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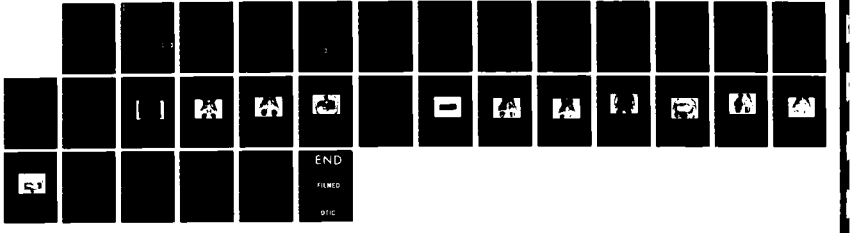

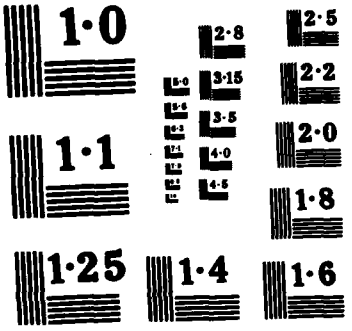

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MANAGEMENT OF HARD TISSUE AVULSIVE WOUNDS AND MANAGEMENT OF OROFACIAL FRACTURES

ANNUAL REPORT

Larry G. McCoy and Craig R. Hassler

July 15, 1979

Supported by

U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
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Research studies on bioceramics were continued to further our understanding of the in vivo behavior of resorbable calcium phosphate ceramics for use in the management of hard tissue avulsive wounds and orofacial fractures.

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Material processing studies were conducted to develop porous tricalcium phosphate materials of different stoichiometry. These two portions of the study were to further understanding of the basic question: Is the optimal material for bone ingrowth and biodegradation going to be produced by alterations in pore structure within the material of a given stoichiometry?

Previously, numerous tricalcium phosphate powders were produced having controlled calcium to phosphate ratios. Specifically, three powders were prepared using the standard technique of modifying composition of tribasic calcium phosphate powders by the addition of phosphoric acid. After three powders of various composition were made at Battelle, the powders were mill-blended and submitted for verification analysis. Materials were then fired and analyzed by X-ray defraction to determine the crystalline phases that might be present in the finished implants. The results of the study indicated that preparation of a single phase variable composition material does not appear possible using standard methods even though beta phase tricalcium phosphate will be the predominant phase in all materials, secondary phases of monetite or hydroxyapatite were always found depending upon what border of the compositional range the compound fell. Consequently, these three different materials were not developed further. Instead, material of various pore structure confirmation was developed for in vivo implant studies.

Three different materials of various pore structures were designed and fabricated into rectangular segments for implanting in the previously used rabbit calvarium model. Animals were implanted and observed for periods of 3, 6, 9, and 12 months, respectively. Each time period, a portion of the animal population was necropsied.

ABSTRACT

This report summarizes results of continued studies for further developing and understanding the *in vivo* behavior of resorbable calcium phosphate for use in the management of hard tissue avulsive wounds and orofacial fractures.

Specific studies have been devoted to the preparation and comparative *in vivo* evaluation of porous tricalcium phosphates having various pore distributions.

The *in vivo* studies suggest that the direction of porosity within the biodegradable material which facilitates bone ingrowth is perhaps the most important parameter determining the success of a biodegradable material which facilitates bone ingrowth.

SUMMARY

Research studies were continued to further our understanding of the *in vivo* behavior of resorbable calcium phosphate ceramics for use in the management of hard tissue avulsive wounds and orofacial fractures.

Material processing studies were conducted to develop porous tricalcium phosphate materials of different stoichiometry. These two portions of the study were to further understanding of the basic question: Is the optimal material for bone ingrowth and biodegradation going to be produced by alterations in pore structure within the material of a given stoichiometry?

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FOREWORD

This study has been conducted at Battelle's Columbus Laboratories utilizing the talents and resources of the Ceramic Materials Section and the Bioengineering/Health Sciences Section. This is the Sixth Annual Progress Report under Contract No. DADA17-69-C-9118, "Management of Hard Tissue Avulsive Wounds and Management of Orofacial Fractures". The Principal Investigator for this research was Mr. Larry G. McCoy. The physiologist for the animal implant studies was Dr. Craig Hassler.

We would like to acknowledge the valuable assistance of Mr. Roger K. Beal for his excellent work in preparation of the porous implant materials, Mr. Lynn C. Clark for the excellent histologic preparations.

In conducting the research described in this report, the investigator(s) adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council (DHEW Publication No. (NIH) 78-23, Revised 1978).

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BACKGROUND, PROBLEM AND APPROACH

Historically, various techniques have been employed for the repair or treatment of osseous diseases, defects, and wounds. Autogeneous bone grafting remains the most satisfactory approach but is not without the disadvantages associated with double surgeries and the limitations imposed on the repair of massive osseous defects.

Since April, 1970, Battelle's Columbus Laboratories has been conducting research under contract with the Dental Research Division, U.S. Army Medical Research and Development Command, on the development of resorbable ceramics for potential application in the repair of hard tissue avulsive wounds. The basic materials have been calcium phosphates. These materials were selected because they contain two of the essential elements of the natural bone mineral phase, calcium hydroxyapatite.

In vivo studies were conducted initially at U.S. Army Institute of Dental Research (USAIDR), using the sintered porous materials and slurries prepared at Battelle from tricalcium phosphate $Ca_3(PO_4)_2$ and other calcium orthophosphate powders $CaHPO_4$ and $Ca(H_2PO_4)_2$, to evaluate the potential use of calcium phosphates to both facilitate repair of bone defects and to determine the best material for future exploration[1-3]. The implant studies indicated that calcium phosphates consisting essentially of the mineral phases $Ca(PO_3)_2$, $Ca_3(PO_4)_2$, and $CaHPO_4$ are well tolerated by the tissue, appear to be nontoxic, are resorbable, and permit rapid invasion of new bone.

Of the various porous calcium phosphate materials investigated, tricalcium phosphate, $Ca_3(PO_4)_2$, was selected for continued development and evaluation since it was easy to fabricate and was found to be both biocompatible and resorbable. Emphasis has been directed toward producing low-density porous materials consisting of single-phase tricalcium phosphate[4-7].

Although previous implant studies at USAIDR have demonstrated that porous tricalcium phosphate is biocompatible, resorbable, and promotes or

permits rapid ingrowth of new bone, histological evidence indicated persistence of a residual ceramic structure as long as 1 year after implantation. This structure appeared to be composed of an isomorphic distribution of small encapsulated ceramic particles. The presence of this residue would be expected to retard complete remodeling of the bone and the attendant strength development.

As a result of this problem, the primary emphasis of continued studies was directed toward the development of porous materials having improved (increased) resorption rates. This objective may be achieved either by changes in structure or chemistry of the ceramic implant material.

To provide basic resorption rate data on the *in vivo* behavior of the tricalcium phosphate bioresorbable ceramics, implant studies were initiated in 1975 at BCL using the rabbit calvarium model[8]. Historic samples of tricalcium phosphate were implanted as a control and samples of two new materials were implanted for comparative observation. These new materials were prepared using the improved processing techniques derived in previous materials development studies and represented significant improvements in the structural characteristics of porous tricalcium phosphate. The characterization of the materials involved and the results of the *in vivo* studies were the subject of the Fifth Annual Report[8].

These results indicated that the improved material exhibited significant increases in resorption rate. In fact, the material resorbed so rapidly that after the ninth month the implant appeared to be granulated and was invaded with connective tissue. This result does not imply lack of biocompatibility but does suggest that such rapid degradation can be deleterious in stress-bearing situations. It is not known whether the enhanced resorptivity resulted from achieving a Ca/P ratio closer to the theoretical for tricalcium phosphate or from the improvements in the structural characteristics of the material.

To discern the effects of structural variations on resorption rate, experimental porous implants were prepared using a single tricalcium phosphate powder but having different pore size distribution. Three materials were prepared for *in vivo* evaluation.

MATERIALS AND METHODS

Porous Materials Development

Material processing and fabrication studies were continued to develop experimental porous tricalcium phosphate implant materials for in vivo evaluation of the effects of structural variations on resorption rate. The effort has involved the preparation of porous implants of a fixed composition in which the pore size distributions were systematically varied to determine if pore size distributions could be selectively modified to control resorption rate. Three materials were prepared for in vivo evaluation. The characteristics of these materials are summarized in Table 1.

The fabrication of the materials was completed in the previous program year. It was the original intent in the preparation of the Group 3 material to induce a microporosity in the 35-45 micron range and thereby enhance the resorption rate by increasing the permeability and internal surface area of the material. However, histologic evidence from previous implant studies became available during later stages of the material fabrication studies, which indicated that materials having the improved Group 1 type structure had such significantly increased resorption rates that further increases would be hazardous to the mechanical stability of the implant. As a consequence, a new Group 3 material was prepared having a coarser pore structure than the Group 1 material. The intent was to induce rapid bone ingrowth into the larger pores while reducing the resorption by having thicker wall sections between the pores.

The new Group 3 material was prepared by using the coarsest (-40/+60 mesh) fraction of the standard (technical grade) naphthalene distribution. The standard technique of intensive roll blending was used to achieve stable phosphate powder/naphthalene blends. Three blocks of material for sectioning into implants were prepared by the standard hydropressing and sintering procedures used for the Groups 1 and 2 materials. Three implants were cut from the two blocks having the most identical structures (Blocks E39 and E41) and were dry heat sterilized at 600°F for 4 hours.

TABLE 1. MODIFIED PORE STRUCTURE EXPERIMENTAL IMPLANT MATERIALS

Batch[a] Number	Designation	Naphthalene[b] Pore Size Distribution	Calculated[c] Mean Pore Size (microns)	Sintered Density
E22	Standard	Group 1	260	48.6
E26	Modified-Fine	Group 2	210	47.0
E39	Modified-Coarse	Group 3	290	49.7

(a) All specimens were prepared using Batch D-22 tricalcium phosphate powder and technical grade naphthalene. All specimens were sintered at 2050°F for 4 hours.

(b) Napthalene particle size distributions (weight percent):

	Mesh Size		
	-40/+60	-60/+80	-80/+100
	Average Particle Size (microns)		
	335	213	163
Group 1	76	18	6
Group 2	40	20	40
Group 3	100	--	--

(c) Assuming spherical shape and 15 percent linear shrinkage during sintering.

The preliminary results of the in vivo studies with these materials are discussed in a later section of this report.

EXPERIMENTAL ANIMAL STUDIES

This portion of the report details the various research procedures which are used in our laboratories to evaluate biodegradable materials. The evaluative procedures include histology, radiography, and blood and urine chemistries. The classical techniques of histology and radiography are the key diagnostic procedures.

Research Protocol

In order to test the biodegradation of large tricalcium phosphate segments, a special experimental model has been devised in this laboratory. We utilize the calvarium of a mature, male New Zealand White rabbit with a minimum weight of 8 pounds. The calvarium has been found to be an excellent implant site for this relatively weak structural biomaterial since stresses upon the calvarium are not extraordinarily high and external stabilization is not required. Consequently, confusing effects which might be due to fixation devices are not seen. Of greater importance is the fact that this implant site provides the researcher with a large, relatively uniform area of material for various simultaneous studies. Additionally, periodic radiography of this flat area is an easy matter.

Standard aseptic surgical technique was used to expose the calvarium of the animal. A rectangular (0.25 inch x 0.75 inch) portion of the calvarium was osteotomized from the animal with no attempt to salvage the periosteum overlying the removed area. To match the curvature of the rabbit calvarium, specifically shaped samples of tricalcium phosphate were fabricated with a thickness of 0.1 inch.

Three different experimental groups of three animals each were followed. These groups were implanted with chemically identical tricalcium phosphate implants which differed in pore size distribution and orientation of

porosity. Four research animals were included in each group. One animal from each group was sacrificed at intervals of 3, 6, 9, and 12 months.

Blood and 24-hour urine samples were taken pre-implant, at each 3-month interval, and at the time of necropsy for all animals and the calcium and phosphorous levels determined. The animals were radiographed at 3-month intervals until the time of necropsy and the excised skulls were radiographed post-necropsy. The histologic analysis consisted of embedding a portion of the excised calvarium and tricalcium phosphate complex in methyl methacrylate and sectioning. The excised sample was stained with basic fuchsin prior to sectioning. Rabbits were stained at 3-month intervals with tetracycline 60 mg/kg, DCAF 20 mg/kg and xylenol orange 90 mg/kg to monitor bone ingrowth. A separate thick section was ground and left unstained for ultraviolet analysis.

Radiographic Examination of Tricalcium Phosphate Biodegradability

Radiographs of the rabbits were taken at 3-month intervals and of the excised skull after necropsy to monitor the biodegradation of the tricalcium phosphate implant. These high resolution radiographs were obtained using fine-grained industrial x-ray film and a Picker Industrial X-Ray Unit. Three animals that are representative of each of the three pore size distribution groups are illustrated.

The radiograph of rabbit C-77 (Figure 1) shows a tricalcium phosphate implant one week after surgery. Note that the implant is readily apparent in the animal's calvarium and distinctly outlined by radioluscence at its borders. This animal is an example of the "group one" pore size distribution. Figure 2 shows the same animal 3 months post-implant. Note that the sample is still observable in the radiograph. However, after 12 months the sample is not visible (Figure 3). This finding is consistent with previous biologic results reported for this project. Namely, due to biodegradation, the radiodensity of the tricalcium phosphate becomes closer to that of bone and is usually not observable after 12 months. However, a different impression of the ultimate fate of this material can be obtained if the radiograph of the excised skull is observed. Figure 4 shows the post-necropsy radiograph

FIGURE 1. RADIOGRAPH OF GROUP 1 TRICALCIUM PHOSPHATE IMPLANT 1 WEEK POST-SURGERY (RABBIT C-77).

FIGURE 2. RADIOGRAPH OF GROUP 1 TRICALCIUM PHOSPHATE IMPLANT 3 MONTHS POST-SURGERY (RABBIT C-77).

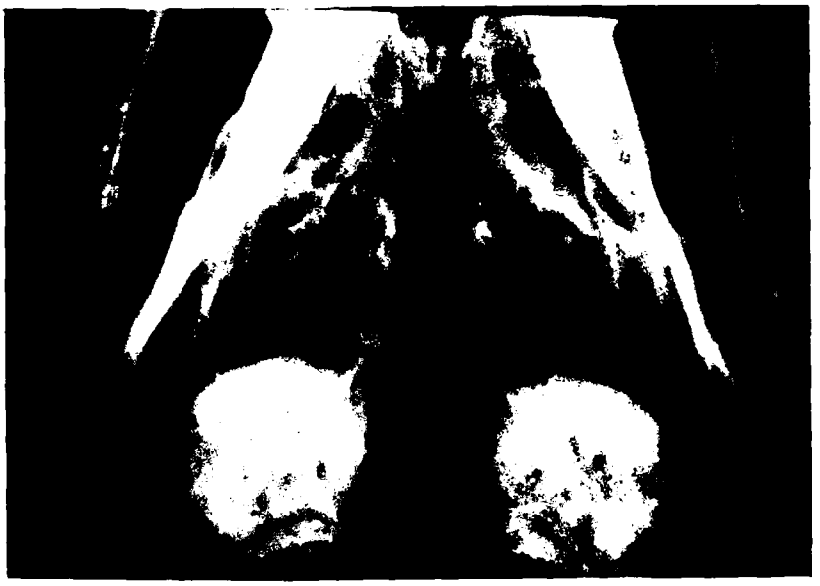

FIGURE 3. RADIOGRAPH OF GROUP 1 TRICALCIUM PHOSPHATE IMPLANT 12 MONTHS POST-SURGERY (RABBIT C-77).

FIGURE 4. RADIOGRAPH OF EXCISED SKULL POST-NECROSPY OF RABBIT C-77 AT 12 MONTHS FROM GROUP 1.

of rabbit C-77. Much greater resolution is obtained since interfering skin and bone have been removed. It is obvious that biodegradation has taken place. The blotchy appearance of the tricalcium phosphate indicates considerable degradation and a tremendous decrease in density of the implant. In some places holes are left at the borders of the implant where the material has degraded and not been replaced by bone tissue. Other portions of the implant show good confirmation to the surrounding bone. An appreciation for the change in the relative density of the tricalcium phosphate can be made by comparing Figure 4 to Figure 5. Figure 5 is a radiograph of tricalcium phosphate prior to implant. The difference in radiodensity between the pre-implant and 12 months after implantation is obvious.

Figure 6 is a radiograph, one week post-operative, of a rabbit (I-77) that is representative of the "Group 2" pore size distribution tricalcium phosphate. It is observed that the implant is similar to rabbit C-77 of Group 1. At 3 months (Figure 7), the outline of the implant can be observed only with difficulty and at 12 months (Figure 8), the outline of the implant is no longer discernable. When the excised post-necropsy x-ray of rabbit I-77 is observed (Figure 9), a striking amount of degradation can be observed. Note that large portions of the implant are totally missing and that the remaining tricalcium phosphate is highly granular in nature. It appears as if the implant has totally lost its integrity. Obviously, the desired result of the replacement of the bioimplant with natural bone has not been achieved.

Rabbit J-77 is representative of the "Group 3" implant material, and is shown one week post-implant in Figure 10. As in the two previous cases, the implant is readily observable with a radiolucent border. In contrast to the two previous material groups, this material is still observable on the radiograph after 12 months (Figure 11). This would indicate a higher density and presumably less biodegradation after 12 months than was observed with the two previous materials. The post-necropsy radiograph of rabbit J-77 (Figure 12) shows considerable degradation has occurred but some of the material is retained. In this particular case, the internal portion of the implant appears to have degraded more than the peripheral portion. This material has apparently maintained its density and integrity to a greater extent than either Group 1 or Group 2 materials.

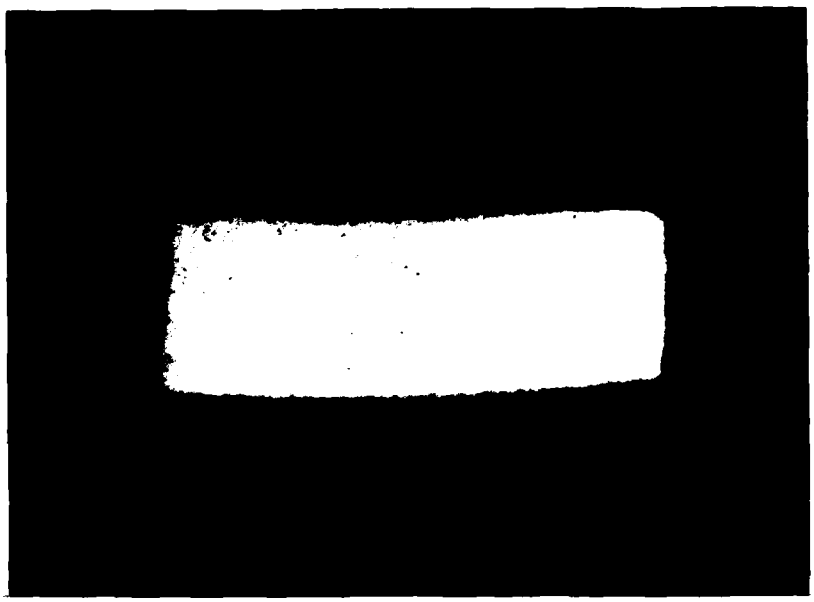

FIGURE 5. RADIOGRAPH OF GROUP 1 TRICALCIUM PHOSPHATE PRIOR TO IMPLANT.

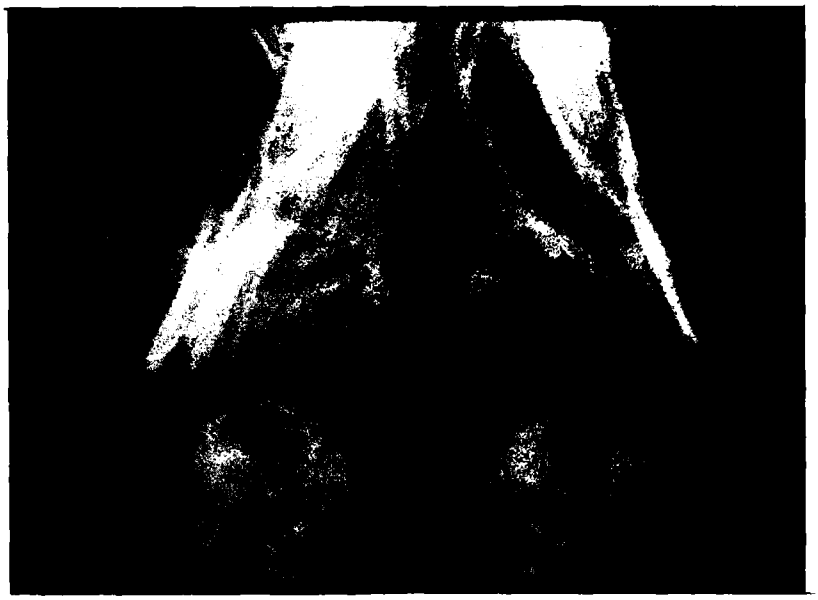

FIGURE 6. RADIOGRAPH OF GROUP 2 TRICALCIUM PHOSPHATE PRIOR TO IMPLANT 1 WEEK POST-SURGERY (RABBIT I-77).

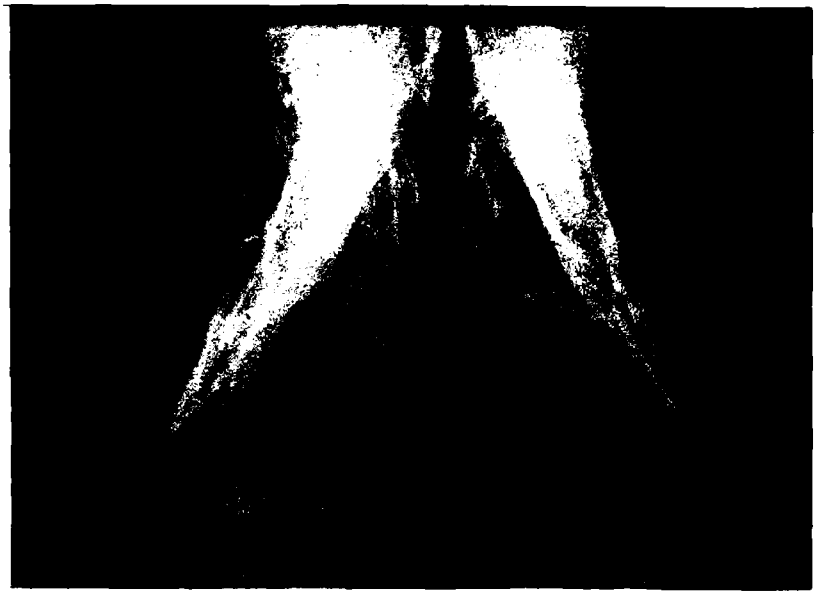

FIGURE 7. RADIOGRAPH OF GROUP 2 TRICALCIUM PHOSPHATE IMPLANT 3 MONTHS POST-SURGERY (RABBIT I-77).

FIGURE 8. RADIOGRAPH OF GROUP 2 TRICALCIUM PHOSPHATE IMPLANT 12 MONTHS POST-SURGERY (RABBIT I-77).

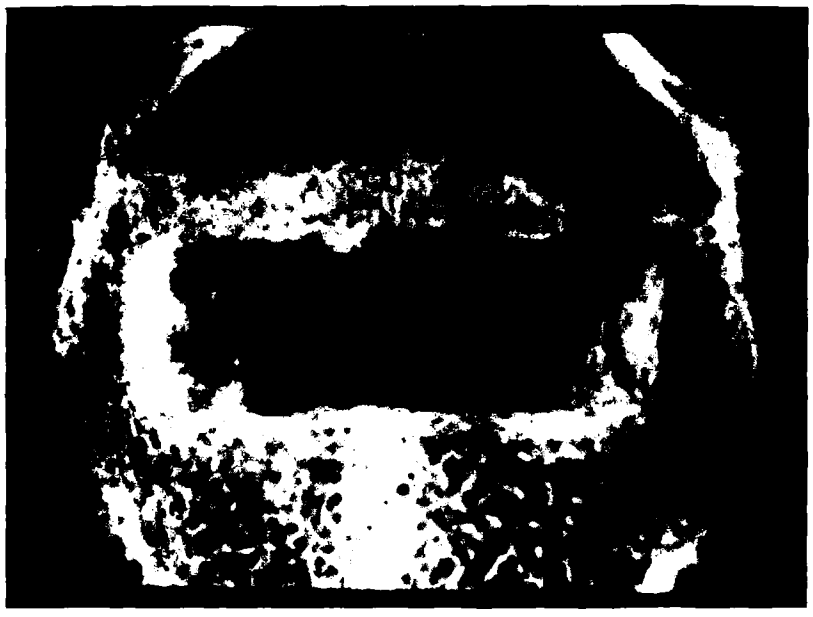

FIGURE 9. RADIOGRAPH OF EXCISED SKULL POST-NECROPSY OF RABBIT I-77 AT 12 MONTHS FROM GROUP 2.

FIGURE 10. RADIOGRAPH OF GROUP 3 TRICALCIUM PHOSPHATE IMPLANT 1 WEEK POST-SURGERY (RABBIT J-77).

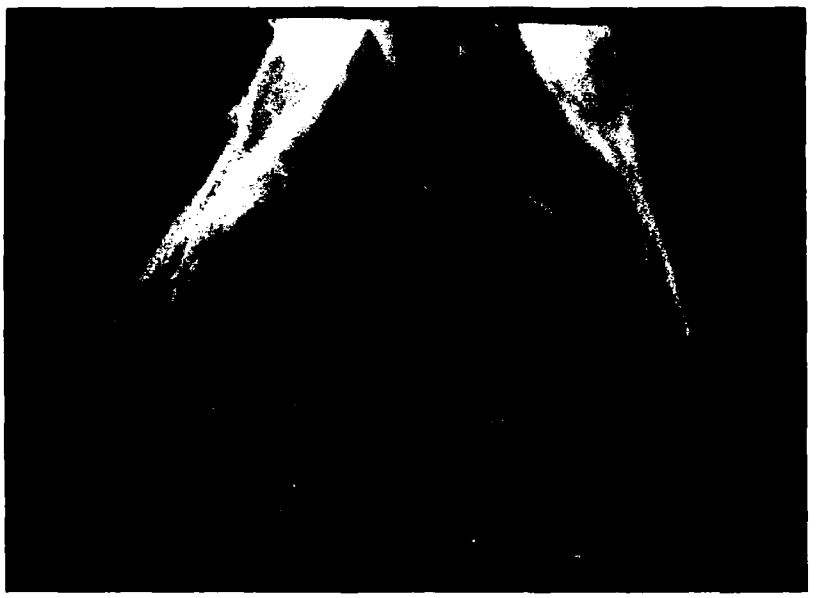

FIGURE 11. RADIOGRAPH OF GROUP 3 TRICALCIUM PHOSPHATE IMPLANT 12 MONTHS POST-SURGERY (RABBIT J-77).

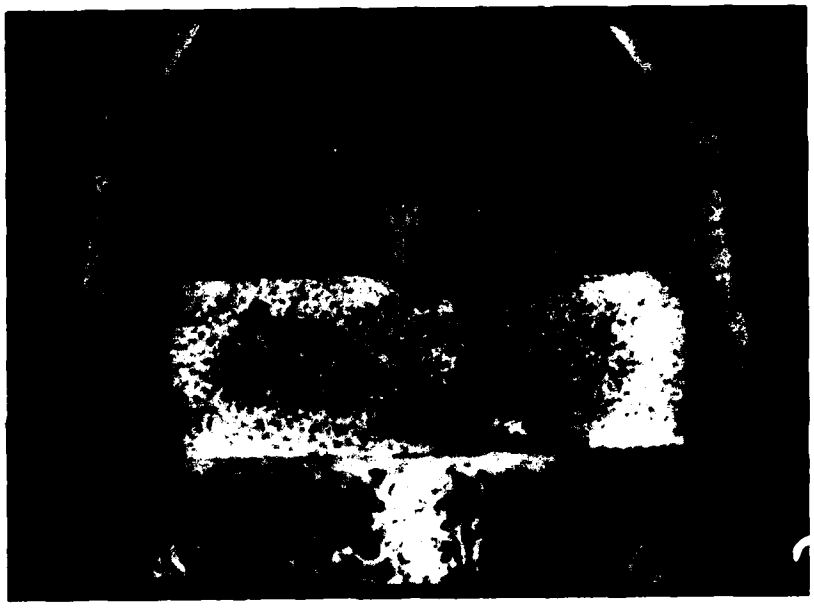

FIGURE 12. RADIOGRAPH OF EXCISED SKULL POST-NECROPSY OF RABBIT J-77 AT 12 MONTHS FROM GROUP 3.

Of the three materials, Group 3 appears to have degraded the least and the Group 2 material the most. These trends are essentially substantiated by radiography on the other implants in the study. Note that with the Group 3 material, the density appears to have been reduced more readily in the middle of the implant instead of at the boundaries, as was seen in the Group 1 and Group 2 materials.

Blood and Chemistry Profiles

Inorganic phosphorous determinations were made using an acid molybdate reaction. Calcium was determined with an orthocresolsphthalein complexone. Reagents were obtained from Dow Diagnostics. Blood was obtained from the animals for serum samples. Twenty-four urine samples were collected from the rabbits by housing them in metabolic cages. Aliquots were removed from a well mixed 24-hour sample for determination. Volume of urine in each 24-hour period was recorded. Multiple determinations were made on all samples. Samples were taken prior to implant, post-implant and then at 3-month intervals until necropsy. No significant alteration in either calcium or phosphorous was noted in any of the animals throughout the experimental period. This result is similar to that seen in all previous rabbits used in this project. Wide individual fluctuations in urine calcium and phosphorous levels can be seen throughout. These fluctuations are due in part to the unusual physiology of the rabbit in which the animal produces a concentrated urine which precipitates and cannot always be completely resolubilized. Some individual upward trends can be seen in values post-operatively. This might indicate the animal is excreting the excess calcium and/or phosphorous arising from the biodegradation of tricalcium phosphatate. These individual fluctuations are lost in the averaged data due to the extremely wide standard deviations.

Stable blood calcium and phosphorous values indicate the animals can easily handle, within its normal metabolic processes, the excess amounts of calcium and phosphorous being placed in its body pool. There are individual indications of increased excretion, but the unusual physiology of the rabbit limits interpretation.

CONCLUSIONS

The animal studies with tricalcium phosphate indicate that it is a biologically compatible material which can biodegrade. Historically, the project to date has shown improvement in the rate of biodegradation as well as an increase in the amount of bone formation into the available porosities. The Group 1 and Group 3 materials are more "successful" than any of the previous materials produced thus far. However, we have yet to produce a material that provides ideal results. A difficult trade-off is suggested in the data. That is proper selection of material strength, biodegradability and pore structure are necessary so that adequate strength of the newly formed bone is available before the biodegradation of the tricalcium phosphate proceeds too far.

Histologic analysis of the recently completed in vivo studies will be coupled with the above presented radiographic evidence to provide a more complete understanding of the biodegradation process.

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