autogenous bone grafting (autografting) involves harvesting bone from another part of the body to utilize within the gap. This technique has a number of disadvantages, including postoperative morbidity such as wound complications, increased operative time, and, sometimes, inadequate amounts of bone to fill massive defects. The complication rates with this technique have been reported to be as high as 20%. Figure 1 shows the harvested autogenous bone ready to be used to fill a gap.

Allografting, or using cadaver bone, has enjoyed a recent increase in popularity. There are several major disadvantages with this technique. These include immune response (rejection by the recipient) in certain cases, possible acquisition of AIDS or other infectious diseases, and difficulty in obtaining the specimens due to religious beliefs or local customs.

Bone substitutes have been used for almost a century. In 1913, Magnussen used cow horn as a replacement for bone. How-

---

*Member, American Ceramic Society.

ever, the proteins present in this material cause rejection of this type of graft. Edbert and Fowler used plaster of Paris (calcium phosphate) to replace defects in bone. The erratic resorption from the body of this material made it fall into disuse.

Biocompatibility and Structure: Key Factors

Biocompatibility, or the acceptance of a material by the body's immune system, is critical in the successful use of a material to replace part of the human body. Additionally, biodegradability, or the resorption characteristics, and the mechanical properties are very important determinants of the structural stability of the bone ceramic construct.

Hydroxyapatite ceramics have excellent biocompatibility. This has been widely documented in the dental as well as the orthopedic literature. Even in cases where the bone ceramic construct has failed, an extremely benign cellular response has been found at the microscopic level.

Calcium phosphate ceramics have been extensively studied in biological systems. Depending on the specific stoichiometry of the compound, they can be permanent (nondegradable by the body), partially biodegradable, or completely biodegradable. Bioresorption, or the ability of the body to degrade the ceramic, is a function of two factors: chemical composition and surface area. The chemical composition of hydroxyapatite (HA) makes it more refractory to resorption. An implant made of HA placed in bone will be present after 3 or 4 years of implantation. Tricalcium phosphate (TCP), on the other hand, is partially resorbable. TCP placed in bone will partially disappear in 6 to 15 weeks, depending on its porosity and exact stoichiometry.

Structure or architecture of the ceramic implant will influence bone ingrowth as well as its resorption. Currently available ceramic implants can be obtained in solid or porous, particulate or unitary, and preformed or slurry forms. A pellet form will soon be commercially available. Pore sizes or spaces between particles must exceed 100 μm for bone ingrowth to occur.

The normal structure of bone is contrasted with a commercially available HA in Figs. 2 and 3. Figure 2 shows the typical microstructure of the matrix within human bone. The advocates of porous ceramics point to the similarity of these channels to the space requirements of bone cells in real bone as a strong reason to use these systems over solid systems.

Properties, Processing, and Applications

The mechanical properties of calcium phosphate ceramics are currently the limiting factor in their widespread utilization. These compounds differ from bone in four important parameters: elastic modulus, ultimate strength, fatigue life, and mode of failure. Table I presents a simplified view of the mechanical properties of bone and the most commonly used calcium phosphate systems. Bone has been characterized as an orthotropic material with much more complex mechanical constants. This table, however, gives the reader a general idea of how bone behaves mechanically.

The elastic moduli of calcium phosphate systems could be twice as high as that of bone, depending on the porosity of the system. The compressive strength is comparable to that of bone. Calcium

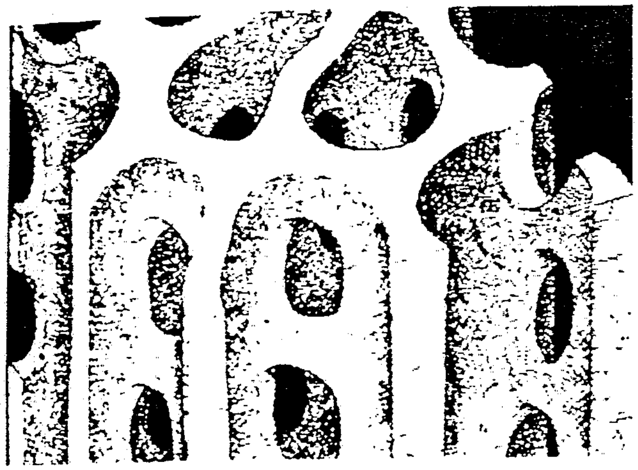

Fig. 2. Microscopic structure of bone matrix. (Ralph E. Holmes, M.D. and Herbert K. Hagler, Ph.D., "Porous Hydroxyapatite as a Bone Substitute in Cranial Reconstruction: A Histometric Study," *Plast. Reconstr. Surg.*, Vol. 81, No. 5, p. 662, May 1988 (reprinted with permission).)

Table I. Simplified Summary of the Mechanical Properties of Bone and Calcium Phosphate Systems

Material	Compressive strength (psi)*	Modulus (psi)*
Calcium Phosphates		
Dense	3–130	5–15
Porous	1–10	
Bone		
Cancellous	6–9	
Cortical	20	2

*1 psi $= 6.9 \times 10^3$ Pa.

Fig. 3. Microstructure of another commercially available porous HA system. (©1989, *Clinical Orthopaedics and Related Research*, Vol. 240, pp. 53–62.)

phosphate systems, however, are extremely brittle and have a poor fatigue life. Additionally, they fail in a brittle fashion with very little deformation to failure. This can be a major problem when the calcium phosphate systems are utilized in weight bearing areas of the skeleton. Much research is currently being conducted to improve mechanical properties by altering the stoichiometry of the ceramic compounds.

Manufacturing techniques to fabricate these ceramic compounds vary, depending on whether a solid or porous HA is being made. The most typical process involves the use of high-pressure powder compaction. In this process, a ceramic powder made using conventional techniques is compacted to a given shape to produce a green form. This green form is then sintered in an oven to temperatures from 1100° to 1300°C, to produce a dense ceramic material. Another mode is hot pressing. With this technique, pressure is applied from all directions while the mold is sintered.

Porous ceramics are currently fabricated in one of two ways: homogenizing different substances such as naphthalene or peroxide particles with the calcium phosphate powder, or by a novel hydrothermal exchange process. With the homogenizing techniques, the mixtures are sublimated with the naphthalene or peroxide removed, leaving a macroporous form of ceramic. The hydrothermal exchange process utilizes a calcium carbonate skeleton obtained from coral. This skeleton is then heated to high temperatures in the presence of an aqueous phosphate solution. This mixture milieu provides for an exchange in which the carbonate is replaced in the coral for phosphate. Depending on the species of coral and the amount of time and temperature, both HA and TCP have been produced.

Calcium phosphate ceramics are widely used as bone replacement in the fields of oral and plastic surgery. In the dental field, the primary applications for ceramics include the filing of pockets and augmenting of deficient mandibular or maxillar ridges, caused by the loss of dentition with advancing age or due to disease. These systems have also been used to replace missing segments in the mandible or maxilla due to trauma and or congenital defects. Plastic surgeons also use these systems to contour congenital or traumatic deficiencies in the bony arches of the face as well as the cranium.

Other Bone Replacement Uses

Orthopedic surgeons could potentially use ceramic systems in trauma, spine, as well as tumor cases. High-velocity trauma often causes major bone loss. Often the missing bone is either left at the scene of an accident or is contaminated to the point of not being usable in a patient. In surgery of the spine, fusion of parts of the spine is often desired to prevent motion and/or stabilize a painful unstable segment. In these cases the amount of bone needed to bridge large regions of the spine makes the use of autologous bone unreasonable. Certain tumors in the skeleton, although benign, cause major loss of structural stability. These tumors usually occur in young patients, and the need to fill these large gaps is often not met by the patient's own bone.

The knee is the subject of high morbidity in high-speed trauma. The tibia, or leg bone, is known to orthopedists as being a problem site for loss of bone. Figures 4 and 5 show the use of a coralline calcium

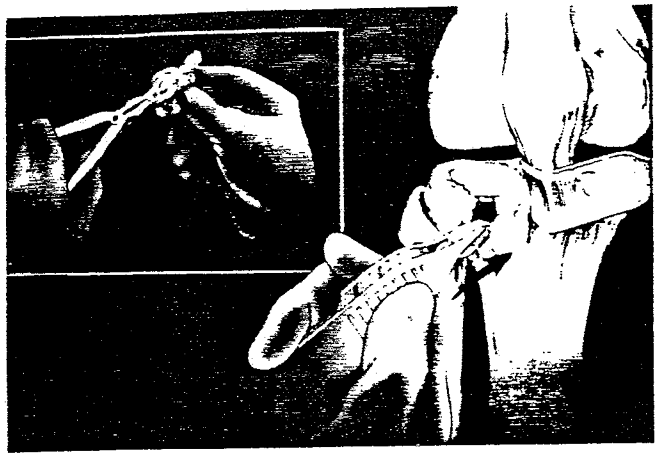

Fig. 4. Defect in the outer portion of the tibia being filled with an HA system after it is contoured to shape. (©1989, *Clinical Orthopaedics and Related Research*, Vol. 240, pp. 53–62.)

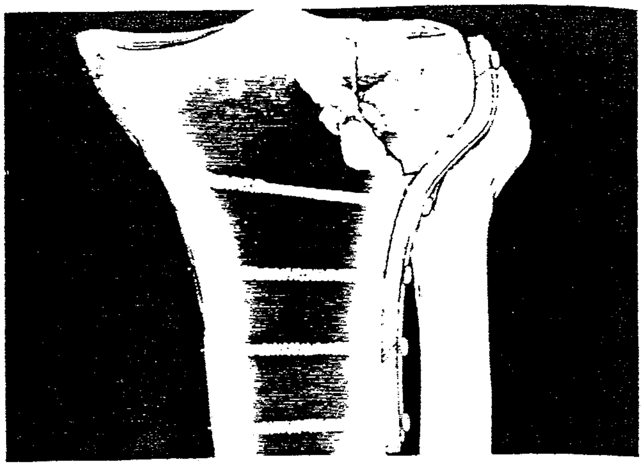

Fig. 5. Completed construct with the fracture fixed and added support provided by metal. (©1989, *Clinical Orthopaedics and Related Research*, Vol. 240, pp. 53–62.)

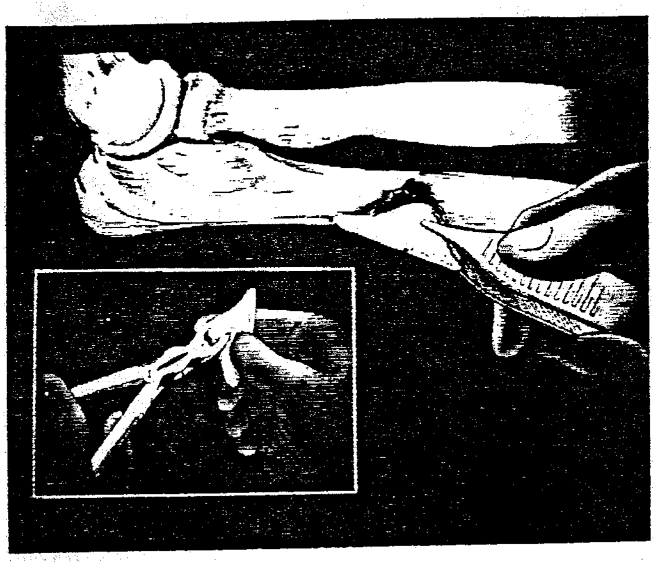

Fig. 6. Defect in the ulna being filled by a ceramic construct after it is contoured to shape. (©1989, *Clinical Orthopaedics and Related Research*, Vol. 240, pp. 53–62.)

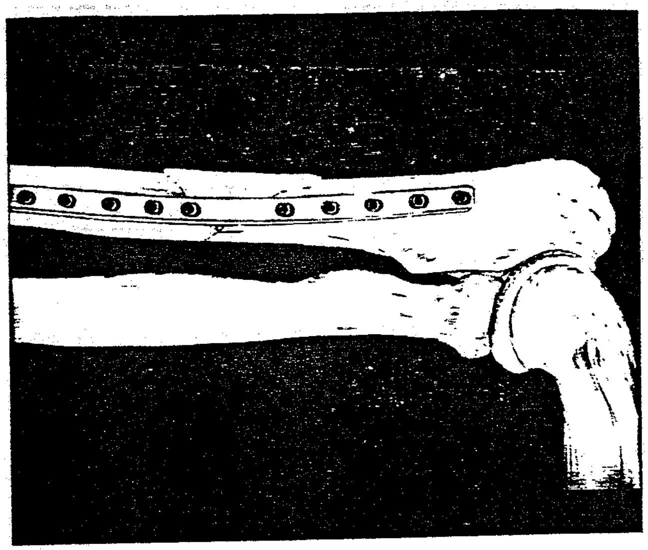

Fig. 7. Completed construct with added metal for support. (©1989, *Clinical Orthopaedics and Related Research*, Vol. 240, pp. 53–62.)

phosphate system to fill a gap created by trauma. These figures illustrate this system being contoured to exactly fit the defect. As shown in these figures, metal has to be used to augment these constructs due to the brittle behavior of the ceramic material. Figure 5 shows the completed construct.

The elbow region is also a troublesome area in high-energy bony trauma. Figures 6 and 7 show a large defect in the ulna (one of the arm bones) being filled with a ceramic system. Metal is necessary to supplement the construct.

Tumors can be the cause of major bone loss as well. Figure 8 demonstrates radiographs of the distal femur (thigh bone) in a 25-year-old patient. This patient had a benign bone tumor, otherwise known as an aneurysmal bone cyst. The size of the defect created by this tumor would have prevented the patient from weight bearing on the affected leg after surgery for at least 6 months. The tumor was removed from within the bone, and a calcium phosphate system was used to fill the gap.

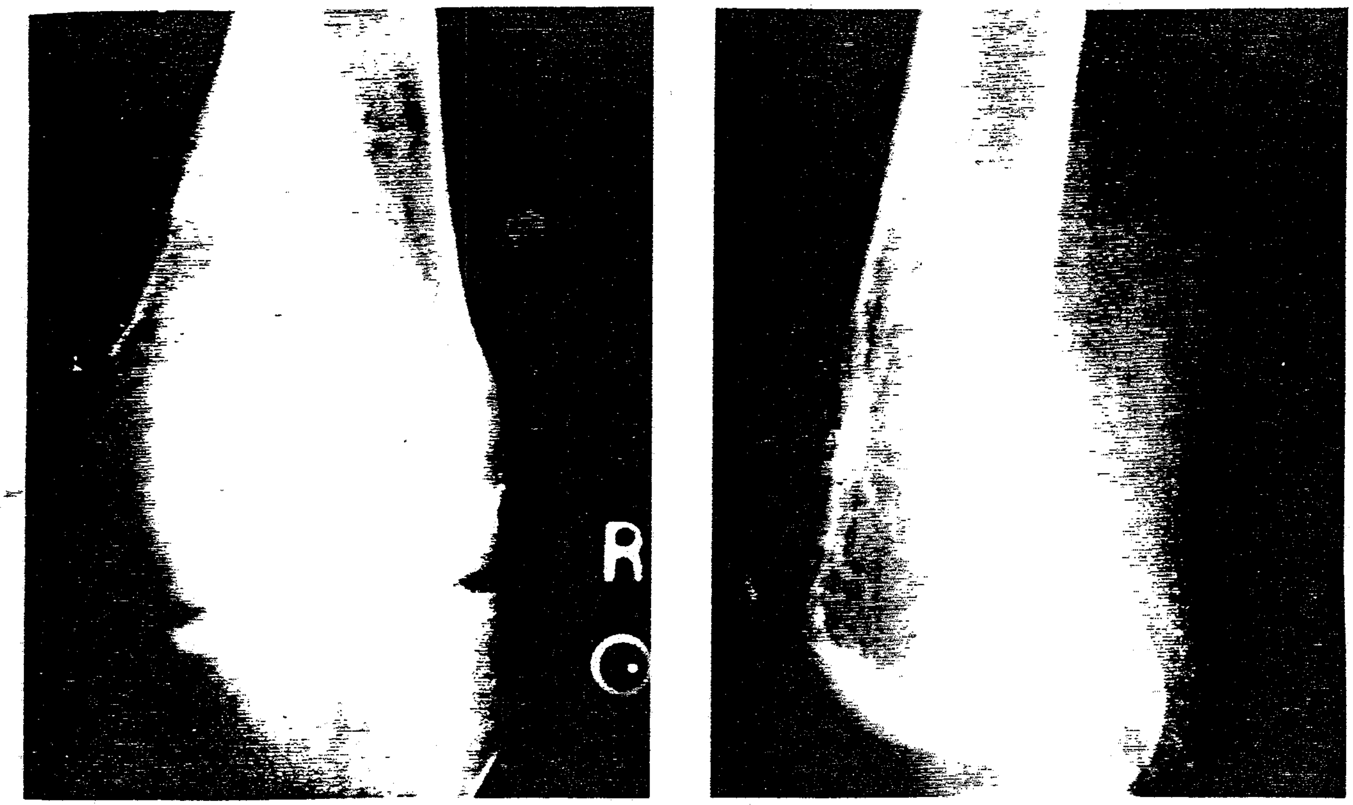

Fig. 8. Anteroposterior and lateral X-rays of the knee of a 25-year-old patient with a benign tumor. Size of the tumor makes it extremely difficult to manage.

Fig. 9. Same knee, in Fig. 8, 2 years after the defect was filled with an HA system after removing most of the tumor.

Figure 9 shows two X-ray views of the leg after the surgical procedure and implantation of the ceramic system. The patient was allowed to bear partial weight after 6 weeks and bear full weight after 12 weeks. The patient is now two years after surgery and doing extremely well. These ceramic systems, although highly osteophilic and osteoconductive, are not osteoinductive. Future research through the use of recombinant DNA will allow the mixing of these systems with organic substances that are osteoinductive. In some centers in the United States, slurry ceramic systems are currently being mixed with hip bone aspirates, rich in osteoinductive substances, to improve and accelerate incorporation of the ceramic system.

Additionally, ceramics are currently being used in orthopedic surgery in the joint replacement field. Hip and knee replacements made of porous metals are being coated with hydroxyapatite to make the replacement systems osteophilic.

Acknowledgment

The authors thank Ralph E. Holmes, M.D. for his assistance with this article.

Bibliography

R. W. Bucholz, A. Carlton, and R. E. Holmes, "Hydroxyapatite and Tricalcium Phosphate Bone Graft Substitutes," *Orthopedic Clinics of North America*, **18** [2] 323–34 (1987).

Fundamental and Clinical Bone Physiology; pp 4–83. Edited by M. R. Urist. Lippincott, Philadelphia, PA, 1980.

Handbook of Biomaterials Evaluation; pp 3–86. Edited by E. F. von Recum. Macmillan, New York, 1986.

R. E. Holmes, "Bone Regeneration with a Coralline Hydroxyapatite Implant," *Plast. Reconstr. Surg.*, 63 [5] 626–33 (1979).

R. E. Holmes, R. W. Bucholz, and V. Mooney, "Porous Hydroxyapatite as a Bone Graft Substitute in Metaphyseal Defects," *J. Bone Jt. Surg.*, **68** (A), 904–11 (1986).

M. Jarcho, "Calcium Phosphates Ceramics as Hard Tissue Prosthetics," *Clin. Orthop. Relat. Res.* [16 June] 259–78 (1981).

M. Jarcho, "Biomaterials Aspects of Calcium Phosphates," *Dent. Clin. North Am.*, **30** [1] 25–47 (1986).

T. D. Driskell and J. R. Paulsrud, "Tricalcium Phosphate—A Resorbable Bone Implant: Review and Current Status," *J. Am. Dent. Assoc.* **105**, 1035–38 (1982).

Operative Orthopedics; pp 97–106. Edited by M. Chapman. Lippincott, Philadelphia, PA, 1988.

A. Uchida, S. M. Nade, E. R. McCartney, and W. Ching, "The Use of Ceramics for Bone Replacement," *J. Bone Jt. Surg., Br. Vol.*, **66** (B), 269–75 (1984). ■