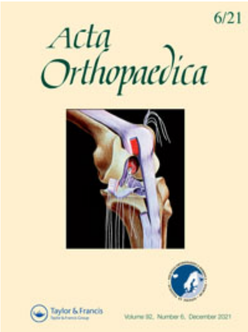

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The Influence of Acrylic Cement on the Femur of the Dog: A Histological Study

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THE INFLUENCE OF ACRYLIC CEMENT ON THE FEMUR OF THE DOG

A Histological Study

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Serious deformation of the hip joint is increasingly treated with total hip replacement arthroplasty, the artificial bearings being fixed in the skeleton by self-curing methylmethacrylate ("acrylic cement").

It is of considerable importance to get an insight into the way in which the bone of the femur reacts to insertion of the polymer. A number of observations have been reported, made on material obtained from patients who had been wearing such a prosthesis fixed with acrylic cement for a number of years (Willert & Schreiber 1969, Charnley 1970, Willert & Puls 1972). The authors describe necrosis of the bone occurring around the cement, followed by repair processes, a sequence leading to the situation in which there is no longer a direct contact between bone and cement. Formation of connective tissue in which multinucleated giant cells are present is seen also.

In papers reviewing clinical results (Parsons 1969, Enderle 1972) mention is made of a loosening of the prosthesis, a complication which possibly is due to changes in the surrounding tissue.

Tissue damage can be the consequence of the local rise of temperature which accompanies polymerization. Another factor can be the non-inertness of the acrylic cement. Various components can escape from the polymerizing mixture: a residue of the monomer, hydroquinone, dimethylparatoluidine and benzoylperoxide. In the long run it is oligomeric methacrylate, formaldehyde and methacrylic acid which may find their way to the tissues (Mark & Mesrobian 1950, Oppenheimer et al. 1955, Ridley 1957, Hastings 1968).

A number of workers (Wiltse et al. 1957, Rietz 1968, Slooff 1970) have performed animal experiments to study the influence on the cortical bone of acrylic cement present in the medullar space. These authors described a necrosis of the inner part of the cortex, which they attributed both to a disturbance of the circulation and to the heat of polymerization. Further mention is made of the formation of connective tissue around the cement and the formation of new bone on the periosteal surface of the bone.

A number of investigations (Ohnsorge & Goebel 1969, Bloch et al. 1970) have shown that the rise of temperature resulting from polymerization after insertion of the prosthesis can be responsible for tissue necrosis. It has also become apparent that inserting a foreign body into the medullary cavity of long bone in itself disturbs the circulation, which in turn leads to alterations in the surrounding cortical bone (Trueta & Cavadias 1955, Danckwardt-Lillieström et al. 1970). The changes consist of necrosis of the inner part of the cortex and the apposition of periosteal bone around the shaft.

Thus, a number of causative factors may be mentioned which lead to alterations of the bone after insertion of a prosthesis:

a. a mechanical injury as a consequence of the trauma of insertion
b. a disturbance of vascularization by interrupting the marrow circulation
c. a rise in temperature during polymerization
d. the escape of non-inert substances from the acrylic cement.

The factors mentioned under a, b and c will in the course of time lose their significance. The liberation of noxious substances, however, may play a role both at an early and at a later stage.

The question underlying the present investigation was: what is the influence of acrylic cement on bone, a) in the short term, b) in the long term?

During a period lasting from 1 day to 21 months the histological picture of a dog's femur was studied after filling the marrow cavity with polymethylmethacrylate. In order to distinguish between the effects of acrylic cement as such on the one hand and the effects of trauma and circulatory disturbances on the other hand, in control experiments the marrow space was emptied without subsequent filling with polymer.

EXPERIMENTAL ANIMALS AND TECHNIQUES

Dogs were chosen as experimental animals. Apart from 12 mongrel dogs of various weights and unknown age, 10 pure-bred beagles, 6 months old and weighing about 14 kg were used.

Table 1. Type of operation, breed, survival time and number of dogs used in each type of operation. The column at the right denotes whether the medullar cavity was emptied and filled with acrylic cement (exp) or just emptied (C). L = left femur, R = right femur.

Survival time after operation	Breed	Number	Type of operation			
			L	R	L	R
24 hours	mongrel	2	Exp	C	Exp	–
2 weeks	mongrel	2	Exp	C	Exp	–
4 weeks	beagle	2	Exp	C	Exp	–
8 weeks	beagle	2	Exp	C	Exp	C
12 weeks	beagle	2	Exp	C	Exp	–
16 weeks	beagle	1	Exp	C		
20 weeks	beagle	2	Exp	C	Exp	C
28 weeks	beagle	1	Exp	–		
10 months	mongrel	1	Exp	–		
12 months	mongrel	2	Exp	–	Exp	–
15 months	mongrel	1	Exp	–		
18 months	mongrel	2	Exp	–	Exp	–
21 months	mongrel	2	Exp	–		

Under general anesthesia the left femur was exposed. The periosteum was removed in two places: 1 cm distal to the trochanter major and 3 cm proximal to the knee joint. At each location a hole 8 mm in diameter was drilled. The cancellous bone between the holes was removed and the bone marrow was sucked off through the distal hole. The cavity thus prepared was filled with prepolymerized methacrylate employing a specially designed syringe with a screw-thread piston. Care was taken to avoid high pressure during insertion.

In eight dogs temperature measurements were performed using a thermocouple; details are given under Results.

In a number of animals a control operation was performed: after complete emptying no methacrylate was inserted. The experiments are listed in Table 1.

For histological study the following techniques were used. Three disks were taken from each femur: one just distal to the upper hole, one from the middle of the shaft, and one proximal to the bottom hole. Half of each disk was fixed in Darlington's fixative (100 parts 90 per cent ethanol, 40 parts undiluted neutral formalin, 7 parts acetic acid) and decalcified electrolytically in a formalin-nitric acid mixture. In the course of dehydration methacrylate was dissolved in chloroform. The stains used were: hematoxylin-phloxin, Mallory stain and a combined Alcian Blue-P.A.S. method.

The other halves of the bone disks were fixed in 80 per cent ethanol, and embedded in polymethyl methacrylate. Microradiographs were prepared using 100 micron thick slices of this material.

RESULTS

Temperature measurements

In eight dogs temperature measurements were performed by means of a needle thermocouple during and after insertion of the methacrylate. On the outer surface of the cortex the maximum rise was 3 to 9° C; it lasted about 50 minutes. At the acrylate-bone interface temperature was measured through a thin hole drilled in the cortex. An increase in temperature to 58° C was observed, i.e. a rise of 24° C. This rise lasted about 25 minutes. The thickness of the cortex was 1.8 to 2.5 mm.

A single measurement carried out in a waterbath on an isolated dog femur filled with methacrylate showed a rise in temperature to 60° C.

These data strongly suggest that the insertion of methacrylate leads to irreversible damage to cellular and intracellular proteins.

The microscopy of bone changes

As mentioned in the section Experimental Animals and Techniques, only a limited number of pure-bred beagles were available. Therefore, mongrel dogs had to be used for a number of the experiments (Table 1). The beagles were used for a continuous series of experiments, viz. for the stages 4 to 28 weeks. Thus, the observations to be described were made in two series of experiments:

Series I: 4 to 28 weeks, a continuous series performed on beagles
Series II: early stages (24 hours and 2 weeks) and late stages (10 to 21 months); these experiments were performed on dogs of various breeds and ages.

The descriptions are based on both histological sections and microradiographs.

Series I. 4–28 weeks

Three areas can be distinguished where alterations were seen: 1) the space between the implant and the cortex, 2) the cortex, 3) the periosteum. In this section changes observed in pure-bred beagles, over the period from 4 to 28 weeks are described. The changes are presented schematically in Figure 1.

Four weeks after the operation the cortical bone was dead, as shown by the fact that the osteocyte lacunae were empty. They contained resorption cavities as a result of wide-spread osteoclastic activity. (Figure 2). Between the implant and the cortex there was a connective tissue

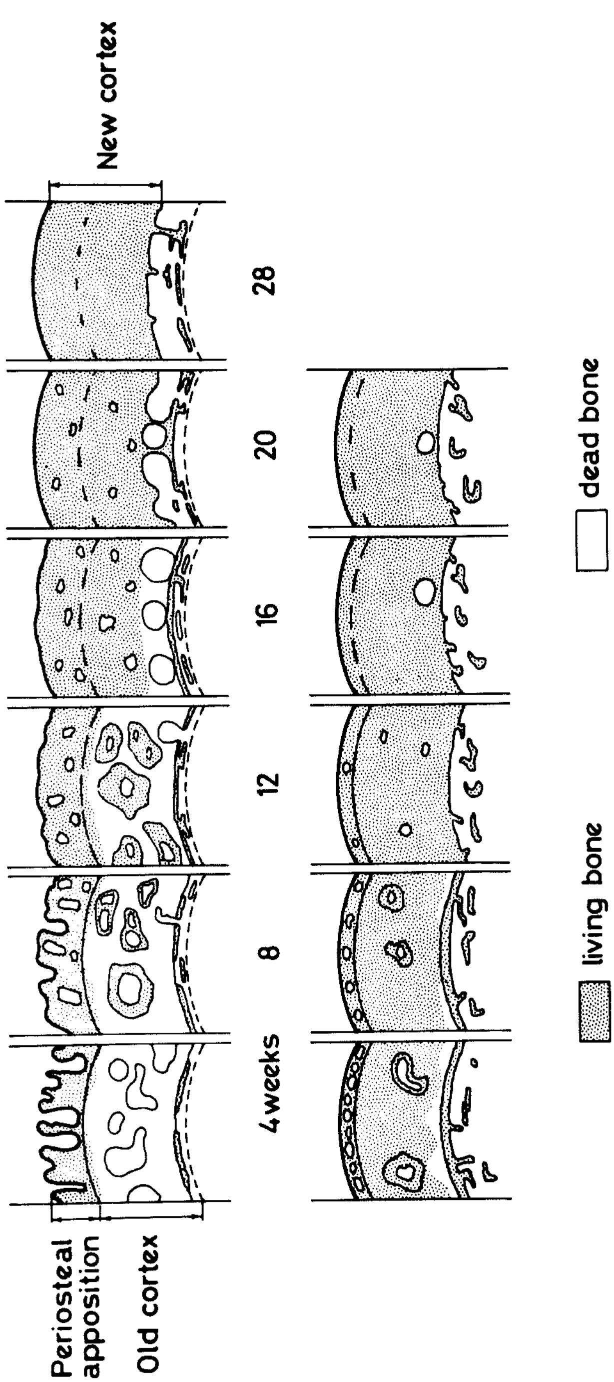

Figure 1. Diagrammatic representation of the changes in the femoral cortex of beagles in the period 4–28 weeks after insertion of acrylic cement (top row). The bottom row illustrates the changes seen after the control operation.

layer about 50 μ thick in which small islands of newly-formed bone were seen; the islands were surrounded by active osteoblasts. Against the inner aspect of the cortex a thin layer of immature bone was deposited. In contact with the implant (foreign body) giant cells were seen occasionally. At the periosteal side of the cortex a broad fringe of immature bone had formed, consisting of radially orientated trabeculae.

Mention should be made here that the following criteria were applied to distinguish immature bone: an irregular non-lamellar structure, large and irregular osteocyte lacunae, stronger P.A.S.-reactivity and, in microradiographs, a greater density of mineral in the matrix.

The appearance of the cortical bone during the following weeks underwent a number of developments, which in the outer part were quite different from the changes in the inner part. In the outer half, 8 weeks after operation, a definite formation of new, immature, bone could be discerned. This process of replacement went on continuously, the formation of immature bone soon being superseded by the formation of mature lamellar bone arranged in Haversian systems. At 16 weeks the outer half of the cortex was completely remodeled to normal living Haversian bone.

In the inner half no new formation of bone was seen (Figure 3). The resorption cavities became larger and more numerous. Merging of cavities eventually resulted in the presence of one large concentric cavity at 28 weeks. The cavity was about 500 μ across and filled with bone marrow.

In the area between cortex and methacrylate the formation of bone, starting from the isolated islands seen at 4 weeks, continued in such a way that after 28 weeks a cylindric bone sheath had formed, 50–100 μ thick (Figures 4 & 5). This sheath was only separated from the

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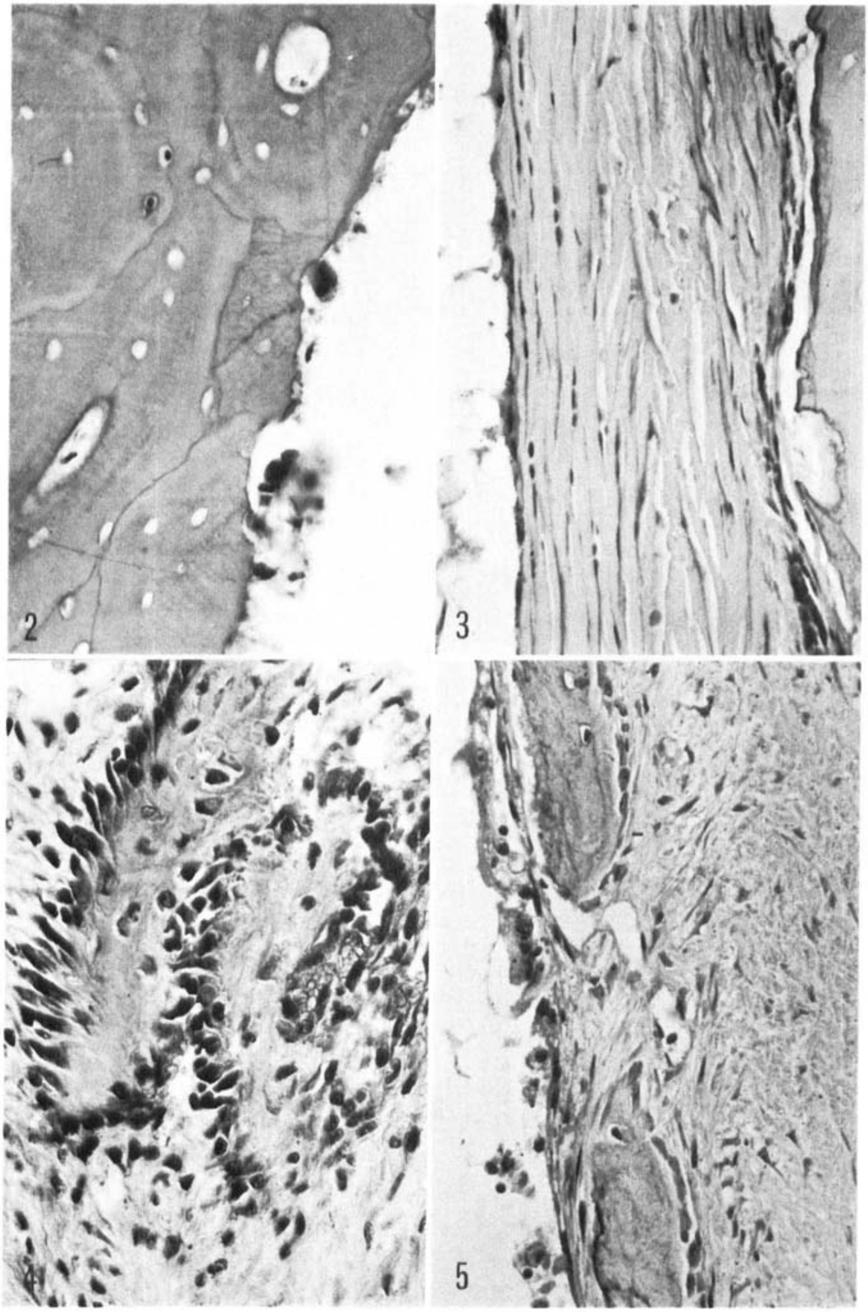
Figure 2. Endosteal part of the necrotic femoral cortex 4 weeks after insertion of acrylic cement. 300 ×. Hematoxylin-phloxin. Irregular profile as a consequence of osteoclasia.

Figure 3. Endosteal part of the necrotic femoral cortex 8 weeks after insertion of acrylic cement. 200 ×. Hematoxylin-phloxin. Between the irregularly eroded bone surface and the (dissolved) acrylic cement a layer of connective tissue and some fluid is present.

Figure 4. Newly-formed islands of bone around the cement 12 weeks after insertion. 250 ×. Hematoxylin-phloxin.

Figure 5. The same as Figure 4. Between the cement and the islands of bone multinucleated giant cells are seen. 200 ×.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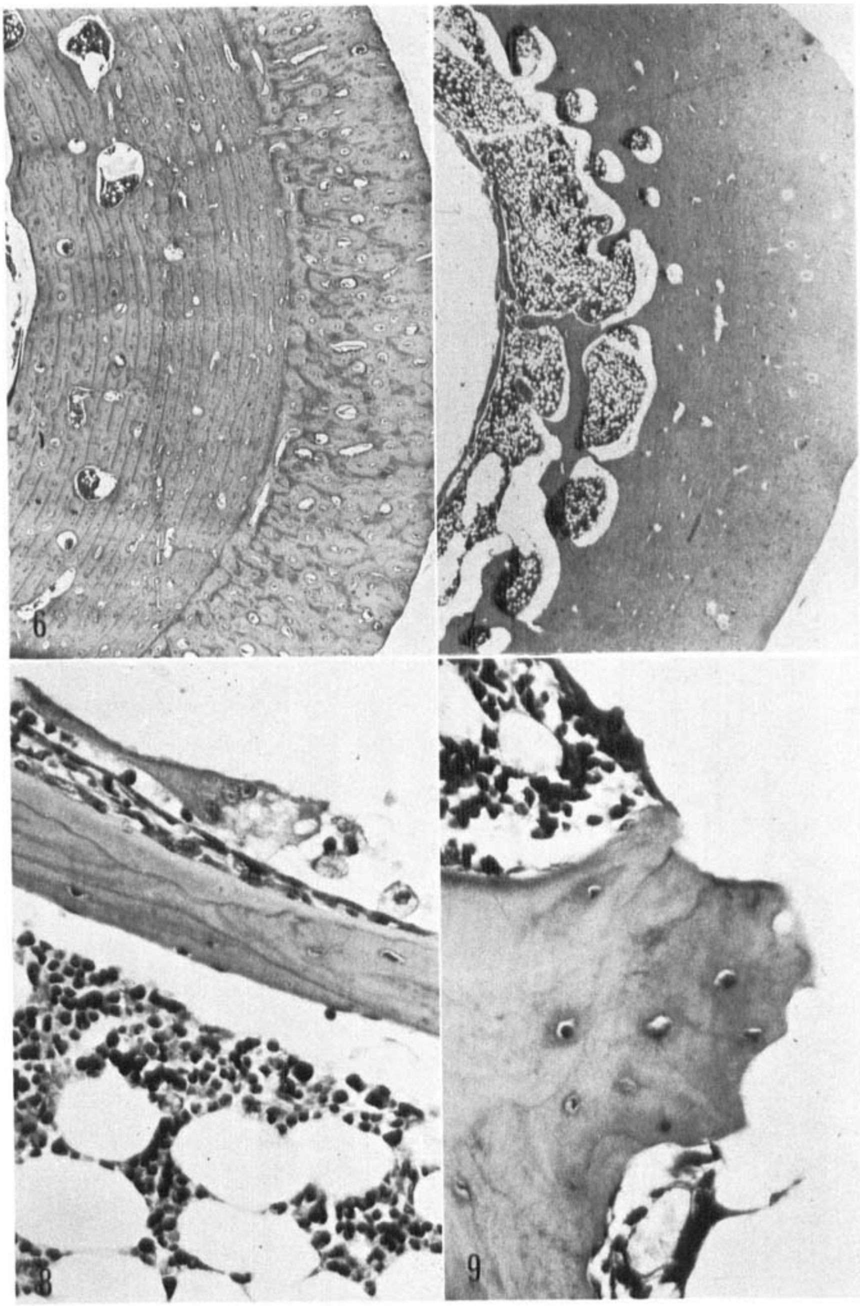
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methacrylate by a thin layer of connective tissue containing multinucleated giant cells.

The thin layer of bone which was deposited against the inner surface of the cortex during the first weeks increased in width until about the 16th week, but subsequently was broken down as the inner half of the cortex gradually became resorbed. As a consequence of the concurrent processes of breakdown and new formation the situation arose that the above-mentioned bone sheath came to border on the large cavity arising from the continuous resorption of the inner part of the cortex (Figures 7 & 8). The contact between the sheath and the remainder of the cortex was then all but lost. Against the implant an almost continuous layer of multinucleated giant cells was present, separated from the bone sheath by a connective tissue layer of some tens of microns in thickness.

The periosteal fringe of newly-formed bone became more compact by the deposition of lamellar bone. Remodeling processes resulted in a completely lamellar structure (Figure 6), the osteons being completely integrated with those of the pre-existing cortex 20 weeks after operation.

In the control experiments, in which the bone marrow was removed but not replaced by methacrylate, the course of the alterations in the period 4–28 weeks showed only a few similarities with the processes observed after the insertion of methacrylate. Bone necrosis remained limited to a few small areas in the inner cortex. Consequently remodeling was almost absent and only a few small cavities remained. Deposition of a layer of new bone at the endosteal side took place to the same extent as seen after methacrylate insertion. This layer, however, was integrated into the cortex without formation of the characteristic concentric cavity. Periosteal bone formation was restricted to a layer the thickness of which was only about one-fourth of the corre-

Figure 6. The femoral cortex 16 weeks after the insertion of acrylic cement. An extensive apposition of bone on the periosteal side has taken place. 25 ×. Alcian-blue—P.A.S.-staining.

Figure 7. The femoral cortex 28 weeks after insertion of cement. An extensive formation of cavities in the inner cortex as well as the deposition of a bone sleeve around the methacrylate is observed. 25 ×. Alcian-blue—P.A.S.-staining.

Figure 8. The same as Figure 7. Detail of the bone sleeve. Between the bone and the acrylic cement a multinucleated giant cell is seen. 300 ×.

Figure 9. Site of contact between connective tissue and bone with acrylic cement (dissolved during preparation) after 21 months. The combined surface of the two tissues consists of serried concavities. Hematoxylin-phloxin. 300 ×.

sponding layer around the femurs on which the complete operation had been performed.

Series II. 24 hours–2 weeks and 10–21 months

The early stages (24 h–2 weeks) and the later stages (10–21 months) had to be studied in mongrel dogs because pure-bred beagles were not available.

After 24 h there were a few small hemorrhages. None of the alterations described above were seen.

After 2 weeks a small scale osteoclasia was apparent at the inner surface of the cortex. On the eroded surface osteoblasts had in a few places started to deposit the new bone seen in the stages from 4 weeks onward. Between the cortex and the methacrylate a thin layer of connective tissue was seen containing a few young thin bone trabeculae.

The osteocytes in the cortex showed signs of degeneration. Both from the outside and from the inside incipient resorption was observed in the form of small penetrating cavities. At the periosteal aspect there was a 400 μ thick ring of newly formed bone consisting of radial trabeculae of immature bone, each trabecula surrounded by active osteoblasts.

Two weeks after the control operation the most important feature was the beginning erosion of the inner surface of the cortex by osteoclasts, followed by the deposition of a rather broad layer of young bone. The osteocytes in the cortex were alive. Periosteally, a layer of new bone had formed the thickness of which was only 1/10 to 1/5 of that after the insertion of methacrylate.

These pictures from the first weeks agree with those of the period between 4 and 28 weeks. Thus, in the early phase it seems of minor importance that mongrel dogs had to be used instead of beagles.

Experiments dealing with the later stages (10–21 months) and performed on mongrel dogs are of limited value. The results varied to such an extent that a chronological sequence of the stages was not clearly reflected in the microscopic pictures. It is highly probable that this variation is due to the heterogeneity of the dogs as regards breed and age.

Even so, a number of observations could be made on the animals in this group, yielding a picture broadly in agreement with the course of events observed in the beagles in series I (4–28 weeks). The outer shaft diameter had increased by 1–3 mm. The cross section of the marrow cavity was in most cases also enlarged even though to a smaller extent than the outer diameter. This points to a definite periosteal apposition and an (even if less extensive) endosteal breakdown. Histologically it was not possible to delimit new formation from the remodeled "old" cortex.

In six out of the eight dogs the histological pictures were in accordance with the development in the period 4–28 weeks observed in beagles: a circular bone sheath had formed which had lost contact with the inner aspect of the cortex. In three out of these six animals the sheath was complete; in the other three only isolated islands of bone were present. In all eight animals remains of necrotic bone were seen in the cortex; signs of remodeling and the formation of cavities were also observed. Multinucleated giant cells with a strongly vacuolated cytoplasm were present in all eight dogs in the 10–21 months series. These cells were always lying in close contact with the acrylic cement, i.e. inside the connective tissue layer surrounding the cement. Also in close contact with the polymer, eosinophilic, amorphous material was seen, probably representing accumulations of a protein-rich exudate. Frequently, both giant cells and exudate showed strings of convex indentations (Figure 9), a configuration which points to a typical shape of the surface of the (dissolved) methacrylate, consisting of sphere segments (Charnley 1970). This phenomenon was also seen in beagles 20 weeks after the operation. In the animals killed after 21 months the same profile, consisting of convexities, was seen in several places at the bone surface in direct contact with the methacrylate. This points to a direct contact between bone and cement. In some places the convexities in the tissue surface, alternately consisting of giant cells and bone, formed a sort of continuous garland.

DISCUSSION

A number of the changes described in this paper have been reported in the literature. Necrosis of a part of the cortex in implantation experiments has been mentioned by a number of authors (*inter al.* Wiltse et al. 1957, Rietz 1968, Slooff 1970). Necrosis after the insertion of acrylic cement in man has been described by Charnley (1971).

Periosteal bone formation in man after the insertion of an intramedullary nail was seen by Küntscher as early as 1941. Periosteal bone apposition under experimental conditions was seen by *inter al.* Trueta & Cavadias (1955) and by Danckwardt-Lillieström et al. (1970). The latter authors made it seem plausible that necrosis of the cortex is largely due to the disturbance of the marrow circulation. If care were taken to prevent an increase in intramedullary pressure during the insertion of a foreign body, bone necrosis remained restricted to a few small areas. It could be shown that when intramedullary pressure in increased fatty marrow were pressed into the Haversian canals, there resulted a massive blocking of the blood vessels.

In the experiments described in this paper an extensive cortical necrosis was seen. Since necrosis in the control experiments was very limited and precautions were taken to prevent an increase in intramedullary pressure it can be concluded that the extensive cortical necrosis seen after insertion of cement was only to a minor degree due to the trauma of the operation or to disturbance of the circulation. Cortical necrosis is therefore largely attributable to unfavorable factors in connection with the insertion of methacrylate: viz. the rise in temperature, and the leakage of monomer and other components.

The question as to what extent long term chemical effects play a role cannot be answered with certainty. The presence of chemical agents derived from the cement seems likely, judged from the occurrence of multinucleated giant cells with a vacuolated cytoplasm after 8 weeks. Multinucleated giant cells in direct contact with the acrylic cement were also seen by Debrunner (1953) and by Charnley (1970). The presence of this type of cells points to the liberating of chemical components which can be resorbed by phagocytic elements (Mittelmeyer & Singer 1956).

A fluid layer around the implant, as seen in the present investigation, is also described by Contzen et al. (1967) around polymers implanted in soft tissue. Possibly the occurrence of exudate also has to be looked upon as a sign of chemical irritation. The formation of connective tissue around various types of implants, *inter al.* bone, has frequently been described (Slais 1959, Rietz 1968).

A bone sheath formed around an implant has also been described. Trueta & Cavadias (1955) and Rietz (1968) have observed such a structure around metal nails inserted in the bone in experimental animals. Collins (1953, 1954) and Thompson (1954) observed it around metal implants in man. Around implanted acrylic cement in human bone, Willert (1972) observed a rearrangement of bone trabeculae in such a way that new trabeculae had formed parallel to the surface. A tight-fitting bone sleeve around acrylic cement, as seen in the present study, has not previously been described to the authors' knowledge.

The concavities seen at the inner surface of the bone sleeve 21 months after the operation, the effect of a close contact with the methacrylate, have not previously been described either. The bone substance of the sleeve seems to have formed in a normal intramembranous fashion. Metaplasia of fibrous cartilage into bone as described by Charnley (1970) was not seen.

It seems probable that the formation of the bone sheath around the inserted acrylic cement is somehow related to a continuous stimulus caused by weak mechanical forces. The sheath is formed in proportion as the cortex loses its contact with the implant by progressive necrosis. The fixation of the implant tends to deteriorate by bone necrosis, but in a way this function is taken over by the bone sheath.

Although the circumstances of the experiments described here differ from those of patients with total hip replacement arthroplasty, some features suggest that a similar reaction pattern is found in man. The relevant data are given in the aforementioned papers by Küntscher (1941), Collins (1953, 1954), Thompson (1954) and Willert (1972) and in a study by Lindwer (1972). Such a similarity would mean that the fixation of the total replacement arthroplasty goes through a critical phase, namely during the period when resorption and remodeling of necrotic bone is taking place but before a supporting bone case has formed. The practical question should be asked as to whether during this period loading of the prosthesis should not be limited as much as possible. Taking account of these considerations it seems advisable not to mobilize patients at too early a stage and to refrain from letting the patient walk without crutches after only a few monhs.

SUMMARY

Using dogs as experimental animals, polymerizing methylmethacrylate was inserted into the marrow cavity of the femur. The influence on bone over a period of 21 months was studied by means of histological techniques and microradiography. To distinguish the effect of the methacrylate proper from the circulatory disturbance resulting from the operation, control experiments were performed in which the marrow cavity was emptied, but no acrylic cement was inserted.

Polymerization of the methacrylate *in vivo* resulted in a local rise in temperature to about 58° C.

In the femurs containing the acrylic cement a consistent picture developed, consisting of: a) necrosis and removal of the central part of

the cortex and b) apposition of a thick layer of bone on the outer surface of the cortex, c) deposition of a cylindrical bone sleeve in contact with the methacrylate. In the control experiments only a minimal resorption at the inside surface of the cortex and the deposition of a thin layer of bone at the outside of the cortex were observed.

It is concluded *inter al.* that circulatory disturbance contributes only slightly to the total reaction of bone to the insertion of methacrylate.

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Key words: acrylic cement; bone remodeling; total hip replacement

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