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Morphological Studies in Tissues Surrounding Alloarthroplastic Joints* **

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Summary. Histological, histochemical and ultrastructural studies were done on soft tissue surrounding alloarthroplastic joints. In 38 cases a prosthesis of the hip joint and in 2 cases of the knee had to be exchanged and replaced. In most of the cases the reoperation became necessary because the anchoring of the prosthetic parts in the bone loosened. Up to 18 months after the first operation infection was responsible for the malfunctioning in some cases. Other complications were luxation and material faults. The morphological changes are determined by the tissue reaction to the different alloplastic materials used and by the time interval they remained in the organism. The large polymerized acrylic cement particles are phagozytosed by multinucleated foreign body giant cells. About 12 months following the implantation of the artificial joints small double refractile particles appear and evoke characteristic morphological changes. These particles are abraded by the continuous friction of the moving alloplastic or metallic surfaces of the prostheses. Usually they are phagozytosed by histiocytes, which form large granulomas and undergo degenerative changes as is indicated by the ultrastructural and histochemical findings.

These alterations are more pronounced and occur sooner in prostheses with parts (rotation ball or cup.) fabricated by polyester than in those made by polyethylene.

The abraded particles not only are transported to the inguinal lymphnodes, but also to the tissue between prostheses and bone, where they induce the same morphological changes as in the capsule. Hence the fibrous membrane separating bone and prostheses increases in width, and the spongy bone is partially destroyed by the proliferating histiocytes. It is assumed that by impairing the anchoring this foreign body reaction to the abraded alloplastic particles is the leading cause of the loosening of this kind of artificial joints.

The permanent success and a satisfactory use of the alloarthoplastic prostheses depend on the quality of the material used and on the firm anchoring of the implants in the bone. Several complications which can endanger the success of this operation frequently are the indication for an exchange operation. These complications occur either in the early acute post operative phase or later after several months or years (Boitzy, 1973). The immediate postoperative course can be influenced by infections of the large wound bed, whereas in the later phase the reactions against the different alloplastic and metallic materials besides mechanical complications become more important and can lead to a loosening of the artificial joints (s. Cotta and Schulitz, 1973).

Charnley (1967) divides the late complications in tissue reactions to particles abraded from the moving and bearing surfaces and in mechanical loosening of the anchoring of the prosthesis in the bone.

* Dedicated to Professor Dr. Wilhelm Doerr for his 60th birthday.

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Our morphological studies in 40 cases however give evidence that these two factors cannot be looked at separately any more. On the contrary we think like Willert and Semlitsch (1974) that tissue reactions to the alloplastic material and loosening of the implants are closely related.

Material and Methods

Patients. 27 patients had a 3-part rotating prosthesis, type Weber-Huggler, consisting of a metal (Protasul, CO-CR-Mo alloy) socket and shaft and a rotating head fabricated from polyester (Polyethyleneterephtalate). 14 patients were female and 12 of male sex. The oldest was 79 and the youngest was 47 years old. The time interval between the implantation and the exchange operation was between 3 and 55 months.

The reoperations were caused 8 times by an infection of the wound bed. These cases had the shortest time intervals lasting from 3 to 18 months. All other cases were reoperated upon because the anchoring of the prosthetic parts loosened in the femur or in the iliac bone. Loosening usually is diagnosed except for by clinical symptoms as pain roentgenologically by a broad radiolucent zone around the implanted parts. 5[1] patients had a "two part endoprosthesis" consisting of a metal shaft and a rotating polyester head. In this type of prosthesis the artificial head rotates in the natural socket. 4 of these patients were female, 1 male. The oldest was 76 and the youngest 39 years old. The time interval between first and second operation was between 17 and 28 months. These patients had to be reoperated upon because of luxation of the prosthetic ball in one case and loosening of the shaft in the others.

6 patients had a "two part prosthesis" type Müller or Charnley-Müller, consisting either of a polyethylene or metal (CO-CR-alloy) socket and metal head. 3 were female and 3 male, the oldest 75 the youngest 53. The time between the two operations was 10 to 30 months. The indication for the reoperation was infection and loosening of the shaft or socket.

2 patients had a total alloarthoplastic knee joint. These prostheses fabricated by polyester and metal (CO-CR-alloy) had to be taken out after 2 years because of a fracture of the metal shaft in the welding zone.

In all patients tissue from the regenerating capsule and in most of the cases tissue from the area between bone and bone cement was taken out during the operations. Inguinal lymphnodes were excised in 2 patients with polyester prostheses.

Usually the tissue was fixed in buffered, neutral 10% formalin for routine embedding and sectioning. The slides were stained by HE, PAS, FE and Safran-Phloxin.

Tissue for histochemical examination was fixed in 10% neutral formalin and prepared for frozen section. The sections were stained with Sudan III and for acid phosphatase (Arnold, 1968). In three cases the tissue was immediately fixed in 3.5% glutaraldehyde, postfixed in OsO_4 and embedded in Araldite and cut on a Porter-Blum ultramikrotome.

In 5 cases formalin fixed and paraffin embedded tissue was reembedded in Araldite and treated for ultrastructural examination.

Results

Histology

Capsule. In 25 patients with endoprostheses type Weber-Huggler capsular tissue was examined (Fig. 1). The regenerating capsule consists of two layers. The inner one surrounding the alloplastic joint is covered by histiocytes which form a synovial lining. Focally there are a fibrinous exsudate and old and recent hemorrhages in different stages of organisation. In the infected cases leucocytes and other inflammatory cells are seen. Underneath this surface there is a loose

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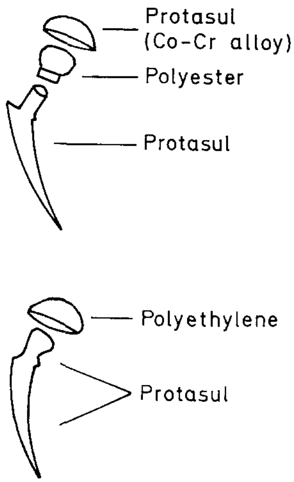
1 We are indebted to Dr. O. Alff (Municipal hospital, Pforzheim) for supplying us with the clinical data on these patients.



Polyester - Prostheses

	n	Infection	Abrasion	Necrosis
< 1 year	6	5	3	-
< 2 years	12	3	12	4
> 2 years	9	-	9	7
Endoprostheses (17-28 mo.)	5	-	5	5

Polyethylene - Prostheses

	n	Infection	Abrasion	Necrosis
< 1 year	2	2	1	-
< 2 years	3	1	2	-
> 2 years	1	-	1	1

Fig. 1. Summary of morphological findings in capsular and osseous tissues surrounding alloarthroplastic hip joints

fibrous granulation tissue with only few blood and lymphatic vessels. The outer layer consists of a dense fibrous scar tissue.

A constant finding in almost all cases are large vacuolated multinucleated giant cells which frequently form small clusters underneath the surface. In paraffin sections these vacuoles appear empty except for some dark irregular particles (Fig. 2). Frozen sections however show the vacuoles to be filled with pale, round and spherical material which takes up a bright orange stain after incubating the sections for 24 hours in Sudan III. Willert (1972) identified the round globules as polymerized acrylic cement pearls and the dark particles as contrast medium (Zirconium oxide or Barium sulfate) used to make the bone cement radiologically visible.

Beginning with the 11th months after implantation small groups of histiocytes appear around perivascular lymphatics. These cells exhibit a coarse somewhat granular cytoplasma which under polarized light contains numerous small irregular double refractile particles. Later these small histiocytic proliferations coalesce and form large sheets of macrophages filled with foreign body material. As the time interval increases larger crystalline double refractile particles appear in multinucleated giant cells. These and the previously mentioned small particles which are not dissolved in paraffin embedding are clearly distinguishable from the bone cement and are a sequel of the abrasion of metal and alloplastic material caused by the continuous friction of the moving parts of the artificial joints (Willert and Semlitsch, 1972, 1974).

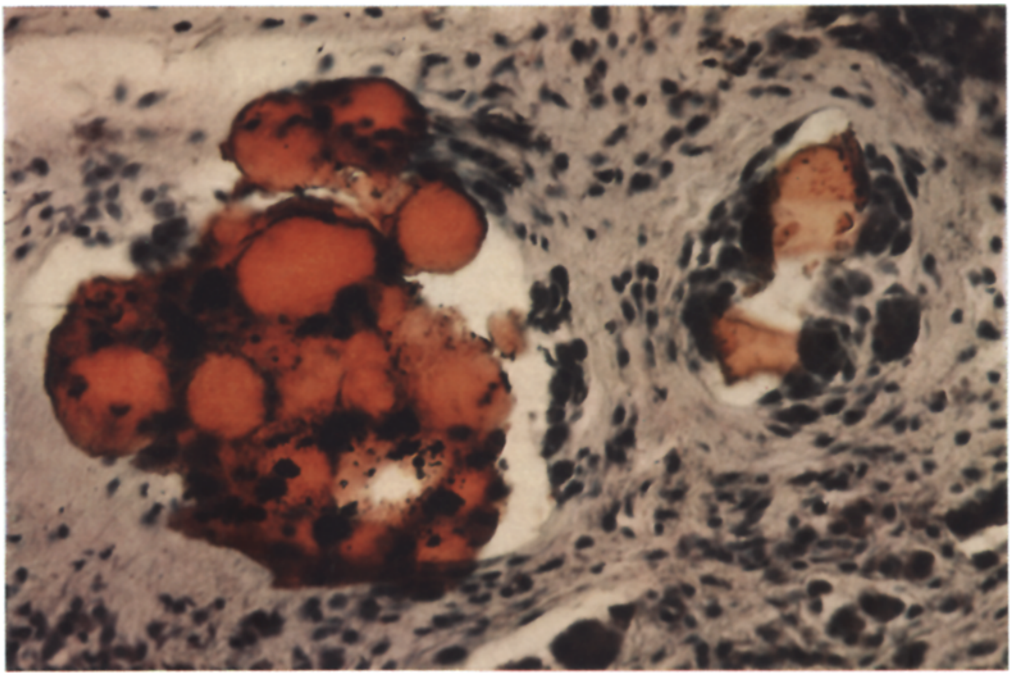


Fig. 2. Polymerized acrylic cement pearls in foreign body giant cells. The dark staining particles are contrast medium (Zirconium or Barium). The macrophages (lower right) show also a positive but weaker staining. (E Nr. 29307/74 Polyester prosthesis, 39 months after implantation. Sudan III, Frozen section, × 52 before reproduction)

After 15–20 months the capsule has a characteristic morphological appearance. The inner layer consists of broad sheets of fibrin and debris, and within this amorphous masses multiple double refractile particles are seen. Underneath this zone the macrophages loaded with abraded particles form large sheets and granulomas. Numerous multinucleated giant cells with alloplastic material are present. Frequently at this and at later times focal central necroses begin to form and are surrounded by the histiocytes similar to a specific centrally necrotizing granuloma. The outer layer consists of a dense fibrous scar tissue with blood and lymphatic vessels. The lymphatics contain sometimes few macrophages with phagozytozed particles and frequently are surrounded by small groups of these cells.

All the cases where the two part endoprosthesis fabricated from polyester were used, displayed similar morphological changes. There are only quantitative differences, abrasion and tissue reaction being more severe. In polyethylene prostheses generally the structure of the regenerating capsule is similar to the polyester cases except there is much less abraded alloplastic material. The cases bearing the prostheses more than 12 months display also small irregular double refractile particles. However in contrast to the above mentioned cases these particles are usually seen in giant cells. Thus the histological picture is dominated by a dense fibrous stroma containing giant cells some of which are vacuolated and filled with bone cement. Macrophages are rarely seen. Not earlier than 30 months

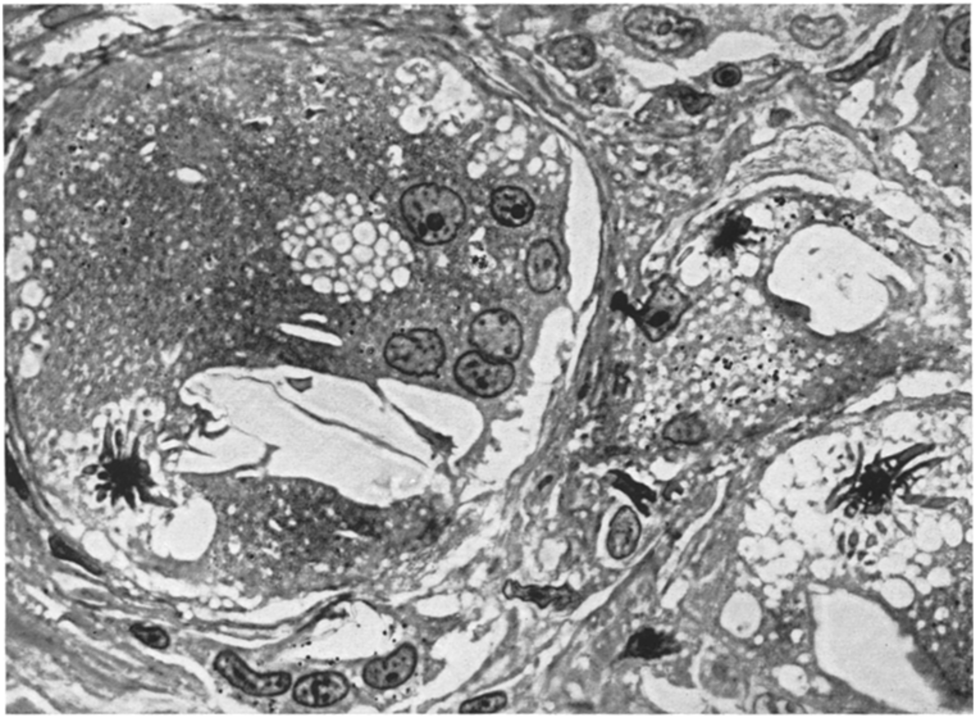


Fig. 3. Asteroid bodies and abraded material in foreign body giant cells (E Nr. 44773/73, Polyester prosthesis 27 months after implantation, Semithin section, $\times 403$ before reproduction)

following the implantation abraded particles become more numerous and granulomas occur similar to the ones seen in the polyester cases.

Bone. In 16 cases tissue from the area between the artificial socket and the surrounding iliac bone and in 8 cases tissue from the femur was studied histologically. Since these two areas do not differ significantly in morphological behavior the histological findings will be described together. The spongiosa of the iliac bone and of the femur are separated from the acrylic cement by a fibrous membrane of changing width. In the early cases complicated by infection, this fibrous membrane covered by a fibrinous exsudate and hemorrhages is infiltrated by inflammatory cells. Later the membrane is lined by histiocytes, macrophages and foreign body giant cells forming a lining sometimes similar to a neosynovia. Frequently there are single or small groups of vacuolated multinucleated giant cells with phagocytosed cement particles. In the deeper parts one sees sometimes necrotic bone fragments. A true meshing between bone and cement is never observed.

Abraded small and gross particles appear the first time 15 months after the implantation of the artificial joints. The resulting morphological changes are essentially the same as described in the capsular tissue. Because of the proliferating histiocytes the membrane increases in width and consists in the later cases almost exclusively of these foreign body granulomas.

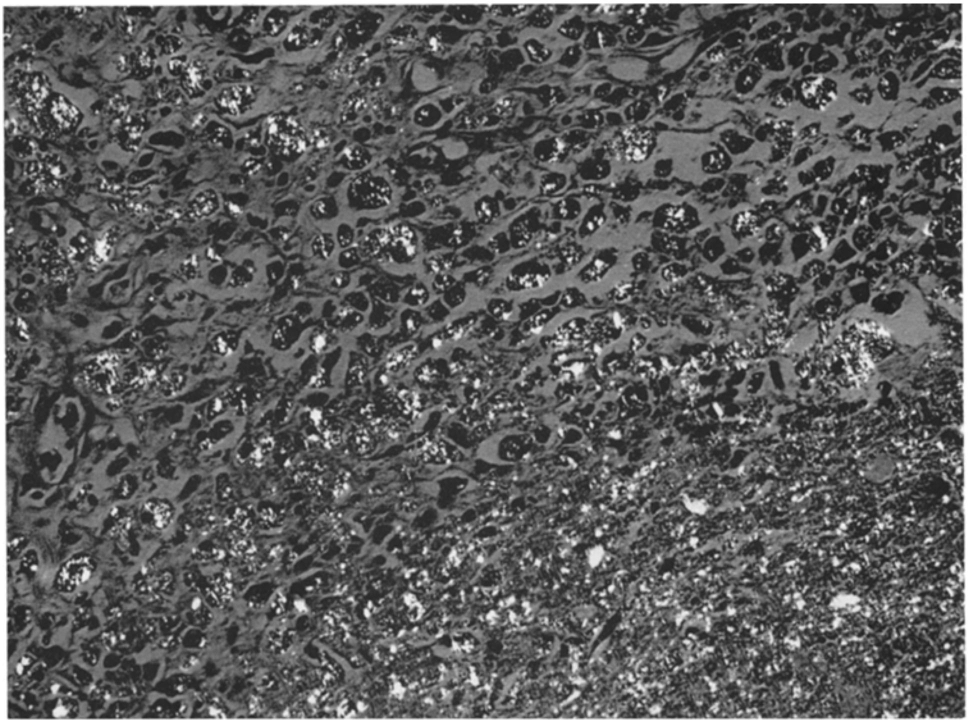


Fig. 4. Macrophages filled with abraded alloplastic particles surround large confluent necroses (lower right) (E Nr. 20317/73, Polyester prosthesis, 55 months after implantation, HE, polarized light, $\times 40$ before reproduction)

In one case the multinucleated giant cells with phagocytosed abraded material contain small star like bodies. These bodies are consistent with the so called asteroid bodies which are usually found in sarcoid and rarely in foreign body granulomas (Lennert, 1961) (Fig. 3).

When parts of the surrounding bone were excised the proliferating histiocytes loaded with double refractile particles are seen to grow aggressively into the marrow spaces between the spongiosa. There is finally also formation of large confluent necroses as in the capsular tissue (Fig. 4).

The early histological changes in the membrane between bone and implants in the polyethylene cases are similar to the above described. Inflammatory cells and giant cells with phagocytosed cement particles can be demonstrated in the first months. Later abraded small particles in giant cells lying in a dense fibrous appear. Histiocytic granulomas occur only in the case in which the prostheses loosened after 30 months.

The joint capsule and the synovial tissue excised in the patients with the total alloplastic knee joint displayed characteristic morphological changes. In contrast to the joint capsule of the hip prostheses the granulation tissue is dominated by sometimes huge foreign body giant cells which are filled with large "floe" like double refractile abraded alloplastic particles. These giant cells frequently contain asteroid bodies. Relatively few macrophages with phagocytosed polyester frag-

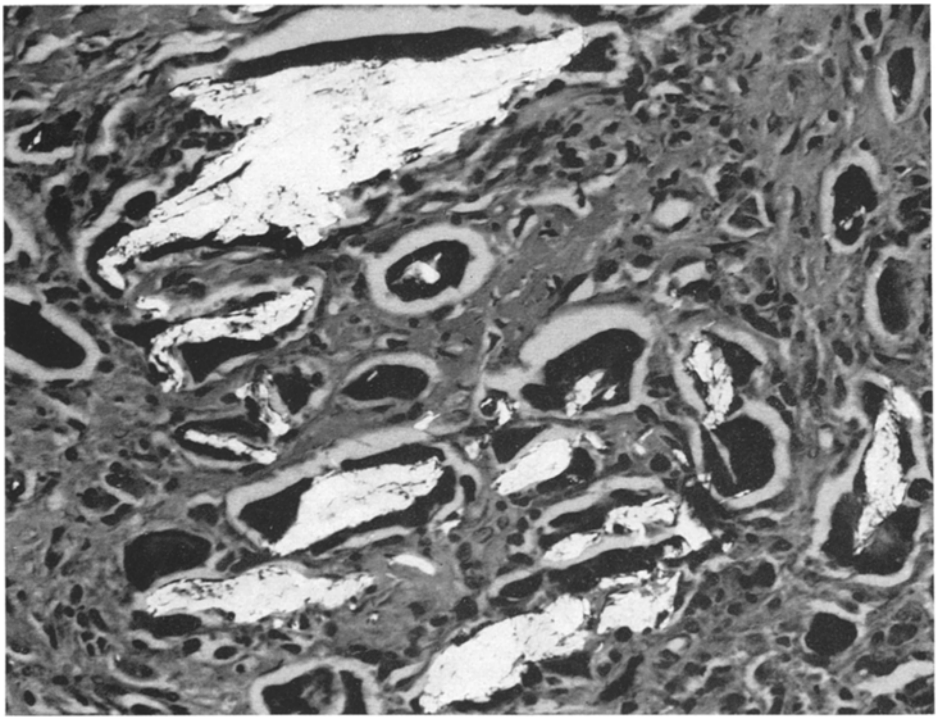


Fig. 5. Polyester particles in foreign body giant cells in a case with an alloplastic prosthesis of the knee. (E Nr. 29535/74, 24 months after implantation, HE, ×42 before reproduction)

ments are seen. However there are necroses and amorphous debris consisting of fibrin and abraded material covering the capsular surface. The outer layer consists of dense fibrous tissue (Figs. 5, 6).

Histochemistry

24 hrs staining of frozen sections with Sudan III gives the already mentioned strong positive reaction with the acrylic cement pearls in the vacuolated giant cells. Methylmethacrylate is fat soluble and therefore takes up this stain. The cytoplasm of the histiocytes is also stained by Sudan III. However this diffuse staining reaction, which results in a brown reddish colour, differs clearly from the bright orange stain of the material in the giant cells. Only some macrophages contain small equally stained particles.

Macrophages and giant cells display a very strong reaction to acid phosphatase. The histiocytes in the granulomas do not take up an equally intense staining. Particularly the smaller histiocytes which usually are seen in the perivascular region give a weaker reaction. Under polarized light there is a correlation between phagocytosed foreign bodies, size of the cell and intensity of staining (Fig. 7).

Ultrastructure

Examination of half and ultra thin sections of the capsular tissue and of the material from the area between bone and prosthesis reveals a marked pleomorphy

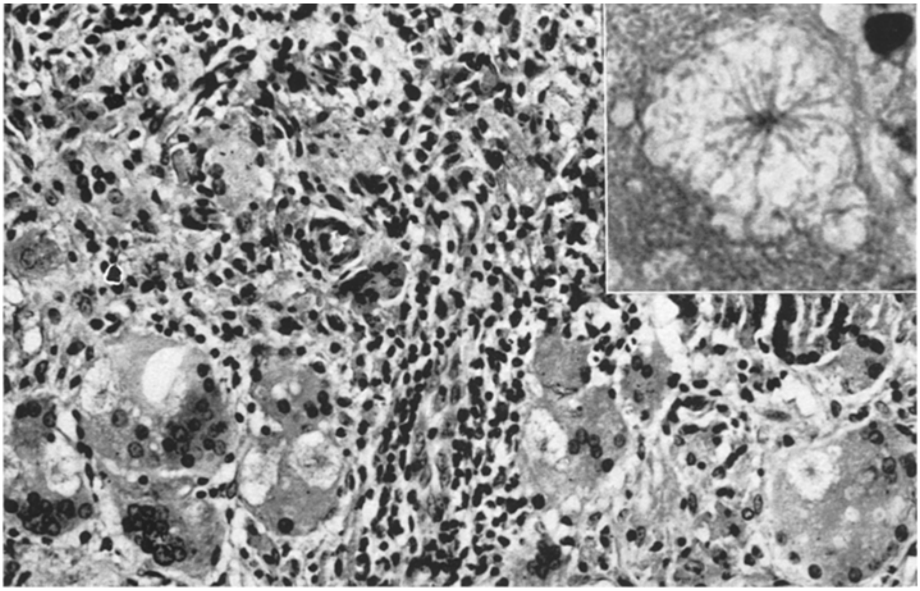


Fig. 6. Same case as Fig. 5. Multiple asteroid bodies in foreign body giant cells. (E Nr. 29535/74, Polyester prosthesis of the knee joint 24 months after implantation, HE, × 52 before reproduction)

of the macrophages. The semithin sections show numerous macrophages of varying size and in different stages of phagocytosis. When examined under polarized light the larger cells exhibit besides the double refractile phagocytosed particles a finely granular, polarizing cytoplasma due to an increase of cytoplasmic organelles. The smaller non-phagocytosing cells have a homogeneous cytoplasma and regular vesicular nuclei, whereas the larger ones show degenerative nuclear changes (Fig. 8).

Ultrastructurally this pleomorphy becomes more evident. There are mononuclear cells with a fine dispersed nuclear chromatin and a homogeneous cytoplasmic ground substance. The rough endoplasmatic reticulum consists of regular tubes, the mitochondria are normal. Other cells have dilated vesicular cisternae of the rough endoplasmatic reticulum and fine filamentous structures in the ground substance. Besides that there are large irregular heterophagosomes with secondary lysosomes and myelin figures. Sometimes electrondense phagocytosed particles (probably metal) are seen in phagosomes. Ultrastructurally only polymerized acrylic cement in foreign body giant cells could be seen. This material is observed in the vacuoles and consists of pale, round pearls. Alloplastic abraded material in macrophages could not be demonstrated since during cutting these particles were driven out and only empty vacuoles were left (Figs. 9, 10).

Lymphnodes. The inguinal lymphnodes are histologically regularly structured. The center of the nodes shows fibrosis. The sinus are dilated and filled with histiocytes, some of which contain double refractile particles. These cells stain also with Sudan III and give a positive reaction to acid phosphatase.

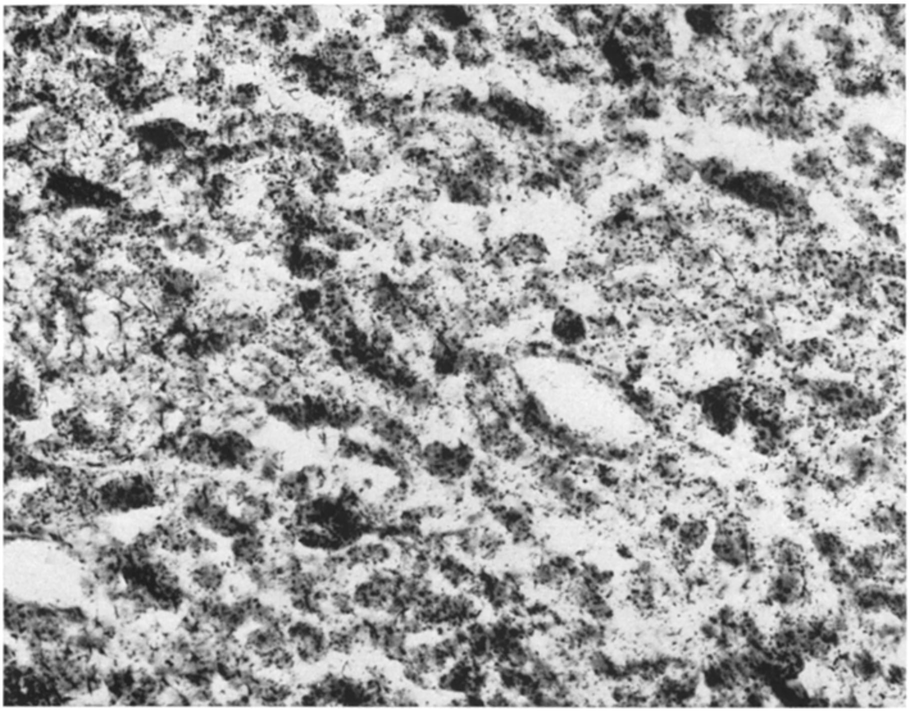


Fig. 7. Reaction to acid phosphatase. The smaller histiocytes in the perivascular region stain less than the larger ones in the surrounding area. (E Nr. 29567/74, Polyester endoprosthesis 19 months after implantation, Frozen section $\times 40$ before reproduction)

Discussion

Our findings and the results by Willert (1973) and Willert and Semlitsch (1974) show that tissue reaction around alloplastic joints depends mainly on the material the prosthesis is fabricated from and on the time span the prosthesis is used by the patient.

These changes taking place in parts which are important for the anchoring and for the free movement of the prosthesis can lead to an impairment of a satisfying function of the artificial joint as it is shown recently by Weber and Stuehmer (1973, 1974) and by Brinkmann et Heilmann (1974).

Each of the alloplastic materials, methylmethacrylate, polyester and polyethylene produces in bone and periarticular tissue its own characteristic morphological picture. Though we could demonstrate also phagocytosed metallic particles, we do not think that they are of importance in causing the granuloma formation since in the cases where the polyester ball rotated in the natural socket the changes were even more pronounced.

The high polymerisation temperature of acrylic cement reaching levels up to 124° C (Contzen, 1962; Hupfauer and Ulatowski, 1971; Schulitz and Puhl, 1973) and the toxic effect of the monemers of methylmethacrylate (Mohr, 1958) and the consequences of the surgical manipulations cause necroses and hemorrhages in the bone surrounding the prosthetic parts (Willert, 1973; Willert and Semlitsch, 1972).

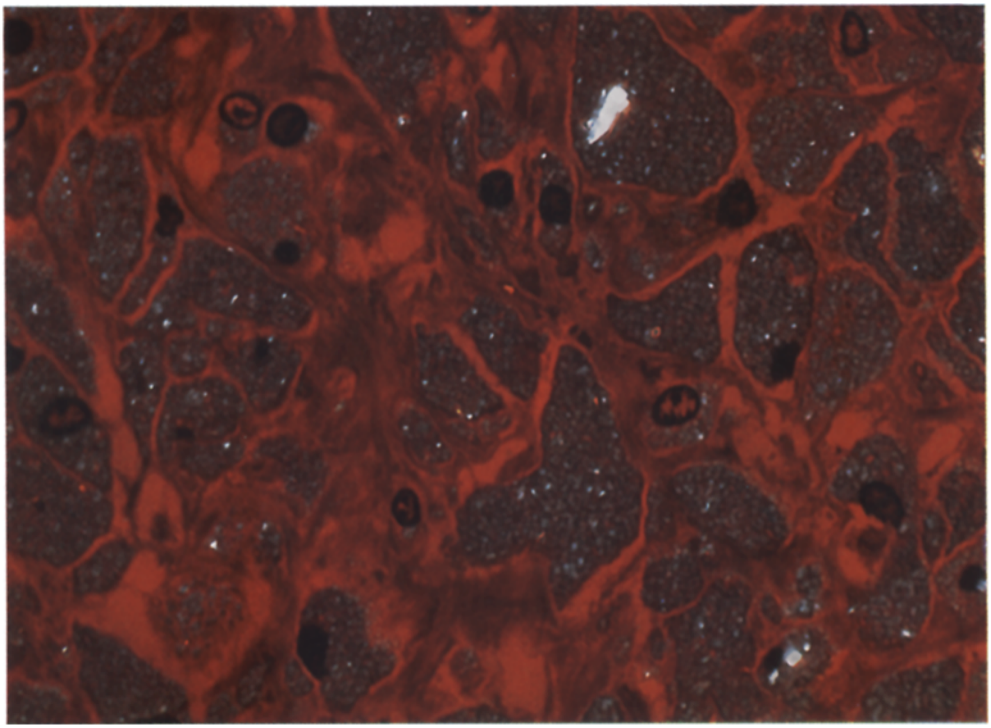


Fig. 8. Macrophages filled with abraded Polyester material. The cytoplasm of the phagocytosing cells is granular and double refractile due to the increase in cytoplasmic organelles and structures. The nuclei show different stages of degeneration. (E Nr. 20317/73, Polyester prosthesis 55 months after implantation, Semithin section, polarized light, ×204 before reproduction)

In our cases we only can demonstrate the results of repair and organisation of these necroses by fibrosing and scarring inflammation with the formation of the described fibrous membrane between bone and cement. This fibrous membrane lined by giant cells and histiocytes represents like the regenerating capsule a huge foreign body granuloma surrounding the implanted parts and leads to their sequestration as it was already observed by Collins (1953). Thus a true meshing of bone and cement becomes impossible. However in most of the cases this anchoring of the prosthetic parts is sufficient for physiologic use of the "artificial joints" at least in the early period.

But any factor which is capable of sustaining the inflammation must impair the anchoring of the implanted parts. One of these factors is infection. In 8 cases of the polyester cases and in 3 patients of the polyethylene cases we could demonstrate histological signs of infection as leucocytes, abscess formation and necroses. Some of these infections are primary and some are secondary by hematogenous spread. In one case for example the same e.coli. could be cultured from the urinary bladder and from the tissue resected during the operation. Another factor capable of sustaining the inflammation are probably the 3 to 5% of toxic monomers (Smith, 1959; Schulitz *et al.*, 1973) which can be released from the polymerized

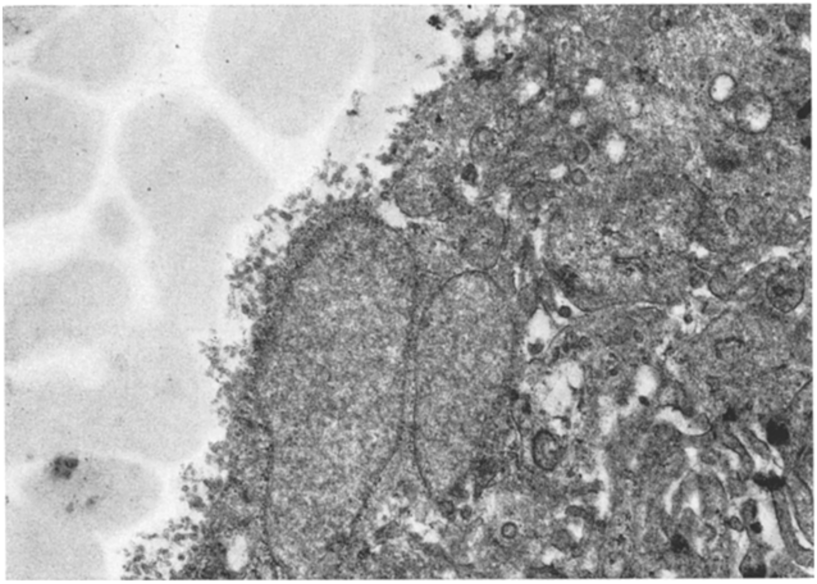


Fig. 9. Foreign body giant cell with phagozytosed polymerized acrylic cement pearls. (E Nr. 253889/73, Polyethylene prosthesis 12 months after implantation, EM, ×9600 before reproduction)

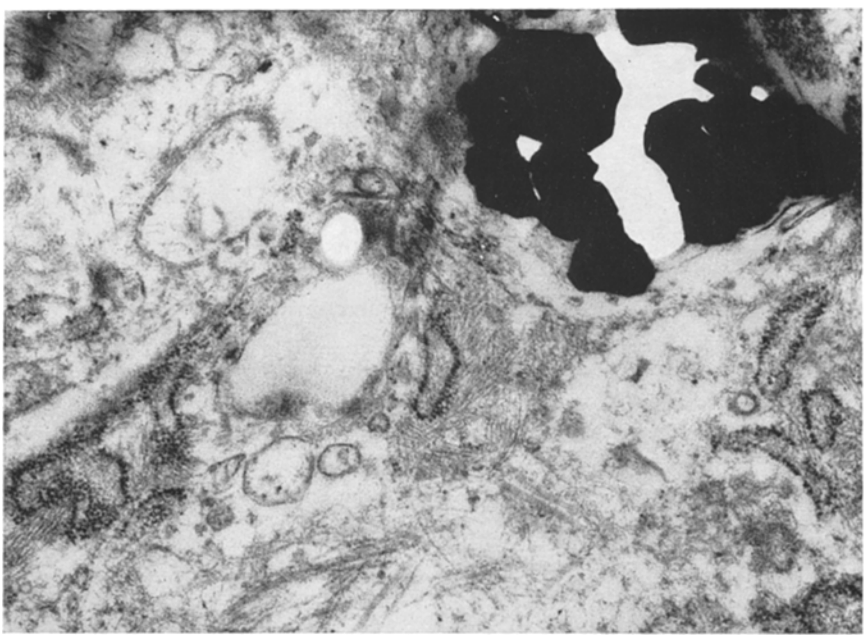


Fig. 10. Macrophages with phagozytosed foreign body material (metal ?). The rough endoplasmatic reticulum is increased. There are numerous filamentous structures in the cytoplasm. (E Nr. 10767/74, Polyester prosthesis 34 months after implantation. EM, ×9600 before reproduction)

cement up to two years after polymerisation (Mohr, 1958). Thus they may cause continuous tissue damage with an inflammatory reaction. Whether the acrylic cement particles seen in the giant cells derive from material dispersed during the operation or from the polymerized cement separated by mesenchymal cells is not clear. Willert and Semlitsch (1972) favour the latter possibility. However we could not find an increase in the deposition of methylmethacrylate in the later periods. According to their large size the cement fragments are deposited mainly in giant cells. There were never any specific inflammation or necroses around the deposits of this material. Proliferation of histiocytes containing this material could not be seen.

As infection and tissue reaction to acrylic cement in the early phase the reaction to the fine foreign body particles abraded by the continuous friction of the alloplastic material with metal or bone are responsible for the inflammatory changes in the later phase.

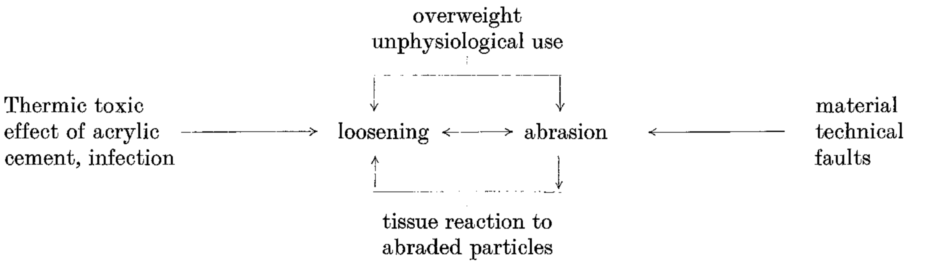
The way the abraded particles reach the area between implanted parts and the bone is probably mechanical and or to a lesser degree by lymphatics. As already described the abraded material forms cheeselike masses which fill out the joint space and so can be pumped by the moving ball of the prosthesis into the bone surrounding the artificial socket or the shaft. Our findings in the knee joint, show that the size and shape of the abraded particles depend of the kind of motion the artificial joint is due to perform. The rotating movement of the ball of the hip prosthesis in the socket and in addition in the three part prosthesis around the pivot of the shaft causes an abrasion of mainly small particles. The limited motion of the knee joint produces an abrasion of the described mostly large "floe" like fragments.

As it is shown histochemically by the high activity of acid phosphatase and ultrastructurally, the phagocytosed polyester particles initiate structural and functional changes as they are seen in the transformation of mononuclear cells into macrophages (Sutton and Weiss, 1966). The enlargement of the rough endoplasmatic reticulum and the formation of cysternae parallel the increase in the synthesis of lysosomal enzymes which are characteristic for phagocytosing cells (Gedigk and Bontke, 1957; Gusek, 1962). The filamentous structures in the cytoplasmic ground substance are probably responsible for intracellular transport or cellular mobility (Sutton, Weiss, 1966). These structural alterations, the multiple secondary lysosomes, the myelin figures and the phagosomes probably cause the characteristic granular, sometimes polarizing appearance of the cytoplasm of the macrophages.

However these changes are not merely an indication for an altered cellular function but they suggest also degeneration and probably cytotoxicity. The myelin figures and the positive fat stain of the histiocytes could be the result of an unmasking of phospholipids (Gusek and Mestwerdt, 1963). This may be important since free phospholipids are thought to be a causative factor in granuloma formation as e.g. in sarcoidosis (Fresen, 1958).

Similar changes but not as extensive as in the polyester cases could be seen in histiocytes phagocytosing polyethylene particles. The difference in tissue reaction is not due to a different size of the abraded particles (Willert and Semlitsch, 1974). Except for one case the polyethylene prostheses showed quantitatively less abrasion. Only the case with the time interval of 30 months, where numerous abraded particles were seen, displayed changes similar to the polyester cases. Thus we can assume that an "overloading" of periprosthetic tissue with abraded particles produces the characteristic granuloma formation with the following necrosis. — Usually foreign body granuloma in humans or experimental animals undergo scarring despite degenerative cellular changes and necroses. In these cases the continuous supply of polyester and to a lesser degree of polyethylene particles prevents a regular scar formation which is only seen in the outer parts of the capsule. In addition to this overloading, cytoxicity of the chemical compounds in the different alloplastic substances could be of importance causing granulomas and necroses. Spector *et al.* (1968) found no difference in inflammatory reaction caused by straight-chain or cross linked polymers. The most determining factor in histiocytic foreign body inflammation caused by polymers is the molecular weight and the quantity of substances. The effect of the "overloading" of the histiocytes is probably augmented by an insufficient removal of the foreign body material by lymphatic vessels. The two lymphnodes we examined showed surprisingly few double refractile substances in proliferating histiocytes. Thus the "overstrained cells" degenerate and finally become necrotic. In the tissue surrounding the prosthesis this proliferation causes a broadening of the fibrous membrane and a further impairment of the anchoring by invasion and destruction of the spongiosa. Finally this leads to the clinically so important loosening of the prosthesis which in most of the cases takes place around the socket.

We can summarize our findings in the following diagram, which shows the different mechanism known to cause loosening of the hip prosthesis (Cotta and Schulitz, 1973). In accordance with Willert and Semlitsch (1972–74) we can add the tissue reaction to the abraded polyester and polyethylene particles as another, probably the most important factor responsible for the malfunction of the artificial joints. Thus it becomes obvious that the durability of these prostheses is limited and that we have to expect more exchange operations for loosening in future times.



We are indebted to Mr. H. Derks ing. grad. for his assistance in preparing the photographs.

Addendum. Between September 1974 and February 1975 we had the opportunity to study material from 20 more patients with loosened prostheses of the hip and knee joint. The structural and histological changes were identical with our findings and confirmed our results.

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