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Comparison of a polymethylmethacrylate and glass-ionomer bone cement using a hemiarthroplasty in the rabbit femur

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Polymethylmethacrylate (PMMA) bone cements present various problems with respect to biocompatibility and stability. In order to study the histological changes at the bone–cement interface following total hip replacement, a small animal model was created by implanting hip prostheses using two different bone cements (PMMA and glass-ionomer cement, GIC). Two problems with the use of GIC for fixation of the prosthesis became evident. One year following implantation, histomorphometric analysis of femurs containing the GIC demonstrated significantly higher amounts of osteoid at the bone–cement interface. This disturbance of mineralization is comparable with osteomalacia and probably due to leaching of aluminum ions. In addition the mechanical properties of GIC proved to be inadequate for the loads placed upon it in this hip replacement model.

1. Introduction

Despite their use in clinical practice over a period of 30 years polymethylmethacrylate bone cements (PMMA) continue to present various problems with regard to biocompatibility and stability. Much research has been conducted to find ways to reduce cortical damage during *in vitro* curing, and to reduce leakage of toxic chemicals (e.g. methylmethacrylate [MMA] monomer, N,N-dimethyl-p-toluidine (DMPT)). Modifications of the application of PMMA bone cements, e.g. high-pressure techniques [1], vacuum application [2], centrifugation [3], as well as variations of composition have been tested. Bone cements have been reinforced with carbon [4], or polyethylene fibres [5] to improve mechanical properties. Other PMMA bone cements have been mixed with materials like tricalciumphosphate [6], carboxy methyl cellulose [7], bone particles [8], and other materials permitting tissue ingrowth into the cement in order to maintain long-term stability. Combining glass particles or hydroxyapatite with PMMA resulted in "bioactive-cements" [9, 10]. Recently, new formulations of bone cements, e.g. polymethylmethacrylate polymer powder with n-butyl methacrylate monomer (PEM/BMA) and methylmethacrylate/n-decylmethacrylate/isobornylmethacrylate (MMA/DMA/IBMA) have been experimentally tested [11, 12].

"Glass-ionomer" (glasspolyalkenoate) cement as a possible alternative bone cement material has been discussed. Glass-ionomer cement (GIC) was introduced in 1969 and has been used in dentistry as a filling and luting material for more than 10 years [13]. These cements are formed by mixing a fluoro-alumino-silicate glass with a polycarboxylic acid. The glassy phase acts both as a filler and as a source of cations to crosslink the polymer chains. Setting of glass ionomer cements is based on a neutralization reaction (salt formation), whereas PMMA-cements set as a result of polymerization. The ionic setting reaction takes place without an essential temperature increase, and initiators or activators are not necessary. The most outstanding property is the excellent adhesion of the glass-ionomer to stainless steel alloys and bone tissue [14]. It is supposed that chemical bonds are formed between superficial calcium ions and carboxyl groups from the polymer chain [15, 16].

Few animal models currently exist to investigate the histologic changes in the bone–cement interface after hip-joint replacement [17, 18]. We performed hemiarthroplasties of the hip joints in rabbits because these animals are easy to handle, inexpensive, and histologic results of PMMA bulk testing in these animals already exist.

Our goal was to compare the biological response to intramedullarily inserted polymethylmethacrylate cement (PMMA = group I) with a newly developed "glass-ionomer" bone cement (group II) in a small animal model under load-bearing conditions.

2. Materials and methods

2.1. Animals and implant materials

We performed joint replacement operations on 12 female chinchilla rabbits, each having an average weight of 3800 g (range 3380–4471 g) and an average

0957–4530

age of 20 weeks. Each group contained six animals. The joint replacement consisted of a hemiathroplasty of the hip joint. In all cases the left femur was used.

The animals were maintained on a laboratory diet (Altromin^R) and water, *ad libitum*. For the first 6 months they were kept in single cages, and after a further 6 months in a free-range enclosure the rabbits were sacrificed. Anteroposterior roentgenograms of the hip joints were taken before, immediately postoperatively, and after 14, 84, 168 and 365 days. After removal of both femurs, anteroposterior and lateral roentgenograms were performed.

The prostheses were made of a cobalt–chromium–molybdenum–alloy (Dentitan^R, Krupp, Essen, FRG). Material content and mechanical properties of this alloy are outlined in Table I. After making models of a number of representative femur cavities of sacrificed animals, prostheses of various shaft lengths (32–35 mm) and diameters (measuring proximally between 3.5 and 4.0 mm, distally 3.0 and 3.5 mm) were produced. After sandblasting the shafts and polishing the heads of the prostheses, sterilization by autoclaving was carried out.

For implantation, either a PMMA bone cement (Refobacin^R-Palacos^R R, Merck, Darmstadt, FRG) or an experimental "glass-ionomer" cement (IONOCEM^R, Ionos, Seefeld, FRG) were used. The cements were mixed in accordance with the manufacturer's instructions. Mechanical properties of both cements are listed in Table II. The GIC-powder was a calcium–aluminium–fluoro–silicate glass, molten from SiO_2, Al_2O_3, CaF_2, Na_3AlF_6, AlF_3 and $AlPO_4$. The liquid consisted of an aqueous solution of a polycarboxylic acid (copolymer of acrylic and maleic acid) and tartaric acid.

2.2. Operative procedure

The animals were premedicated with 5 mg/kg subcutaneous (s.c.) xylazin (Rompun^R, Bayer, Leverkusen, FRG), and 25 mg/kg s.c. ketamine hydrochloride (Ketavet^R, Parke, Davis & Co., Berlin, FRG). Anaesthesia was maintained using small doses of a 1:1 xylazine–ketamine hydrochloride saline mixture which was given intravenously (i.v.) into the lateral auricular vein.

Each animal received a prophylactic dose of aminoglycoside antibiotic (10 mg/kg gentamycin = Gentasum^R, Albrecht, Aulendorf, FRG) prior to operation.

Using sterile technique, an arthrotomy of the left hip joint through an anterolateral approach was performed. The lateral surface of the hip was exposed by incising the tensor fasciae lata, and releasing the gluteus maximus and gluteus medius muscles from their points of insertion on the femur. After incision of the vastus lateralis and the opening of the joint capsule along the anterior aspect, the caput ossis femoris ligament was incised. By gentle external rotation, abduction and flexion the femur was then in each case dislocated. A resection of the femoral head using an oscillating saw was performed. After drilling into the proximal femur, the medullary cavity was prepared by manually brushing and irrigating with sterile saline. The femurs were filled from distal to proximal using a cement syringe, the implants were inserted into the cement bed and were axially compressed until the cement had cured. The head of the implant was then placed in the acetabulum. The hip joint ligaments and muscles were carefully reconstructed and sutured to their points of insertion. All rabbits recovered quickly and stood shortly after surgery bearing their full weight on both hind legs.

TABLE I Chemical composition and material properties of the cobalt–chromium alloy Dentitan^R

Co	69.5%
Cr	24.0%
Mo	4.5%
Ti	2.0%
E-modulus	220.000 N/mm^2
0.2% proof stress	min.370 N/mm^2
tensile strength	min.550 N/mm^2
elongation	15%
density	8.3 g/cm^3
hardness (Vickers)	300 HV 10

TABLE II Mechanical properties of the investigated bone cements (polymethylmethacrylate [PMMA] and glass-ionomer [GIC])

Parameter	PMMA	GIC
Compressive strength (MPa)	90	145
Flexural strength (MPa)	65	15
Tensile strength (MPa)	35	16
E-modulus (N/mm^2)	2300–5000	18000

2.3. Histologic evaluation

After 365 days the animals were sacrificed with an overdose of intravenous barbiturate (Narcoren^R = Pentobarbital, Rhone Merieux GmbH, Laupenheim FRG), and their femurs harvested.

The femurs containing the GIC-bone cement were manually cut with diamond saws in the middiaphysis and fixed for 4 weeks in 4% formaldehyde solution. They were then dehydrated in progressively increasing concentrations of ethyl alcohol up to 100%. Subsequent to serial dehydration, the bone-implant segments were immersed in acetone and embedded in MMA solution (methylmethacrylate Nr. 12244, Merck, Darmstadt, FRG). The solution was allowed to cure at 37 °C for a period of up to 10 days. The femurs were then cut perpendicularly to their long axes into six blocks (Fig. 1). These bone-implant segments were designated A, B, C, D, E and F from proximal to distal. Each block was mounted on a plexiglass slide with cyanoacrylic glue and cut into 100 μm sections using a semiautomatic sawing microtome (Exakt, Norderstedt, FRG). All sections were ground to a thickness of 30–50 μm with silicon carbide paper using a grinding machine (Exakt, Norderstedt, FRG).

The femurs containing the prostheses implanted with Refobacin^R-Palacos^R R were manually cut into six blocks (designated A to F). Following fixation in neutral, buffered formaldehyde solution according to

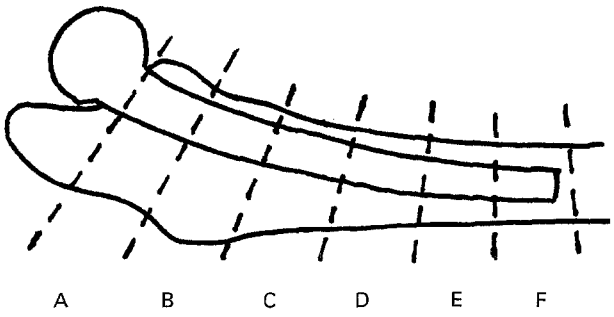


Figure 1 Schematic presentation of the bone-implant segments. The six blocks (A–F) with the undecalcified surrounded tissue were cut into thin sections for observation by light microscopy (LM).

LILLIE, specimens were dehydrated in increasing concentrations of ethyl alcohol (60 to 100%). The bone segments were then placed in a 1:1 solution of alcohol and a light-curing resin (Technovit^R 7200 VLC, Kulzer & Co GmbH, Wehrheim, FRG) to preserve the PMMA surrounding the implant. After three days of immersion they were placed in special moulds and mounted using glue (Technovit^R 7230 VLC, Kulzer & Co GmbH, Wehrheim, FRG). The specimens were then embedded in the above-mentioned resin (Technovit^R 7200 VLC). Light-curing was carried out in a photopolymerization apparatus (Histolux^R, Heraeus Kulzer GmbH, Hanau, FRG) in two phases. The curing was completed after approximately 10 h of exposure.

After cutting and grinding all sections, they were stained either with GIEMSA surface staining (Nr 9204, Merck, Darmstadt, FRG; containing eosin, methylene blue, methylene azure, methylene violet and distilled water) or, alternatively, with von KOSSA-Fuchsin solution [19]. Soft tissues and nuclei were differentiated according to the method of counterstaining selected.

The histologic sections were evaluated qualitatively and quantitatively using light microscopy (Orthoplan^R, Leitz, Wetzlar, FRG). They were examined qualitatively with respect to the general type and composition of the tissue at the cement–bone interface, to periosteal apposition and cortical remodelling. Evaluation of the sections was carried out at magnifications up to 400-fold.

The percentage of bone, osteoid, chondroid bone, soft tissue and bone marrow at the bone–cement interface was evaluated in a histomorphometric analysis. The images of the histologic sections were digitized using a videocamera (LDK 12, Philips, Eindhoven, Netherlands) connected to a microcomputer (PCD 3T, Siemens, Erlangen, FRG) and displayed on a monitor. Each section was evaluated (80 × magnification) by randomly placing a grid (0.35 × 0.35 mm) at 12 different locations at the bone–cement interface. The surface area of the above-mentioned tissues were manually outlined in different colours using a tracing device (SUMMASKETCH^R Plus, Summagraphics Co., Fairfield, USA). Measurements were converted to terms of percentage of total area of bone–cement interface. For each segment (A to F) means and standard deviations of each parameter were calculated. On the average, six histologic sections were evaluated for each bone segment. A total of 36 sections per animal was analysed. The significance of differences between the measurements was assessed with the Mann-Whitney U test.

3. Results

3.1. Complications

Two rabbits died intraoperatively during insertion of the PMMA-cement (group I). Immediate attempts at cardiopulmonary resuscitation failed. One animal with a glass-ionomer fixed implant (group II) was sacrificed at 18 days because of an accidental vertebral fracture. Another animal of group II developed osteomyelitis of the hip joint on the operated side which resulted in nearly complete loss of mobility of the hind leg.

Four animals in each group functioned well throughout the observation period and survived to the conclusion of the experiment.

Postoperative roentgenograms showed optimal position of the endoprostheses with good filling of the medullary cavity. In all cases the bone cement extended beyond the tip of the prosthesis. Neither prosthetic loosening nor broken prosthetic stems were observed. One animal out of each group suffered a cement fracture in the region of the distal stem of the prothesis. In two cases in each group, the heads of the endoprostheses were dislocated with consequent formation of a "neo-acetabulum" indicating normal weight bearing. All animals evidenced a stable prosthetic joint with a normal range of passive motion.

All implants were found to be well fixed after autopsy. In group II a colourless fluid was found in the hip joint. The joint fluid of the animals in group I was clear and greenish in colour. The joint capsule was thickened, scarred, and fibrotic in all operated joints in both groups.

3.2. Histologic examination

The histology of the four specimens of the PMMA-group was consistent throughout. A thin (10 to 20 cell layer) connective-tissue membrane surrounded the cement. Direct bone–cement contact was visible at only a few points (Fig. 2). Bone trabeculae exhibited regular mineralization; osteoid was minimal. In areas without direct bone–cement contact, marrow tissue bordered on a connective tissue membrane intervening between the cement and the marrow. The intact haematopoietic bone marrow contained only a few foreign body giant cells. No acute or chronic inflammation was seen.

The cement dough was complete in all sections, no cracks or clefts were observed in the cement in contrast to the GIC-group.

Cortical reaction (Fig. 3) was most pronounced in the segments E and F which showed periosteal apposition approximately exceeding 50% of the cortical thickness. In the segments A and B (the most proximal segments) only minimal cortical reaction was observed. Cortical thickness in the proximal parts was reduced in comparison to the contralateral femur.

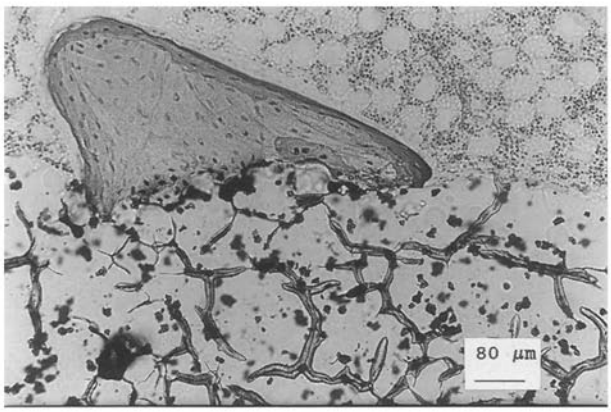
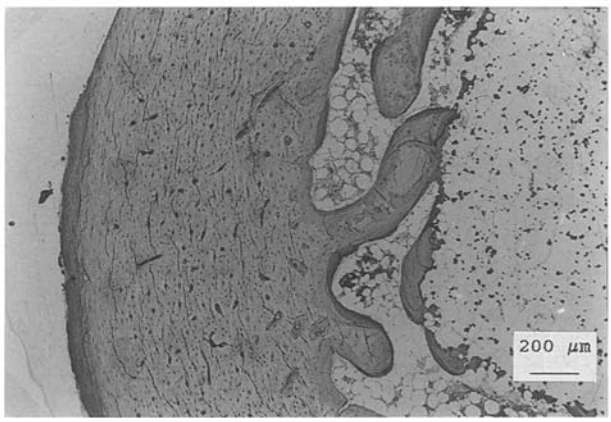


Figure 2



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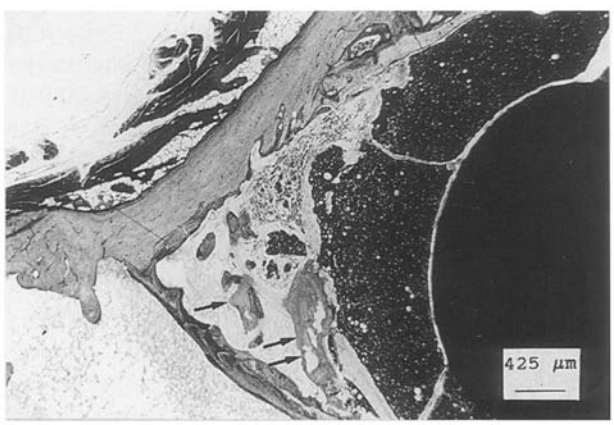

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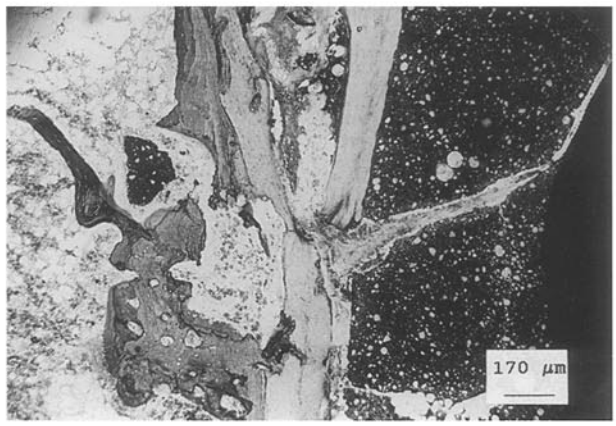

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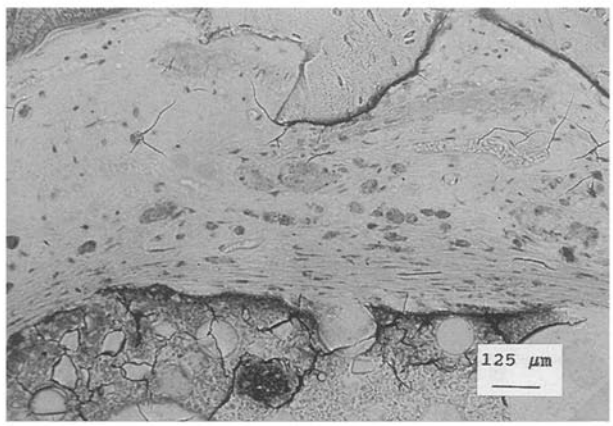

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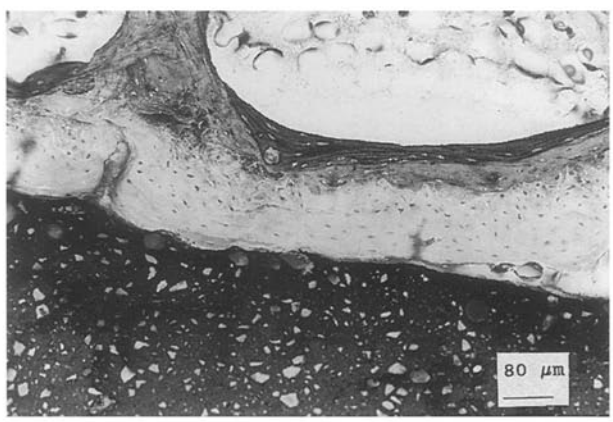

Figure 7

The most striking feature of the GIC-group was the presence of immature osteoid bone at the cement surface. In some spots osteoid was in direct contact with calcified bone tissue or separated by only a fibrous membrane adjacent to the surrounding bone marrow (Fig. 4). The bone cement showed cracks which at some places were invaded by soft tissue (Fig. 5). GIC particles were frequently observed at the surface of the bone cement.

Particles which were too large for phagocytosis were embedded in loose connective tissue (Fig. 6). Macrophages were frequently observed in the surrounding bone marrow. Only at a few places was bone in direct contact with the cement surface (Fig. 7). In the von KOSSA-Fuchsin stain the bone around the GIC-plug stained lighter brown and not dark brown/black. This picture suggests demineralisation of the bone.

3.3. Histomorphometric results

Histomorphometric analysis of the two types of bone cement revealed a higher percentage of osteoid bone formation at the GIC interface in all sections. The highest percentage of osteoid was found in segment C with 29.9 $\pm$ 17.7% of the measured area at the GIC surface. Segment C demonstrated the greatest percentage of osteoid at the PMMA surface; 2.8 $\pm$ 1.8%.

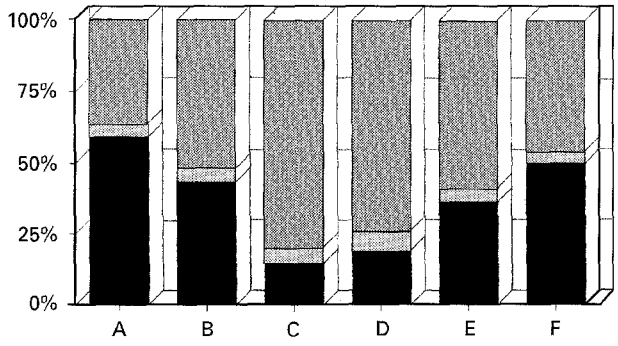

Figure 8 Results of the histomorphometrical analysis of the tissues at the bone–cement interface after 365 days of implantation of the PMMA-implanted prostheses (group I). Percentages of bone (■), soft tissue (▩) and bone marrow (▩).

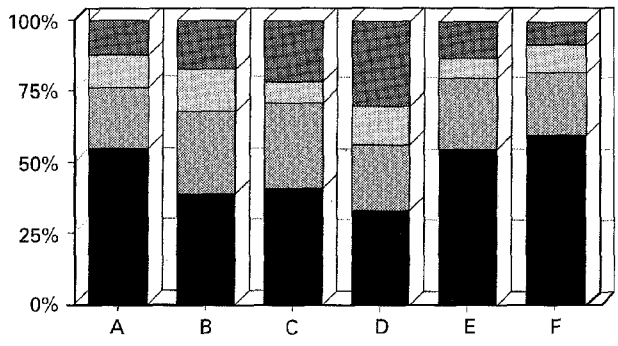

Figure 9 Results of the histomorphometrical analysis after 365 days of implantation of the GIC-implanted prostheses (group II). Percentages of bone (■), osteoid (▩), soft tissue (▩) and bone marrow (▩) found at the bone–cement interface.

The measured bone surface area in the PMMA-group (Fig. 8) was greatest proximally (59 ± 23.4% in segment A), and least in the middle sections (15.2 ± 13.7% in segment C). In the distal sections an increase of bone surface area was noted (49.8 ± 23.3%).

The distribution of bone surface area in the different sections in the GIC-group (Fig. 9) was more homogeneous. The greatest values were measured in segments F (60.2 ± 20.3%) and E (55.1 ± 22.8%), followed by segment A (54.9 ± 29.0%). The smallest bone areas were observed in the mid-prostheses (segment D) with a value of 33.2 ± 29.5%.

The amount of soft tissue in group I (PMMA) ranged between 4.1 ± 2.9% (segment F) and 7.1 ± 4.4% (segment D).

Measurement of soft tissue areas in group II (GIC) revealed values between 7.0 ± 5.4% in segment E and 14.9 ± 11.8% in segment B. In both groups no chondroid bone was found.

Application of the Mann-Whitney U test ($U \leqslant U^*$) to these data showed no significant differences at the 95% confidence level between the percentages of bone between the two groups. The GIC-group showed higher osteoid values in all segments, a result that was significant at the 95% ($0 \leqslant 5$) and the 99% ($0 \leqslant 1$) confidence level. Group II (GIC) gave specimens with soft tissue values greater than the specimens of the PMMA-group. These values were significantly different at the 95% confidence level ($1 \leqslant 5$) and the 99% level ($1 \leqslant 1$) as well.

4. Discussion

The small-animal model described in this paper is valuable because it approximates the mechanical demands on a prosthesis during recuperation from hip arthroplasty. In addition, the application of histomorphometric analysis allows the reproducible and quantitative evaluation of tissue reaction to different cements and prostheses. Two animals in the PMMA-group died during insertion of the bone cement, indicating the potential systemic risks of PMMA-cements. The exact pathophysiology is, as yet, unknown; and may be secondary to hypotension, negative inotropic and chronotropic effects, cardiac arrest, and/or thrombo-embolic events [20].

The glass-ionomer cements seem to have less systemic but more local side effects. This is probably the reason for the osteomyelitis observed in one animal of the GIC-group.

In both groups the radiographic changes at the bone–cement interface were quite similar. All animals demonstrated resorption of the calcar femorale. The significance of this radiological finding is not clear. Some investigators have thought that it represents an insignificant biological change [21]. Others believe that this is a direct manifestation of, or a precursor to movements of the prosthesis which are too small to be directly detected, which may, however, lead to gross displacements [22]. The difficulties of interpretation of the radiological changes underline the necessity of histological investigations.

Our histological results correspond with previous studies in rabbits [23, 24]. The reactions to PMMA bone cement have already been described by various researchers. Willert [25, 26] described the three fundamental stages of tissue reaction. The repair of postoperative tissue damage is followed by adaptation of the bone structure to the load transfer which results in a relatively stable implant bed. The permanent implant bed is established one to two years after cement insertion. It consists of a thin (0.1–1.5 mm) connective-tissue membrane with fibres oriented parallel to the surface. Only a few chronic inflammatory cells are observed in secondarily formed medullary cavities.

The most striking feature of the GIC-group is the abundant amount of osteoid tissue seen one year post-operatively. This is probably an expression of a disturbance of mineralization comparable to the osteomalacia produced by administration of Al and Mg antacids [27].

Albrektsson and Johansson demonstrated that aluminum leaking from titanium alloy implants resulted in an impaired bone formation in comparison to pure titanium implants. Hypothetically, aluminum may compete with calcium in apatite formation [28]. In previous experiments, we tested different ionomeric cement compositions with different setting characteristics and different powder-to-fluid ratios in femurs of Sprague-Dawley rats [29]. The osteoid regenerated increased with longer implantation periods. The best histological results were obtained by the compositions with the shortest setting times and the lowest powder to fluid ratio. With regard to clinical application

techniques, this suggests that the operative field initially must be dry, and after 10 to 15 minutes it must be moist. These prerequisites are seldom fulfilled in hip joint replacements. Our results are also contradictory to the studies of Jonck and Grobbelaer [15] who found no inhibitory effect on bone tissue development in baboons. In addition, no fibrous tissue interposition between the cement insert and the bone or its bone marrow constituents was observed.

We found cracks in the GIC-plug and loose cement particles in the surrounding bone marrow. This indicates that the mechanical properties of the glass ionomer cement tested are probably not sufficient for joint replacements and load-bearing conditions. Changing the composition of the glass component may improve the mechanical properties [14]. Desirable would be a reduction of the aluminum content in the ground glass resulting in an increase in the concentration of calcium. However, aluminum is necessary in the production of the setting reaction of glass ionomer cements.

The described rabbit hip replacement model offers the possibility of reliably studying different materials under load-bearing conditions. Histomorphometric analysis of the interface structures allows accurate and reproducible assessment of the quality of biological response to various implant materials. Cortical remodelling responses to different prostheses may also be studied.

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