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Bone repair of defects filled with a phosphocalcic hydraulic cement: an *in vivo* study

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A quickly setting calcium phosphate-based hydraulic cement mixed with particles of tricalcium phosphate (TCP) ceramic was implanted in 56 metaphysial defects made in the long bones of ten adult mongrel dogs. Microradiography, histology and scanning electron microscopy (SEM) demonstrated the slow resorption of the cement and the bony incorporation of the calcium phosphate ceramic particles which were consistently embedded in bone. The original structural pattern of the bone tended to be restored 7 months after implantation. The cement did not hinder the incorporation of the calcium phosphate ceramic particles, neither did it elicit any inflammatory or foreign-body response. The cement was easily shaped and allowed a perfect filling of any defect, resulting in close contact of the whole implant surface with the host bone at the time of surgery, associated with appreciable mechanical strength. Most of the practical problems associated with the use of calcium phosphate ceramics in the repair of bone defects could be overcome with the cement.

1. Introduction

Many biocompatible substitutes are available for the repair of bony defects or the restoration of anatomical structures in orthopaedic or reconstructive surgery, but only bone grafts and calcium phosphate ceramics or calcium carbonate can be ultimately replaced, in part or completely, by living bone. It is now widely admitted that calcium phosphate ceramics such as TCP or hydroxyapatite are osteoconductive, which means that bone has a specific tropism for these materials, allowing bone growth along their surface, as long as stability and some initial contact with living bone is provided. This newly formed living bone is closely apposed to the ceramic and probably bonded to it by physicochemical interaction [1–5].

The major problem with these materials is the difficulty of making them fit with the bone bed and of shaping them in the adequate form, particularly in maxillofacial surgery in which precise structures are to be restored. As massive blocks with good compressive strength, they are difficult to trim because of their brittleness. In alveolar ridge reconstruction there is a great danger of mucosal protrusion if any sharp edge is present. When in particulated form, shaping may be easier but the repair has no mechanical resistance and secondary migration of the ceramic grains is often observed. A cement-type material, handled as a paste and setting after adequate shaping in the right place, would overcome these practical problems in so far as its resorption or dissolution does not elicit a foreign-body reaction and is sufficiently slow to allow the replacement of the cement by ingrowing bone. Knowing the setting ability of some calcium phosphate compounds and the remarkable bony incorporation of calcium phosphate ceramics, we looked for a resorbable, quickly setting hydraulic cement made of calcium phosphates.

A hydraulic cement is a very finely particulated material which is at least partially solubilized in water and is then able to recrystallize and set. Binding to the surrounding structures occurs only by mechanical interlocking and is not comparable with a glue effect or a chemical reaction. As in concrete, a more or less particulated, inert material such as sand or gravel can be added to this cement. In previous papers we described the composition, the physicochemical and mechanical properties of some types of calcium phosphate-based cements and concretes [6–9]. The aim of this work was to study, *in vivo*, the quality of bony incorporation of this type of biomaterial by assessing

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TABLE I Composition of the implants

Inert material (granulometry 50–1000 μm)		
TCP	$Ca_3(PO_4)_2$ minus 0.2% if $CaCO_3$ added	56%
Quickly setting hydraulic cement powder (granulometry < 5 μm)		
TCP	$Ca_3(PO_4)_2$	8%
MCPM	$Ca(H_2PO_4)_2 \cdot H_2O$	16%
Calcium pyrophosphate	$Ca_2P_2O_7$	5%
Calcium sulphate hemihydrated	$CaSO_4 \cdot 1/2H_2O$	15%
Calcium carbonate (optional)	$CaCO_3$	0.2%
Water	H_2O	0.24 ml g^{-1}

the absence of soft tissue intervening between the resorbing concrete and the ingrowing bone, as well as the absence of foreign-body reaction against the grouting agent and the ceramic particles.

2. Materials and methods

A cement powder made of monocalcium phosphate monohydrate (MCPM), TCP, calcium pyrophosphate and calcium sulphate hemihydrate was used. Particulated (50–1000 μm) sintered TCP was added as a partially inert material [8]. In 27 of 56 implants calcium carbonate (calcite) was added to the dry cement powder as a porosity-inducing agent acting at the time of mixing with water by producing gaseous carbon dioxide, forming extra porosity in the cement [9]. The calcium monophosphate was mixed with water for about 10 s. This suspension was then added to the other components and thoroughly mixed for 30 s. The paste set in about 10 min, allowing easy handling during that period. The composition of the implants is summarized in Table I. It was used either as hard, dry, preset cylinders 10 mm in diameter and 20 mm long, or as a paste, prepared at the time of implantation. The material (powder or blocks) was sterilized with 25 kGy gamma-irradiation.

A total of ten adult mongrel dogs (weight approximately 25 kg) were operated on. Implantation was performed alternatively in six different locations in eight dogs. Two additional dogs received each only four metaphysial implants. Under general anaesthesia the proximal metaphysis of both the humerus and the proximal and distal metaphysis of both femurs were exposed through a lateral approach. Holes 10 mm in diameter and about 20 mm deep were made in the metaphysis with a trefine, taking care to respect the internal cortex. In order to remove the bone plug made by the trefine, the instrument was gently wiggled around. This might slightly enlarge the hole in its distal part. Subsequently each hole was filled with an implant according to the distribution summarized in Table II. When the material was used as a paste, the cement was mixed with water as described above. The paste was introduced in a 2 ml syringe from which the top had been cut, making the outlet as large as the plunger. The paste was injected from the syringe into the defect, about 1–2 min after mixing. No control was used, since the study of the chronological sequence of bone repair was not the objective of this investigation.

TABLE II Implant repartition and location

Dog no.	Paste[b]	Block	Paste + $CaCO_3$	Block + $CaCO_3$	Total
1[a]	D_r/P_r	D_l	S_l	S_r/P_l	6
2	S_r/P_r	D_l	D_r	S_l/P_l	6
3	S_l/P_l	S_r/D_r	D_l	P_r^d	6
4	D_l/P_l	S_l/S_r	D_r/P_r		6
5	S_l	P_r	D_l/P_l	S_r/D_r	6
6		S_l/D_r	P_l/P_r	S_r^d/D_l	6
7	S_l/D_l	S_r/D_r	P_l	P_r	6
8	S_r	S_l/P_l	D_r/P_r	D_l	6
9[c]	D_l/D_r		P_r/P_l		4
10[c]	D_r/P_r		D_l/P_l		4
Total	16	13	16	11	56

[a] Killed 24 h post-operative.
[b] S_l, S_r, proximal humeral metaphysis, left and right; P_l, P_r, proximal femoral metaphysis, left and right; D_l, D_r, distal femoral metaphysis, left and right, respectively.
[c] Killed after 4 months.
[d] infected site.

One dog was killed on the first post-operative day, the two dogs with four implants were killed after 4 months and the seven remaining dogs after 7 months. Before the dogs were killed with a lethal dose of Nembutal (Abbott Laboratories, Belgium), a double fluorescent labelling was performed in all of the long-term dogs with calcein green (Merck, Darmstadt, FRG) and procion red H8BN (ICI, UK), respectively 2 weeks and 1 day before death. High-definition radiography of the explanted bones was performed to localize the implants. The metaphysis was cut in blocks with a band saw and fixed for 3 weeks in 10% phosphate-buffered neutral formalin before dehydration in methanol and embedding in methyl methacrylate. In addition, two implants of each type were coloured *en bloc* with basic fuchsine [10] before embedding. Serial sections 200 μm thick were made with a diamond saw (Leitz, Wetzelar, FRG) and then ground with silicon carbide (SiC) paper to a thickness of 80 μm before microradiography. After microradiography and observation for fluorescence, some sections were further prepared for histology. These sections were glued with an epoxy resin (Araldite AW 106; Ciba–Geigy, Switzerland) on plane-parallel ground glass slides, placed in a slide holder (Struers, Denmark) and further ground and polished on a rotating grinding machine (Planapol 2; Struers, Denmark) to a thickness of about 10–20 μm with SiC

paper up to 4000-grit. Those not stained with basic fuschine were stained by methylene blue and Von Kossa's silver staining. Other sections used for microradiography were further polished with diamond paste (Struers, Denmark) and coated with carbon before scanning electron microscopy (SEM) back-scattered electron imaging (Leica, Videoscan 260; Cambridge, UK). As reported by Holmes [11], the sharp tissue boundaries and high tissue contrasts on the images obtained with this technique allow precise identification of the implant, bone and soft tissue.

3. Results

Two out of 50 long-term implantation sites were infected. All others had healed uneventfully, and macroscopically the implants were very difficult to localize. Implants harvested from the dog killed 1 day post-operatively were well hardened *in situ*. Sections obtained from these implants showed the structure of the material before any resorption or ingrowth. When the concrete was used as a paste, excellent filling of the defect was achieved, whereas this was not possible with hard cylinders if the hole did not match exactly the shape of the implant (Fig. 1a and b). Upon microradiography the cement in between the particles of sintered TCP was by far more radiolucent.

After 4 and 7 months implantation bone was observed in direct contact with the resorbing cement and the ceramic particles. Obviously, when comparing the size and the amount of tricalcium phosphate ceramic particles at the time of implantation (Fig. 2a) with those found after 7 months (Fig. 2b–d), there was a resorptive process of the ceramic associated with various amounts of new bone formation. The small grains of ceramic had disappeared, whereas the sharp edges of the larger grains had been rounded off and were consistently embedded and united by bone trabeculae while Haversian remodelling was occurring. Fig. 3 shows several microradiographs of each of the four types of implants. A core of unresorbed cement was often found in the centre of the implants after 4 (Fig. 3a) and sometimes 7 months implantation (Fig. 3d, g and j). The pattern of bone ingrowth and implant resorption was highly variable for the same type of implant. In a cortical defect very large bone trabeculae were formed, restoring the original cortical structure (Fig. 3b), whereas where the trabeculae were small and scarce, most of the ceramic was resorbed and only a few small trabeculae were formed (Fig. 3c, f, h and i). In the epiphysis the dense trabecular structure was consistently restored (Fig. 3g and l).

Except for the irregular outer contour of the implants inserted as a paste, 7 months post-operatively it was not possible to determine by any morphological criteria the type of a given implant: block or paste, with or without calcium carbonate.

Histology and SEM back-scattered electron imaging demonstrated bone deposition on most of the surface of the residual cement (Figs 4a, b and 5) or the fragments of ceramic (Fig. 2b–d). The surface of the ceramic or the cement not covered by bone or osteoid was in direct contact with normal marrow cells (Figs 6 and 7). In no case did the cement or the TCP elicit an inflammatory or foreign-body reaction with giant cells. Some macrophages containing ceramic particles were observed in the bone marrow. Direct contact between bone and implant was confirmed in all but the two infected implants by the different morphological techniques used in this study.

4. Discussion

It has been demonstrated that many biomaterials (ceramics, metals and polymers) can be "osteo-integrated" [12, 13] which means, according to Albrektsson and Albrektsson [14], that at least 95% of the implant surface is in direct contact with bone. This can

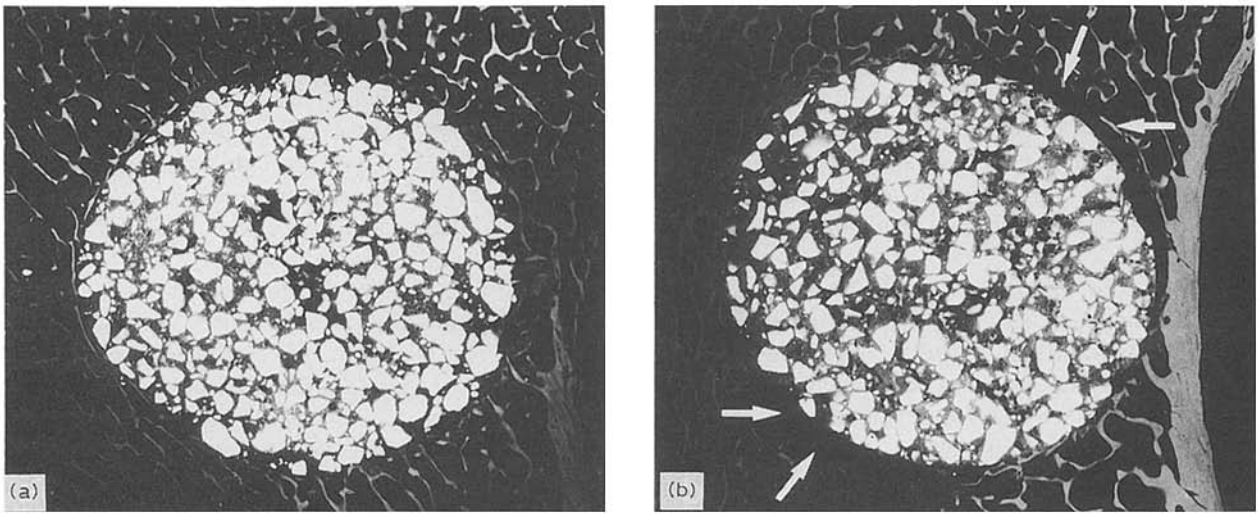

Figure 1 (a) Microradiograph of a first post-operative day sample implanted as a paste without calcium carbonate. Note the concrete-like structure of the implant. No dead space is observed between the bone and the implanted material (diameter of implant 10 mm). (b) Microradiograph of a first post-operative day sample implanted as a block without calcium carbonate. There is a gap between the implant and the host bone.

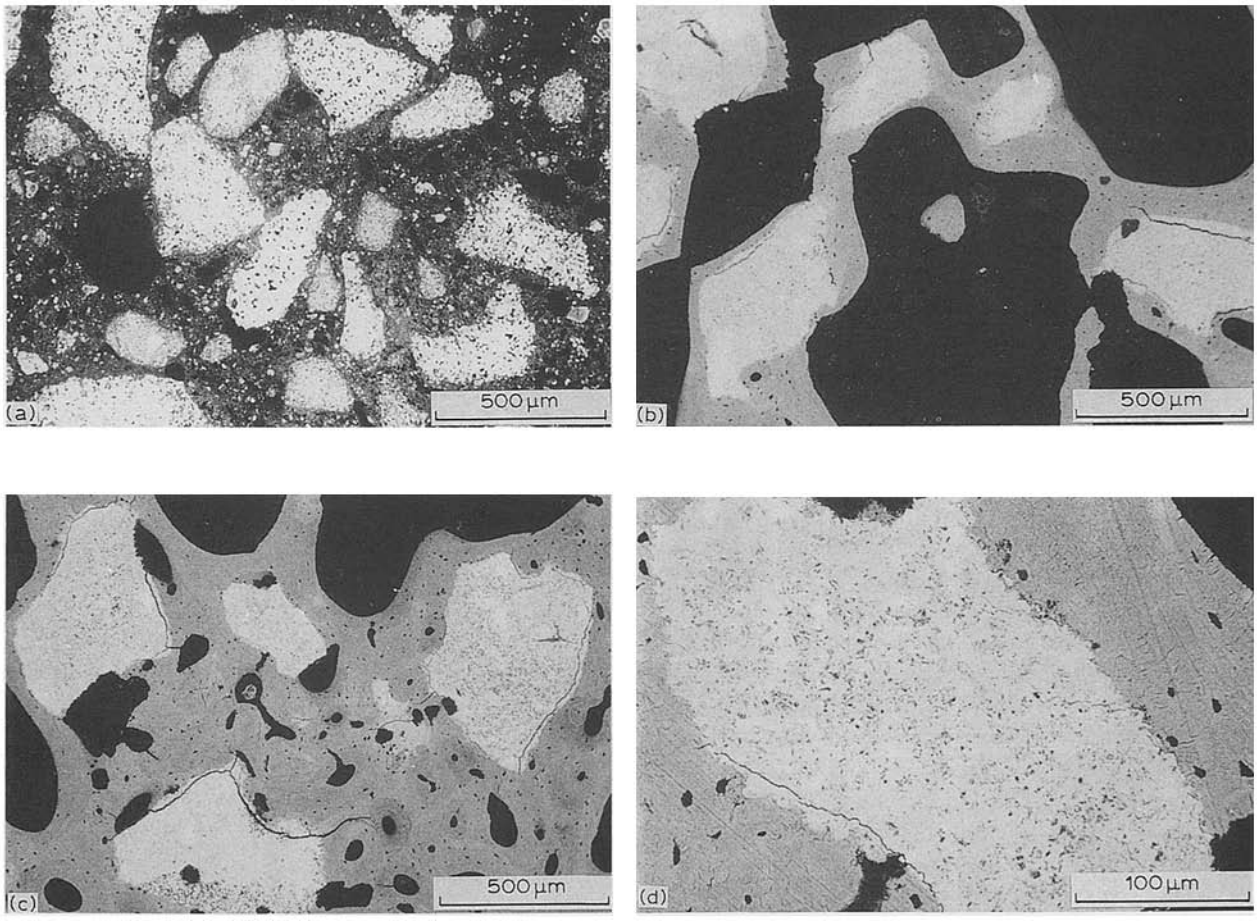

Figure 2 SEM back-scattered electron image. (a) First post-operative day. Cement and blocks of TCP. (b) and (c) Figures obtained from one section of implant $8D_1$. The particles of ceramic are surrounded and united by bone. The trabecular pattern (b, cancellous or c, cortical) is correlated with the surrounding bone pattern. (d) Higher-magnification view of the smallest fragment of ceramic in (c). Direct apposition of bone on the ceramic.

occur only if the initial stability and close contact between most of the implant and the bone is provided immediately at the time of implantation [13, 15]. To obtain secondary osteo-integration of a stable implant having only limited initial contact with the host bone bed, a real tropism of the bone for the implant surface is needed. Extensive and reproducible osteoconduction along the surface of implants has been reported only with bone grafts [16], bioglasses [17, 18], calcium phosphate ceramics [1, 3, 5, 19–22] and calcium carbonate [23, 24]. Osteoconduction must be distinguished from periosteum-induced bone deposition, often observed on the surface of osteosynthesis plates or bone ingrowth in a porous surface which occurs by a different mechanism as shown by Galante and Rivero [25].

Despite the exceptional bony incorporation of calcium phosphate ceramics, its clinical use is limited by its fragility and the difficulty of shaping blocks or keeping the particulated ceramic together, especially in applications such as alveolar ridge augmentation or zygomatic bone reconstructions [26]. Mixing with fibrine glues [27] or collagen extracts [28] helps to some degree to overcome these difficulties, but these very high-cost additives do not bring appreciable mechanical strength to the reconstruction. Poly(lactic acid) polymers have also been used [29] and do provide mechanical strength. However, this material has been shown to elicit massive foreign-body reactions under some circumstances, when being resorbed [30]. For all of these reasons there have been several attempts to design some type of concrete made of calcium phosphate ceramic particles bound together with a cement allowing shaping in the desired form and providing appreciable mechanical strength after setting.

Methyl methacrylate is the most widely used non-resorbable cement in orthopaedic and dental applications. The living tissues in contact with this cement often produce a fibrous tissue encapsulating the material [31, 32]. Although some authors did observe areas of direct bone contact with methyl methacrylate, these areas were often limited in surface and did not involve any adhesion between the cement and bone [33, 34]. Methyl methacrylate mixed with calcium phosphate ceramics particles is used by some surgeons. The binder in this case being non-resorbable, one can expect a surface effect of the ceramic providing some adhesion with bone without bone ingrowth only as long as the particules of ceramic located at the surface of the cement are not covered by a thin layer of polymer.

The oldest-known resorbable cement is plaster of Paris. Various reports did mention its use since the end of the 19th century for filling bone defects in osteomyelitis or bone tumours [35]. Peltier, in 1961,

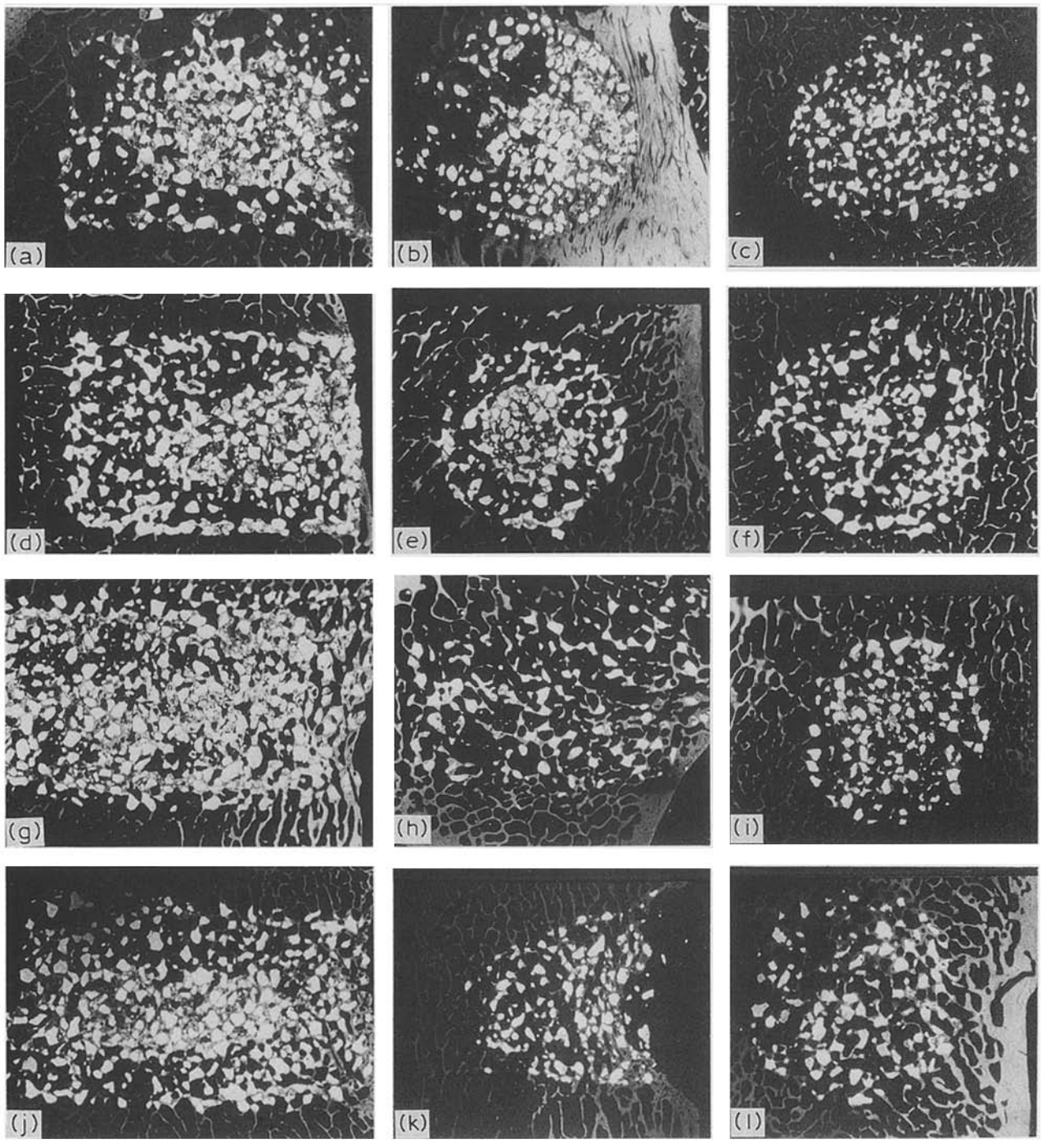

Figure 3 Microradiographs of three sections of each of the four types of implants. The most important factor affecting the bone formation and the course of resorption of the implants seems to be the original bone structure at the site of implantation (diameter of implants 10 mm).

Origin of the sections presented in Fig. 3a–l

Paste	(a) $9D_r$	(b) $10P_r$	(c) $7D_l$
Block	(d) $6S_l$	(e) $7S_r$	(f) $7S_r$
Paste + $CaCO_3$	(g) $4D_r$	(h) $9P_r$	(i) $5D_l$
Block + $CaCO_3$	(j) $8D_l$	(k) $6D_l$	(l) $2P_l$

reported on his clinical and laboratory work with plaster of Paris in the form of dry preset pellets. Although satisfied with his clinical results, he stated that plaster of Paris did not provide internal support or stimulate osteogenesis; the material was completely resorbed within weeks or months [36]. Hanker *et al.* filed a patent in 1984 for a mixture of calcium phosphate ceramic particules with plaster of Paris in the proportions of approximately 0.5–6 parts calcium phosphate per part of plaster [37]. The major disadvantage of plaster of Paris is its solubility and rapid break-up (< 24 h) in aqueous medium, with loss of all mechanical strength. In all "on lay" applications of the material, dispersion can occur as soon as the plaster dissolves, resulting in the same problems as those observed with granules alone.

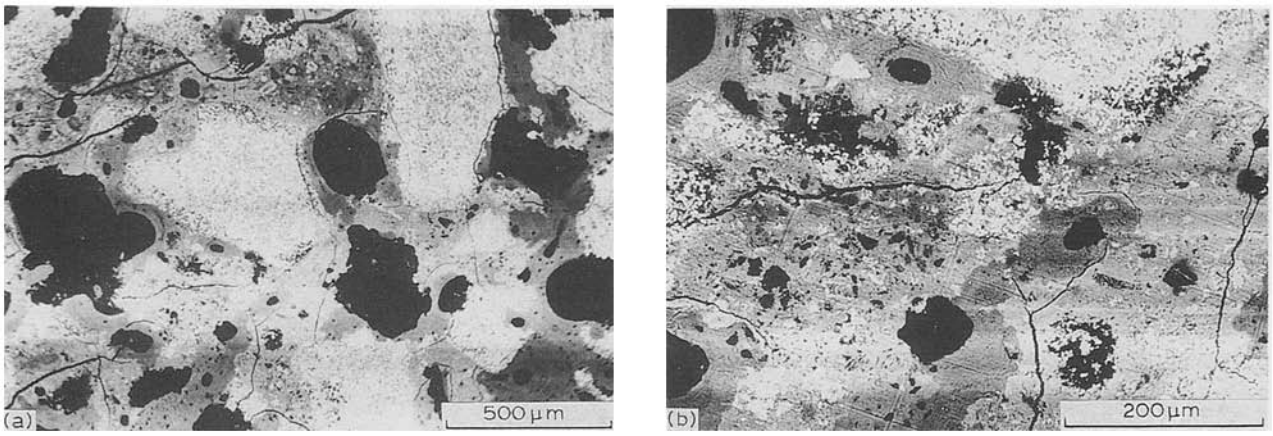

Figure 4 (a) SEM back-scattered electron image. Bone is directly apposed to the ceramic particles and the residual cement left between the particles (b) Higher-magnification view of the lower left part of (a).

Brown and Chow [38], Lemaître *et al.* [6], Mirtchi *et al.* [7] and Monma *et al.* [39] have published papers about calcium phosphate-based cements. For the present application we developed an MCPM-based cement with setting regulators (plaster of Paris 15 wt % and calcium pyrophosphate 5 wt %) in order to prolong the working time of the slurry from 30 s to about 10 min. In a previous paper it was demonstrated that the cement-like behaviour can be ascribed to the dissolution of MCPM followed by the precipitation of dicalcium phosphate dihydrate (brushite; DCPD) [8]. The diametral tensile strength of the cement increased from 1 to 3.2 MPa with the addition of plaster of Paris. However, upon ageing in saline solution (0.9 wt % NaCl in distilled water) this value decreased sharply within 1 day, to reach about 60% of its initial value with a weight loss corresponding to the expected amount of solubilized calcium sulphate dihydrate (hydrated plaster of Paris, CSD). After 6 weeks ageing in saline the residual tensile strength (2 MPa) of this cement was still increased compared with MCPM cement alone (1 MPa). This is a consequence of an increase of DCPD formation during CSD dissolution [8]. In this application plaster of Paris first acts as a setting regulator, exactly why it is used in Portland cement used in construction.

In vivo, resorption of a calcium phosphate ceramic depends on its chemical and crystallographic nature and on its macro- (> 50 µm) and microporosity [40]. TCP [$Ca_3(PO_4)_2$] is much more resorbable than hydroxyapatite [$Ca_5(PO_4)_3OH$] [41] which, in dense form, is almost not resorbable [2]. *In vitro*, the setting of the concrete was not affected by replacing the particles of TCP with hydroxyapatite. Although the chemical reactions at the interface between bone and TCP or hydroxyapatite may [42] or may not be similar [43], morphologically, besides the resorption of TCP, no qualitative difference in bone apposition on to the surface of these two ceramics has been reported [40]. Therefore, whereas in this experiment we used particules of TCP, they might be replaced by particles of hydroxyapatite, preventing or slowing down significantly the resorption of the "inert" part of the concrete, which appears preferable in many maxillofacial applications. In orthopaedic applications immediate extra compressive strength can be provided by using large ceramic blocks in combination with the cement.

When the material is used as a paste, it is most important to keep the implantation site as dry as possible. This can be done by packing a surgical sponge in the defect until filling with the cement. In a well-contained defect, as in this experiment, there was no problem of impregnation of the cement by outwards blood flow. In a defect that is not as well contained, if outwards blood flow is important, it should be useful to pressurize the cement during the setting period to avoid its impregnation with blood which would compromise setting.

The morphological observations of the present experiment demonstrate the constant bony incorporation of the ceramic particles. The binding material was progressively resorbed within months, leaving the ceramic particules embedded in bone instead of cement. No inflammatory or foreign-body reaction was elicited by the cement or the particles of TCP. Normal bone, osteoid and haematopoietic marrow cells were consistently found in direct contact with the residual material.

Within each implant the resorption of cement and TCP as well as the ingrowth of bone occurs in a centripetal fashion. On any section of an implant areas that are equidistant from the host bone bed can be observed. Nevertheless, as shown in Fig. 3, the bone deposition and the implant resorption may be very different at a same distance from the host bone bed for the same implant. It appears that the thickness and density of the new bone trabeculae, as well as the degree of resorption of the ceramic grains, is closely related to the original bone structure in the vicinity of the area of the implant considered. Similar observations of replication of the original bony structure with blocks of porous ceramic were reported by Holmes *et al.* [19]. Morphologically, the addition of calcium carbonate did not significantly affect the course of resorption or incorporation. Given the obvious correlation between the local bone architecture and implant remodelling, no attempt was made to quantify

Figure 5 Section obtained 7 months post-operatively (implant $3D_1$). Bone (brown) is directly apposed to residual cement (blue material) and ceramic particles (grey). Von Kossa and methylene blue staining (× 200).

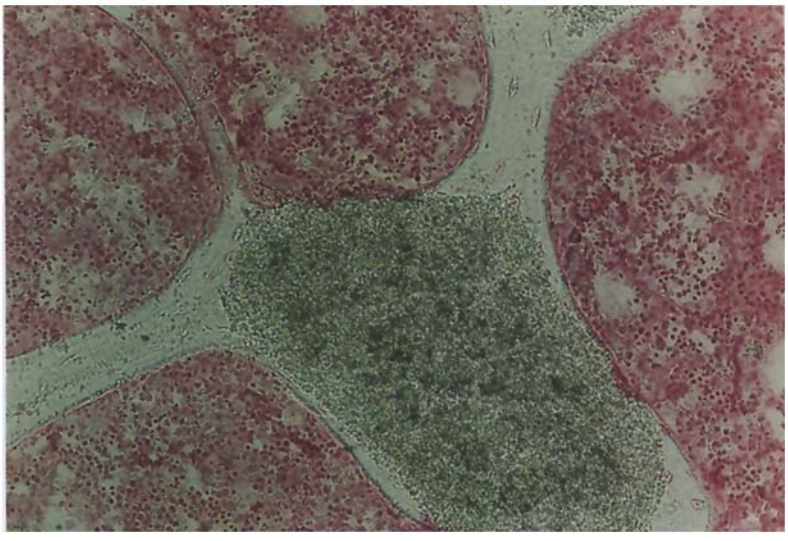

Figure 6 Section of implant 5S, stained with basic fuchsin. Bone, osteoid or bone marrow is in direct contact with the ceramic particles (× 200).

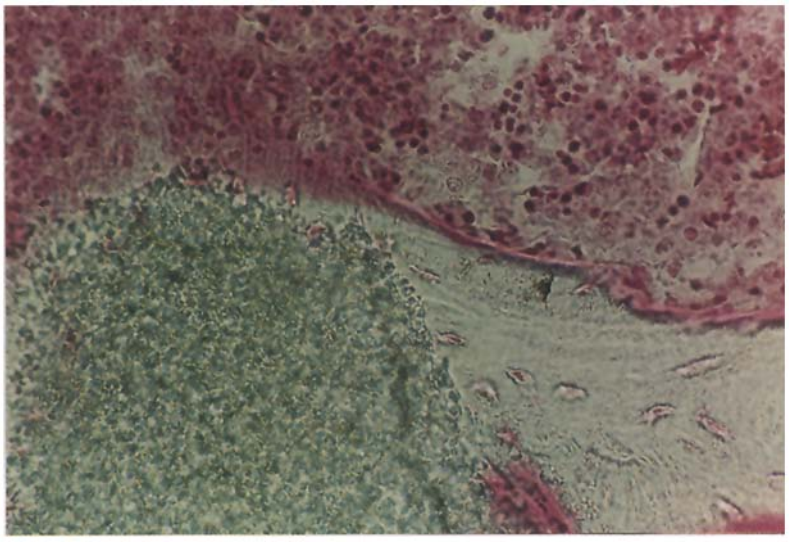

Figure 7 Same implant as Fig. 6 at higher magnification (× 400).

the resorption rate of the material or the ingrowth rate of the bone. Indeed, the quantification of this would have shown large variations even for the same implant, reflecting only the variety of bone structures encountered.

5. Conclusions

This *in vivo* experiment demonstrated clearly that the quickly setting, calcium phosphate-based cement described did not detrimentally affect the quality or extent of incorporation of calcium phosphate ceramics. The cement allows complete filling of any osseous defect, providing direct contact of the whole outer surface of the implant with the host bone bed. We can thus overcome most of the problems associated with the use of calcium phosphate ceramics in the repair of bone defects. Secondary migration of ceramic particles is prevented, as well as the sharp edges or inadequate filling observed with massive blocks. By filling the bony defect exactly, stability is provided to the concrete block after setting, preventing the fibrous encapsulation sometimes observed even with calcium phosphate ceramics when relative motion occurs between the bone and the implant.

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