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MORPHOLOGICAL CHANGES IN BONE FOLLOWING INTRAMEDULLARY IMPLANTATION OF METHYL METHACRYLATE

Effects of Medullary Occlusion: A Morphometrical Study

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Using a computerized, semi-automatic morphometrical system, the morphological effects on diaphyseal rat femur following intramedullary implantation of methyl methacrylate were studied. Furthermore a comparison with the effects of periosteal elevation and removal of the bone marrow by suction was made. The changes in bone morphology were studied with the aid of microangiography, microradiography, fluorescence microscopy and histology. The results showed that there were evident differences between the postoperative course of the three procedures regarding vascular changes in the femoral cortex, bone remodelling and extent and duration of cortical necrosis. Implantation of methyl methacrylate caused greater vascular disturbance than elevation of the periosteum and removal of the bone marrow.

Key words: bone cement; bone remodelling; circulatory disturbance; diaphyseal bone; microangiography; rats

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Methyl methacrylate has been used clinically as bone implant for about 30 years. However, implantation of methyl methacrylate into bone has certain side-effects . These have been related to the temperature rise while curing, the leakage of toxic monomer and the surgical trauma produced at the operation. The importance of each of these factors has been differently interpreted by different authors. Disturbance of the normal blood supply followed an intramedullary implant is part of the surgical trauma and exerts a prolonged effect on bone morphology (Canckwardt-Lilliestrom et al. 1970, Rhinelander 1973, Brookes & Gallannaugh 1975, Rhinelander et al. 1979). A tubular bone offers a good model for studying the adaptability of the vascular system and the effect on bone tissue that different degrees of severance to the normal blood supply causes.

The present investigation was undertaken on diaphyseal rat femur and the aim was to study the morphological effects of methyl methacrylate occlusion of the medullary canal of the femur.

In order to apply an objective, quantitative method for measuring the morphological bone changes a computerized, semi-automatic morphometrical system was used.

MATERIAL AND METHOD

One hundred and twenty young adult male Sprague-Dawley rats weighing 369 ± 17 g (mean ± S.D.) at the start of the experiment were used in the investigation.

Surgery was carried out under sodium pentobarbital anesthesia in the following ways:

I – *Sham operation (SO):* After skin incision and dis-

section through muscles and periosteum the bone surface of the femoral diaphysis was exposed. The periosteum was elevated around the entire diaphyseal bone surface.

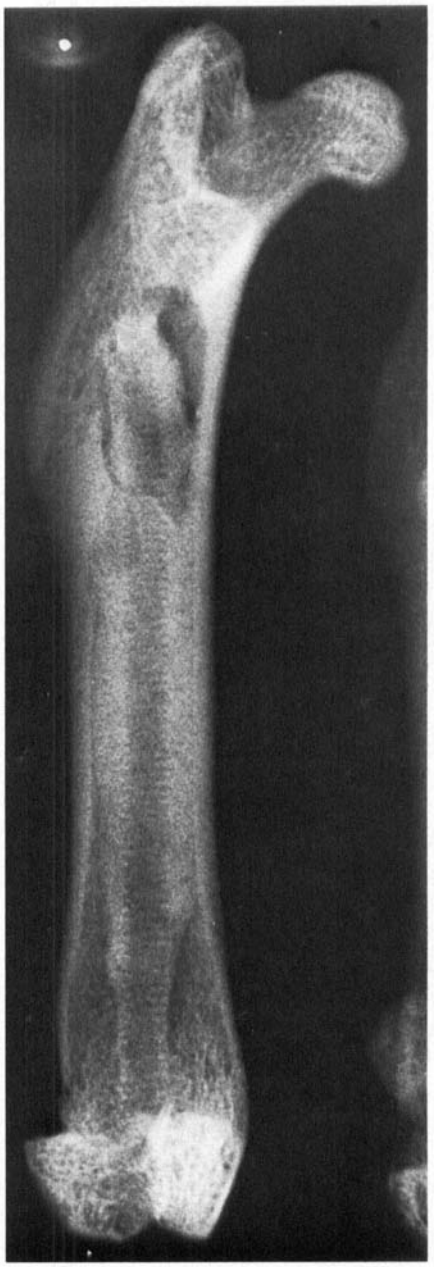

Figure 1. Roentgenogram showing rat femur after intramedullary implantation of methyl metacrylate and Teflon® rod.

II – *Removal of bone marrow (RBM):* After surgical exposure of the femoral diaphysis according to I, a hole through the cortex was created with a dental bur (Ø 2.5 mm) in the proximal diaphysis. The bone marrow was sucked out through that hole with a cannula and the medullary cavity was washed with saline solution.

III – *Implantation of methyl methacrylate (IMM):* After surgical exposure the bone marrow was removed. Methyl methacrylate (Palacos®, Schering Corp., USA) was mixed in a standardized fashion and injected with a syringe and cannula through the bur hole into the medullary cavity until this cavity was completely filled. In order to press the methyl methacrylate against the endosteal surface a Teflon® rod (Ø 1.25 mm) was inserted into the medullary cavity. Figure 1 shows a femur with the medullary cavity filled with methyl methacrylate and a Teflon rod.

In all techniques the wounds were closed in layers with interrupted sutures.

The rats were divided into groups of 40. In the first group the femora of each rat were operated according to surgical techniques I and II, in the second group I and III and in the third group II and III.

Observation times. The observation times were 14, 35, 70 and 112 days. At 112 days the femur length was measured with a caliper after dissection.

Fluorochrome labelling. Three fluorochromes were used for bone labelling. Oxytetracycline (OTC, Terramycin® with Xylocain®, Pfizer, Sweden) was given i.m. at a dose of 15 mg/kg, tetracycline chloride (TC, Achromycin® Lederle; Sweden) was injected i.v. at a dose of 12.5 mg/kg and hematoporphyrine (HP, hematoporphyrin dihydrochloride, Sigma Chemical Company, USA) was given s.c. at a dose of 300 mg/kg. The hematoporphyrine solution was prepared as described by Olerud & Lorenzi (1970).

The following protocol was used for the fluorochrome labeling:

14 day group	OTC day 7, HP day 12
35 day group	OTC day 28, HP day 33
70 day group	OTC day 28, TC day 63, HP day 68
112 day group	OTC day 28 and 105, TC day 63, HP day 110

Microangiography. Two randomly chosen rats from each group and observation time were subjected to microangiography. India ink in saline (1:4) was used as medium and infused as described by Danckwardt-Lilliestrom (1969). After fixation of the femora in 4% neutral formalin about 1-mm-thick cross-sections were sawn from the femoral middle. The methyl methacrylate was dissolved with chloroform and the sections were embedded in paraffin after decalcification. 100–200-μm-thick sections were cut and cleared according to the method of Spalteholtz as described by Linder (1976) and Danckwardt-Lilliestrom (1969).

Fluorescence microscopy and microradiography. 1-mm-thick cross sections were sawn from the middle of the femur. They were processed and examined in a way earlier described (Rosenquist 1973).

Histology. Immediately proximal to the midle of the femur a cross section was sawn. After fixation in 4% neutral formalin, the methyl methacrylate was dissolved with chloroform and decalcification was carried out with 30% formic acid. After embedding in paraffin, 7-μm-thick cross sections were cut and stained with hematoxylin-eosin.

Morphometry. Morphometrical analysis was performed using a Leitz ASM (Ernst Leitz, Wetzlar, Germany) computerized, semiautomatic morphometric system.

The extent of vascular changes in the cortex was measured on the microangiographical cross sections. In each cross section a careful evaluation of the intracortical vascularization was made. Areas lacking visible blood vessels were graded as avascular areas. Areas where blood vessels were fewer than normal but not totally missing were graded as hypovascular areas. All other areas were graded as normally vascularized. The avascular and hypovascular areas as well as the bone area of the cross sections were measured with the Leitz ASM system. The percentage avascular and hypovascular bone was calculated in the RBM and IMM femora.

On the fluorescence sections from the 14 day group, the area of newly formed (labeled) bone periosteally was measured. The labeled bone area was expressed as percentage of the bone area of the cross section. On the microradiographs the following areas were measured (Figure 2):

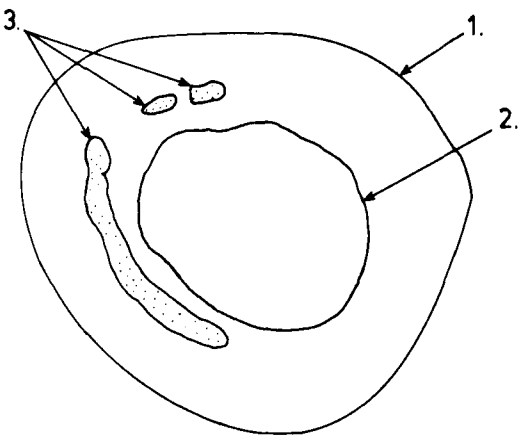

Figure 2. Areas measured by morphometry on microradiographs. 1. Total area (TA). 2. Central medullary area (CMA). 3. Cortical cavities (CC). Total medullary area (TMA) = CMA + CC. Bone area (BA) = TA – TMA.

Total area (TA) of the cross section. *Central medullary area* (CMA) – the area occupied by the medullary canal. *Cortical cavities* (CC) – the sum of all cavities in the cortex. *Total medullary area* (TMA) – the sum of CMA and CC. *Bone area* (BA) – the area occupied by bone in the cross section.

The error of the morphometrical measuring method on the microradiographs was calculated according to Eränkö (1955) and was found to be 1.66% of the mean.

The extent of bone necrosis, i.e. the areas lacking stainable osteocyte nuclei, was measured on five consecutive cross sections in the RBM and IMM femora and expressed as percentage of the bone area.

Statistics. The levels of significance were tested with Student's *t*-test.

RESULTS

Recovery after operation was uneventful. All animals moved in a normal way. No signs of infection were seen.

During the observation time the mean body weight increased from 369 ± 17 g to 502 ± 21 g with no difference between the groups. There was a slight difference in mean femur length ($P < 0.05$) at 112 days between the SO femora (43.3 ± 0.5 mm) and the RBM and IMM femora (43.5 ± 0.6 and 43.5 ± 0.5 mm respectively).

Microangiography. In the SO femora an increased number of blood vessels was seen in the periosteal, newly formed bone at 14 days. There were no other vascular changes at any observation time.

The RBM femora also showed an increase in the number of periosteal vessels at 14 days. At 14 and 35 days an increased number of medullary vessels was seen. At 35 days the middle third of the cortex had an increased vascularization with small sinusoids and arch-shaped vessels. Hypovascular areas, situated in the endosteal third of the cortex, were seen at all observation times (Table 1).

In the IMM femora the number of periosteal vessels was increased at 14 days. The avascular and hypovascular areas occupied a larger part of the cortex than in the RBM femora at all observation times (Table 1). These areas were situated in the endosteal half of the cortex. At 35

Table 1. Mean percentage avascular and hypovascular bone in cross sections from diaphysis of RBM and IMM femora (mean ± S.D.)

Observation time, days	Group	No. of femora	Avascular areas, per cent	Hypovascular areas, per cent	Total, per cent
14	RBM	4	0	21.3±10.5	21.3±10.5
	IMM	4	52.5±10.9	19.5± 6.9	72.0± 8.7
35	RBM	4	0	11.5± 8.7	11.5± 8.7
	IMM	4	13.9± 7.4	22.4± 6.9	36.3± 8.1
70	RBM	4	0	16.5± 5.0	16.5± 5.0
	IMM	4	13.6± 3.5	19.5±12.0	33.1±13.4
112	RBM	4	0	13.9± 4.9	13.9± 4.9
	IMM	4	8.6± 5.1	30.4± 7.7	39.0± 5.4

RBM, removal of bone marrow.
IMM, implantation of methyl methacrylate.

days, accumulations of India ink were seen in the middle third of the cortex, and these areas gradually enlarged with time.

Fluorescence microscopy. In all differently treated femora there was a broad zone of oxytetracycline (OTC)-labeled trabecular bone periosteally at 14 days. The amount of periosteal labeled bone at 14 days was largest in the IMM femora and smallest in the SO femora (Table 2). The hematoporphyrine (HP)-labeling was seen on the periosteal surface and on the trabeculae. The periosteal labeling from 35 days and throughout the experiment did not differ in the differently treated femora.

In the SO femora the cortex showed very little labeling and the endosteal perimeter was labeled approximately 10–30 per cent of its length with thin labels at all observation times.

Table 2. Mean percentage labeled periosteal bone/bone area in cross sections from diaphysis of SO, RBM and IMM femora 14 days postoperatively (mean ± S.D.)

Group, per cent	SO	RPM	IMM
	18.7±5.6[a]	22.1±4.6	24.1±2.2[a]

Number of animals in each group: 10.
SO, sham operated.
RBM, removal of bone marrow.
IMM, implantation of methyl methacrylate.
a, statistically significant difference, $P < 0.01$.
Probability estimated by t-test.

In the RBM femora labeling in the cortex was seen at 14 days around cavities, situated both in the periosteal one third of the cortex and near the endosteal surface. At later observation times, the labels were seen periosteally to the cavities. The endosteal surface was at 14 days partly unlabeled and irregular and partly broadly labeled with OTC and HP. At 35 days a thin, scattered label of OTC and HP was seen endosteally, and at 70 and 112 days the labeled zone was broader. Occasional lacunae in the endosteal surface were seen at 35 and 70 days. At 70 days the surface of the lacunae was labeled with the 63 and 68 day label. The medullary cavity of the RBM femora showed large amounts of labeled trabecular bone at 14 days.

The IMM femora contained many cavities in the endosteal one third of the cortex at 14 days and some of these cavities were labeled with the 12 day label. At 35 days these cavities were either unlabeled or irregularly labeled with OTC or HP. The label was mainly situated on the periosteal side of the cavity. At 70 days numerous small cavities in the inner third of the cortex were labeled with the 28 or 63 day label. In the mid-part of the cortex cavities were also seen labeled with three labels in a centripetal direction. Labeled areas within the cortex were seen. At

112 days large cavities adjacent to the endosteal surface were seen with one to three labels on their periosteal side. In the midpart of the cortex large areas, centripetally labeled, were often seen. The endosteal surface of the IMM femora showed no label at 14 days. At 35 days labeling with the 28 and 33 day labels was seen around the endosteal perimeter. Endosteal labeling was also seen at 70 and 112 days.

Microradiography. The results of the morphometrical analysis of the microradiographs is shown in Table 3.

The total area (TA) of the cross section decreased between 14 and 35 days in all differently treated femora. At 70 days the TA of the SO femora was of approximately the same size as at 14 days while the TA of the RBM and IMM femora exceeded the 14 day value. At 112 days the TA of the SO and RBM femora was approximately the same, while the TA of the IMM femora was significantly greater. The per cent change between the TA value of 14 and 112 days was greatest in the IMM femora.

The bone area (BA) had the same development by time as the TA. The per cent change in BA between 14 and 112 days in the IMM femora was greater than the change in TA.

The cortical cavities (CC) generally occupied the largest area in the IMM femora and the smallest in the SO femora.

There was a broad zone of trabecular bone periosteally at 14 days in all the differently treated femora. This trabecular bone was not seen at the other observation times.

There were more cortical cavities in the RBM femora than in the SO femora at 14 and 35 days. The cortical cavities of the RBM femora were situated partly in the periosteal third of the cortex and partly near the endosteal surface. In the lat-

Table 3. Morphometrical analysis of microradiographical cross sections from diaphysis of SO, RBM and IMM femora in mm² (mean ± S.D.)

	Surgical technique	Observation time, days				Change between 14 and 112 days, per cent
		14	35	70	112	
Total area	SO	17.74±1.32	17.05±1.55	17.80±0.97[a]	19.46±0.75	+ 9.7
	RBM	18.31±1.14	18.12±1.20	19.19±0.80	19.86±0.93	+ 8.5
	IMM	18.69±1.29	17.86±0.40	20.29±1.83	22.38±2.53[b]	+ 19.7
Central medullary area	SO	6.42±0.70	6.38±0.75	6.53±0.44	6.88±0.35	+ 7.2
	RBM	6.22±0.75	6.52±0.39	6.66±0.59	6.75±0.40	+ 8.5
	IMM	6.34±0.47	6.63±0.31	6.58±0.60	6.66±0.65	+ 5
Cortical cavities	SO	0.02±0.02[b]	0.07±0.08	0.13±0.23	0.05±0.09	+150
	RBM	0.11±0.08	0.20±0.13	0.11±0.13	0.09±0.16	− 18
	IMM	0.23±0.13	0.13±0.09	0.24±0.23	0.26±0.26[c]	+ 13
Total medullary area	SO	6.44±0.71	6.45±0.86	6.66±0.52	6.93±0.35	+ 7.6
	RBM	6.33±0.80	6.72±0.54	6.77±0.56	6.84±0.52	+ 8
	IMM	6.57±0.57	6.76±0.50	6.82±0.66	6.92±0.73	+ 5.3
Bone area	SO	11.30±0.99	10.60±0.92	11.14±0.69[a]	12.43±0.68	+ 10
	RBM	11.98±0.73	11.40±1.00	12.42±0.82	13.02±0.59	+ 8.7
	IMM	12.12±1.16	11.10±0.65	13.47±0.83	15.46±2.18[b]	+ 27.6

SO, sham operation.
RBM, removal of bone marrow.
IMM, implantation of methyl methacrylate.
Statistically significant difference from corresponding values of other femora at same observation time:
[a]$P < 0.001$. [b]$P < 0.01$. [c]$P < 0.05$.
Probability estimated by t-test.

Table 4. Mean percentage of cross sections from diaphysis of RBM and IMM femora showing necrosis (mean ± S.D.)

		Observation time, days			
		14	35	70	112
Per cent necrosis	RBM	39.8±23.1	20.5±13.4	19.6±10.0	7.1± 7.0
	IMM	64.9±15.5	42.0± 8.4	39.2±11.2	23.4±10.8

Number of animals in each group: 10.
RBM, removal of bone marrow.
IMM, implantation of methyl methacrylate.

ter cavities, the endosteal surface was irregular, indicating resorption. In the IMM femora cortical cavities were small but numerous at 14 days. At 35 and 70 days the cavities had an irregular surface and the size was relatively small. At 112 days the cavities adjacent to the implant region were large.

Histology. In the SO femora as well as in the other femora there was a broad subperiosteal layer of trabecular bone at 14 days. This layer had disappeared in the SO femora at 35 days, and the rest of the cortex had a normal histological appearance.

In the RBM femora there were some areas of trabecular bone left at 35 days but after that no such bone was seen. In the endosteal part of the cortex areas of dead bone were seen, i.e. areas where osteocytes lacked nuclei. These areas occupied a large per cent of the cortex at 14 days, but then gradually decreased in size (Table 4). Some large vessels were seen in the necrotic areas. Normal bone cells were seen around these vessels. At day 35 a thin layer of bone, i.e. 2–3 rows of osteocytes at an average, with stainable osteocyte nuclei was observed endosteally and directly outside that layer the area of necrosis commenced. At 112 days the RBM femora showed an almost total restitution of the bone necrosis. In the medullary cavity the bone marrow had a looser appearance than in the SO femora.

In the IMM femora the same development subperiosteally was seen as in the RBM femora. A large part of the cortex lacked osteocytes with stainable nuclei at the different observation times (Table 4). At the last observation time 23 per cent of the cortex still lacked such osteocytes. Some blood vessels surrounded by normal bone cells were seen in the necrotic areas, but they were fewer than in the RBM femora. As in the RBM femora, a thin layer of vital bone had appeared endosteally at 35 days. Relatively large cavities were seen at 70 days, both in the middle of the cortex and near the endosteal surface. These cavities had osteoclasts on their endosteal surface and lamellar bone deposits on their periosteal surface. A fibrous tissue between the implant area and the endosteal bone surface was often seen. At 112 days large cavities containing bone marrow were seen outside the thin endosteal bone sleeve. This bone often had a scalloped surface towards the implant.

DISCUSSION

In the present study we found a tendency towards an activation of the epiphyseal plate caused by the intramedullary operation. This has been supported in a further study. The rats in these studies had a certain growth potential left. In a comparative study on older rats an attempt will be made to evaluate whether growth has any effect on the femoral morphology in addition to the intramedullary implantation.

The effects of polymerization heat and monomer toxicity have not been separately studied in this experiment. However, this has been done by several other authors. At polymeri-

zation in vivo many authors have found a temperature rise to between 40° and 50°C at the bone/cement interface (Biehl et al. 1974, Labitzke & Paulus 1974). The effect of heat on bone has been studied by Lundskog (1972) who found that a temperature of 50°C for 30 s caused little disturbance of the osteocytes and that no influence on bone regeneration capacity took place. The chemical trauma inflicted by the monomer has been investigated i.a. by Linder (1976) who concluded that the monomer did not add to the surgical trauma and that no influence on bone regeneration took place. Lee et al. (1973) found that after curing the leakage of monomer was very low. Thus the effects of polymerization heat and monomer toxicity are probably much less important than the trauma effected by blocking of the normal medullary blood supply.

In both the RBM and IMM femora a disturbance of the intracortical vascularization was seen in the endosteal part of the femora. A difference was seen between these femora both regarding the extent of and the type of vascular disturbance. In the RBM femora no totally avascular areas were seen, yet considerable areas with osteocytes lacking nuclei were found. In the IMM femora on the other hand both avascular and hypovascular areas were frequently seen. The avascular areas showed a decrease with time, especially between 14 and 35 days while the total area of disturbed vascularization in the IMM femora did not show any variation from day 35 and throughout the experiment. This is in agreement with the findings of Brookes & Gallannaugh (1975). In a study using microspheres they showed that the bone tissue became hypovascular after implantation of methyl methacrylate in the rat tibia and that this reaction still persisted after 112 days. Rhinelander et al. (1979) found that medullary reaming of the femur in dogs resulted in devascularization of large areas in the diaphyseal cortex. After 6 months revascularization had taken place. Obturation of the medullary cavity with methyl methacrylate on the other hand resulted in extensive devascularized areas still present after 1 year.

In the IMM femora, where occlusion of the normal medullary blood supply had caused the most extensive vascular damage in the cortex (Table 1), the periosteal reaction was the most extensive (Table 2), while the SO femora, which showed no disturbance of the intracortical vascularization, had less newly formed periosteal bone at 14 days. Thus the extensive formation of subperiosteal trabecular bone observed at 14 days was not only a result of the manipulation with the periosteum, but also a reaction to the damage to the medullary blood supply.

A widespread necrosis of the cortex was seen in both the RBM and the IMM femora initially and there seemed to be a correlation between the extent of necrosis and the extent of vascular disturbance throughout the experiment. Necrosis of bone was assessed when no stainable osteocyte nucleus was present, which according to Axhausen & Bergmann (1937) is a definite sign of necrosis, although some falsely empty osteocyte lacunae can appear when the section does not cut through the nucleus. In the present study, a comparison with the SO femora showed that these contained no areas where the osteocytes lacked stainable nuclei, and therefore the areas in the RBM and IMM femora lacking osteocyte nuclei were regarded as necrotic. In the IMM femora there were still large areas of necrosis at the end of the experiment, indicating that the permanent occlusion of the normal medullary blood supply effected by the methyl methacrylate implant had a more persisting impact on the bone than the removal of bone marrow alone.

It is well known that intramedullary procedures initiate a periosteal reaction (Danckwardt-Lilliestrom 1969, Sloof 1971, Lindwer & van den Hooff 1975, Feith 1975). The morphometrical study of the microradiographs showed that the total area of the RBM and IMM femora increased faster than the total area of the SO femora. At 112 days, however, the SO femora had caught up with the RBM femora, while in the IMM femora even after 112 days a significantly larger total area was seen ($P < 0.01$). The significant increase in bone mass that was seen in the IMM femora (Table 3) compared with the RBM and the SO femora was due, in part, to this subperiosteal bone formation but also to an inhibition of the endosteal resorption as the CMA in the IMM femora was smaller than in the others. In the present study the result was not statistically

significant and therefore the tendency will be pursued in a further investigation.

A thin endosteal bone sleeve containing osteocyte nuclei was seen at 35 days in both the RBM and the IMM femora. This bone sleeve was, especially in the IMM femora, labeled with the 28 and 33 day label, while at 14 days no endosteal labeling was seen in the IMM femora. The generation of the endosteum and the formation of a bone sleeve around the implant progressed faster in our study on adult rats than in studies on dogs (Lindwer & van den Hooff 1975). Regarding the nutrition of the endosteal bone sleeve, no conclusions could be drawn as to its origin based on the microangiographical technique used. Rhinelander et al. (1979) found a hemolyzed layer of blood present between cement and bone after 1 week and they stated that this layer became organized into a fibrous membrane bringing in regenerative medullary blood supply. A thin fibrous membrane endosteally was seen also in this study and it seems likely that it served the same purpose. However, the differences in morphological findings could be due to different surgical technique and different animal species. Moreover, more careful preparation techniques are necessary to allow for a more conclusive interpretation.

The microradiographs showed partly a scalloped surface toward the implant and this was probably not due to resorption but to a modeling of the bone against the polymer balls.

One disadvantage in the section preparation was that the implant had to be removed. This did not allow for an examination of the interface between bone and implant. At the time when the present study was carried out, the Epon embedding technique used in a further study had not yet been developed.

It is concluded in this study that intramedullary implantation of methyl methacrylate in the rat femur after removal of the bone marrow leads to greater morphological changes in the diaphysis than elevation of the periosteum and removal of the bone marrow. Although polymerization heat and monomer toxicity cannot be excluded as the cause of some changes, the major cause, especially in the long term observations, is probably the blocking of the normal medullary blood supply. In further studies the permanent effects of this occlusion of the blood supply will be examined and the effect of induced calcium deficiency on the bone will be studied.

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