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The Effect of Polymethylmethacrylate on Bone: an Experimental Study

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Summary. In order to assess the response of bone to low-viscosity polymethylmethacrylate, CMW or Simplex acrylic cement was digitally packed while in a doughy state into drill holes in the proximal diaphysis in each of four long bones (humeri and tibiae) of mongrel dogs. Histological assessment was performed in areas of minimal load at the interface between the viscoelastic bone and the acrylic cement. Decalcified and undecalcified sections were evaluated and a remodeling or activity index calculated. Fluorescent labeling studies were performed in order to assess bone growth. Animals were killed at 2, 4, or 5 months. Histological analysis showed a thin connective-tissue membrane containing scattered giant cells and histiocytes at the bone-cement interface. Inflammation was not an important facet of this response. The marrow and trabecular bone were viable, except for scattered localized areas of marrow necrosis and fibrosis immediately adjacent to the cement. The bone adjacent to the cement showed a lower remodeling or activity index, fewer fluorescent bands, and smaller distances between successive bands, suggesting decreased bone formation and turnover. The etiology of these findings may include a vascular disturbance secondary to disruption of the cortical and marrow circulation, temperature effects during cement polymerization, and/or chemical effects from the acrylic monomer.

A number of investigators have reported on the reaction of bone to acrylic cement in the loaded state [1–6, 8–12]. Charnley [1] described the histological changes of bone in contact with acrylic cement at postmortem in 23 patients who had had an uneventful clinical course for up to 7 years after implantation of an artificial joint. He observed a 0.5-mm thin layer of necrotic bone near the acrylic cement surface. At the interface between the bone and the cement a connective-tissue membrane had formed which, in non-weight-bearing areas, contained foreign-body giant cells. There was no evidence of chronic inflammation. Fibrocartilage developed in the weight-bearing areas by metaplasia induced by mechanical pressure. Charnley considered this fibrocartilaginous layer essential for load transmission. New bone formed within this fibrocartilage and replaced the necrotic osteons adjacent to the cement.

Willert et al. [11, 12] studied the histological reaction of bone to acrylic cement in cases of uni- or bipolar hip arthroplasty. They described three histological phases which occurred over several years: the phagocytic phase, the repair phase, and the phase of stabilization.

Freeman et al. [5] felt that the macrophage and the osteoclast were the key cells at the bone-cement interface that were responsible for the lucency in total knee replacements.

Sloof [10] and Lindwer et al. [6] documented the histological reaction of bone to acrylic cement introduced into the medullary cavity of the canine femur. Feith [4] utilized the medullary canal of the rabbit for similar studies. In the experiments of these investigators, the cement implant which filled the femoral medullary canal functioned as a load-sharing device in a way similar to that of an intramedullary nail. Although their histological findings were comparable, these investigators disagreed on the etiological factors.

Radin et al. [8] commented on the radiographic, histological, mechanical, bacteriological, and chemi-

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cal changes around the components in a plastic-on-metal hip replacement in sheep. They felt the mechanical properties of the interface (decreased torsional rigidity) were related to bone resorption and to the development of a fibrous bone-cement interface with subsequent loss of mechanical integrity.

The previous studies on the effect of acrylic cement on bone did not separate two significant variables, namely, the primary effects of acrylic cement on bone and the possible secondary effects of load transmission on this primary interaction. This experimental study was therefore undertaken to define the histological reaction of bone to acrylic cement in the minimally loaded state.

Materials and Methods

Four mongrel dogs were used in the study. In order to use an area in bone relatively free of internal stresses we chose the proximal humeral and proximal tibial metaphysis at a point away from the tension-and-compression trabecular system. With the dog under general anesthesia and in an aseptic environment, the lateral cortex of the proximal tibial and proximal humeral metaphysis was exposed. At a predetermined point the lateral cortex was pierced with a 3.5-mm drill bit. A sharp curette was then used to create a uniform pear-shaped defect, approximately 2 cm × 1 cm × 1 cm, in the underlying cancellous bone. The defect was cleansed of debris with physiological saline and was ready for implantation of acrylic cement when it had been completely dry for a 5-min period. CMW (first tibia, first humerus) or Simplex (second tibia, second humerus) acrylic polymer was mixed with the monomer, and when the cement was doughy it was finger-packed into the defect. Excess cement was carefully removed from the area. The wound was then closed in layers.

Postoperatively, the limbs were not protected, and the animals were allowed to bear weight at will. Routine clinical examinations were carried out to ensure adequate mobilization and good health. The animals were killed at 2, 4, or 5 months following the operation.

Beginning 6 weeks prior to their being killed, the animals were given intravenous fluorochrome labels on a weekly basis. This consisted of calcein (2 weeks), alizarine (2 weeks), and tetracycline (2 weeks). Labeling for 2 consecutive weeks was performed to ensure adequate fluorochrome incorporation. Animals were killed 1 week after the last intravenous label.

After the dog had been killed the appropriate bone was removed and cut on a band saw into suitable longitudinal and transverse sections of the cemented area, surrounding bone, and soft tissue. Decalcified specimens were prepared using a routine celloidin double-embedding technique, cut into 5-μm sections with a sledge microtome (Leitz), and stained with H and E and WHO. Undecalcified sections were embedded in butoxymethanolglycolmethacrylate, cut into 6 to 7-μm sections using a Yung K microtome, and mounted unstained, then stained with toluidine blue and H and E. During the preparation of the specimens, methylmethacrylate was dissolved away by immersion of the specimen in methylmethacrylate monomer inhibited by 25 ppm hydroxyquinone.

Decalcified sections were examined for evidence of bone and marrow necrosis, repair, and membrane formation. The number of histiocytes, giant cells, polymorphonuclear leukocytes, lymphocytes, and plasma cells was assessed in the area surrounding the cement. The sections were examined for birefringent material using polarized light. A four-grade semiquantitative system was used in the histological assessments of the components of the reaction mentioned above: 0 = none, 1 = minimal, 2 = moderate, 3 = severe.

Undecalcified sections of the bone stained with toluidine blue were examined for the percentage of trabecular bone which was inactive or resting, or covered by osteoblasts and osteoclasts. A remodeling or activity index was calculated by observing 100 equally spaced areas along the endosteal surface with an eye-piece micrometer.

$$\frac{\text{osteoblasts + osteoclasts}}{\text{osteoblasts + osteoclasts + resting bone}}$$

Undecalcified, unstained sections were observed under a Leitz microscope with fluorescent equipment. With an eyepiece micrometer and 1000× magnification, the number of fluorescent bands and the distance between successive bands were documented, using averaged data on five measurements. In the calculation of the activity index and in the fluorochrome studies, counts taken in the bone immediately surrounding the cement were compared with counts taken in an area deeper in the bone, away from the cement.

Results

Radiology

Fine-detail radiographic examination of the bones revealed that the more radio-opaque cemented area had merged gradually with the surrounding bone (Fig. 1). Occasional radiolucent small "cysts" were seen in this area, corresponding histologically to areas of deeper cement penetration into the surrounding cancellous bone (Fig. 2).

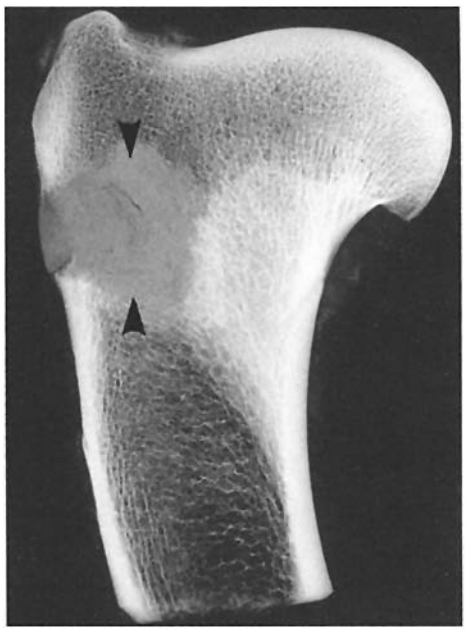

Fig. 1. X-ray of section of humerus with cement plug in situ. *Arrows* point to interfaces examined, which were minimally loaded

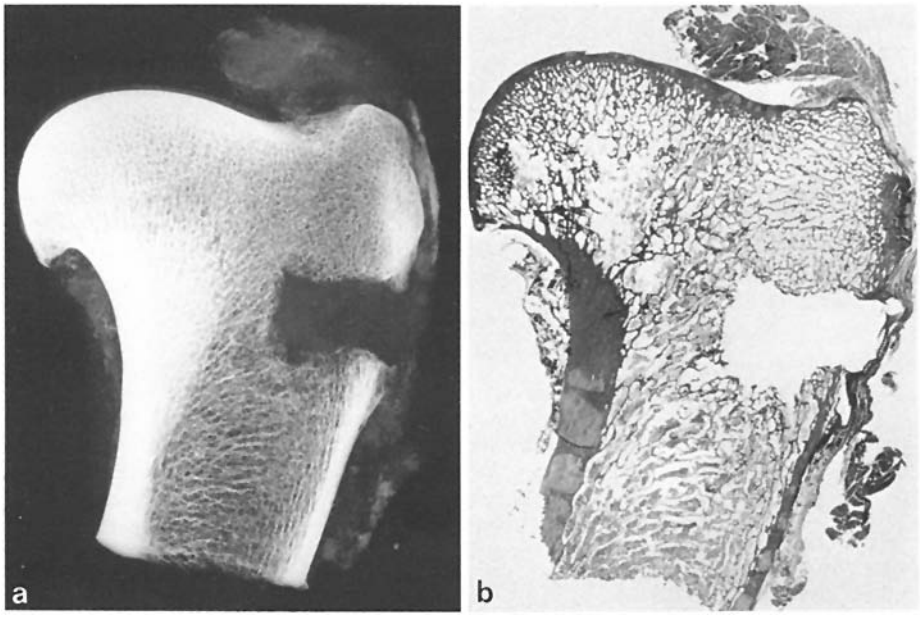

Fig. 2a, b. X-ray (**a**) and histological section (**b**) of humerus with cement implant dissolved away. Note the lucent spaces left by the intruded cement around the main bolus

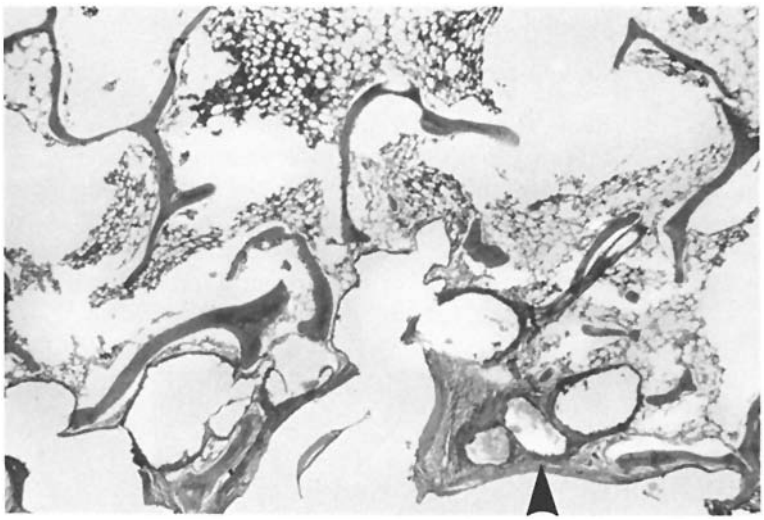

Fig. 3. Cement-bone interface (located at the bottom of this photomicrograph). Note the fibrous tissue lining membrane, "cement cysts" containing remnants of polymethylmethacrylate *(arrow)*, and viable trabeculae and marrow abutting the interface. WHO, × 19

Histology

On microscopic examination of the 4- and 5-month animals, the cement was bordered by a thin layer of connective tissue which contained a few histiocytes and multinucleated giant cells. A minimal number of acute and chronic inflammatory cells were observed within this layer (Figs. 3–5). The cells were scattered and were not arranged or concentrated in any area.

Outside of the connective-tissue rim, viable trabecular bone was found with little evidence of necrosis. Viable marrow elements were noted extending to the connective-tissue membrane (Fig. 3). However, localized areas of marrow fibrosis or atrophy could be found within 500 μm from the implant. Although histiocytes and multinucleated giant cells were also located in the marrow space immediately adjacent to the membrane, their occurrence in the marrow rapidly diminished toward the deeper bone, away from the implant. Inflammatory cells were notably absent in this area.

Small remnants of acrylic cement were found in the marrow spaces and in the haversian canals, often up to 1 mm from the connective-tissue rim, indicating fingerlike penetration beyond the confines of the main bolus. The cement plugging the haversian canals resulted in localized areas of bony necrosis. In these areas the cement was in intimate contact with bone with no intervening cellular reaction. When located in the cancellous marrow, a localized histiocytic and giant-cell response was noted, with adjacent areas of marrow atrophy and fibrosis.

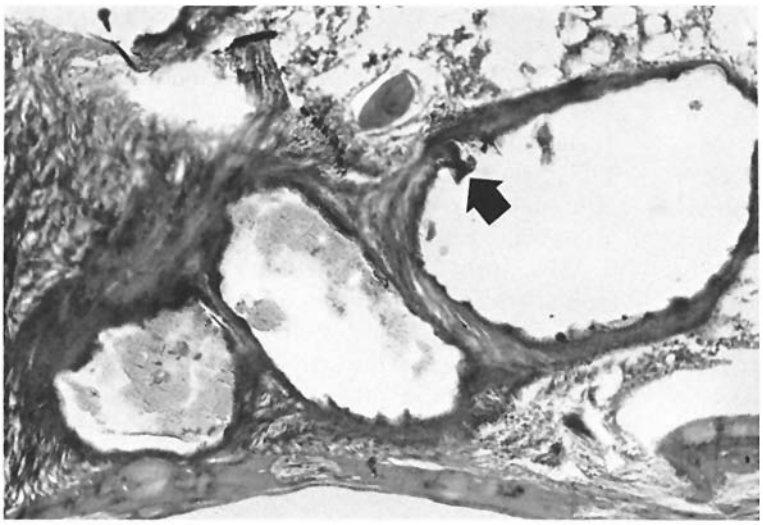

Fig. 4. Higher power photomicrograph of Fig. 3. Polymethacrylate remnants are surrounded by fibrous connective tissue. A giant cell is noted *(arrow)*. WHO, × 190

Fig. 5. The membrane at the cement-bone interface. Fibrous tissue is seen, with several multinucleated giant cells *(arrow)* abutting cement remnants. WHO, × 300

Polarized-light microscopy failed to reveal any birefringent material in the bone or the surrounding soft tissues. In particular, the gray-green amorphous material representing cement remnants was not birefringent. No differences were noted in the histological assessments between animals receiving CMW or Simplex cement implants. The animal killed at 2 months showed a similar but less developed histological response around the implant. The fibrous membrane was more poorly defined, although the same complement of cells was noted as in those animals killed later.

Activity Index

The paired *t*-test was used to compare the activity indeces in the bone immediately surrounding the cement implant and in the bone distant from the cement. Significantly less remodeling (lower activity index) was found in the bone surrounding the cement implant than in the area away from the cement ($P < 0.01$).

Fluorescent Labeling

Fewer fluorescent bands were seen in the area adjacent to the cement implant than in the bone distant from the implant. The bands in the area adjacent to the cement were generally more fuzzy and indistinct and were separated by smaller distances. As the number of animals was small, no statistical analysis could be performed on these factors.

Discussion

This study has shown that the bone adjacent to a minimally loaded acrylic cement implant undergoes a

characteristic histological reaction. This is manifested by the encapsulation of the cement by a thin, delimiting connective-tissue membrane which contains scattered histiocytes and giant cells. Inflammatory cells were infrequent, which indicates that inflammation is not an integral part of this reaction. The presence of the histiocytes and giant cells denotes a foreign-body reaction. The connective-tissue membrane did not contain synovial-like cells or fibrocartilage, which would suggest motion, as previously reported, in areas surrounding inadequate screw fixation in bone [9], or fibrocartilaginous tissue, as reported by Charnley [1], which would suggest weight-bearing and local pressure. We therefore conclude that this cement plug was minimally loaded and did not undergo motion.

Although localized areas of marrow necrosis were found surrounding the cement implant, viable marrow elements were found in most areas right up to the connective-tissue membrane. This finding makes it unlikely that the cement was elaborating harmful materials. The minimal bony necrosis noted in the cortical bone was associated with cement plugs located in the haversian canals adjacent to the cement implant. This is most likely the result of the digital pressing of the doughy cement into haversian canals communicating with the implant. One may speculate that with the increased use of low-viscosity cement inserted under higher pressure increased ischemic necrosis of the surrounding bone will result.

Determination of the bone activity index and the fluorochrome labeling studies suggest that decreased bone formation and turnover occurred in the bone immediately surrounding the cement implant. One of the authors (JS—unpublished studies) has shown that drilling a long bone does not incite a fibrous tissue membrane or a foreign-body reaction or lead to decreased bone formation. Indeed, active remodeling and new bone formation have been found in bones that have been drilled without cement implantation as early as 2 weeks later [6]. Therefore, the histological and metabolic changes in bone found in this study cannot be accounted for by mechanical injury alone. Vascular disturbances caused by acrylic cement plugging the haversian systems may be responsible; however, temperature effects during polymerization cannot be ruled out. Whether the monomer escaping after implantation of acrylic cement contributes to the tissue changes is not certain. The presence of viable marrow elements right up to the delimiting membrane makes it unlikely, however, that cement by-products are detrimental. Our results agree with those of Radin et al. [8].

Several investigators have commented on the highly refractile nature of methylmethacrylate under polarized light [2, 7]. Our studies do not substantiate this finding. Indeed, cement remnants located in the tissues under transmitted light were not refractile under polarized light, and acrylic cement scraped from failed prostheses and ground up into small particles is not refractile under polarized light.

This study has defined a baseline histological primary reaction of bone to acrylic cement in the minimally loaded state. With this knowledge at hand one can distinguish the effects of other superimposed variables, such as the tissue response to acrylic cement under load or polyethylene wear debris, when considering cemented prosthetic implants. These studies are currently being done by our group and will be reported on later. The addition of other superimposed variables on the pure response to a minimally loaded cement implant may account for the differences in the histological findings between those reported in this study and those mentioned previously.

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