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The Foreign Body Reaction in Total Hip Arthroplasties

A Correlated Light-Microscopy, SEM, and TEM Study

U. E. Pazzaglia[1], C. Dell'Orbo[2], and M. J. Wilkinson[3]

[1] Institute of Orthopaedics of the University of Pavia, Via Taramelli, I-27100 Pavia, Italy
[2] Institute of Anatomy of the University of Pavia, Via Taramelli, I-27100 Pavia, Italy
[3] Department of Biomedical Engineering, Brockley Hill, Stanmore, Middlesex HA7 4LP, United Kingdom

Summary. An in vivo histological and ultrastructural study of the cellular reaction to particulate material currently used in orthopaedic surgery produced evidence that, on a strictly cellular level, the main damage is done by the smallest particles produced by hip prostheses, i.e. metal particles, irrespective of differences in their chemical composition. Particle size and release rate are the critical factors, although other mechanisms of cellular damage may be active once granulation tissue is formed.

Candidate biomaterials are evaluated by a number of methods to assess their mechanical and biological suitability for implantation. With regard to biological suitability, the factors of size, shape and temporal effects are of particular importance.

The relevance of the form and size of foreign materials has been observed in tumor induction studies [12, 13]. These factors are also of significance in the foreign body reaction to wear and corrosion debris released from hip prostheses [1, 15].

The time parameter is also relevant: If particles are presented to cells at a rapid rate they will be enveloped by a capsule of connective tissue [4]. If particles are released slowly into tissue they will be phagocytosed with a significantly greater degree of associated cellular reaction. The latter condition is typical of the mode of release of wear and corrosion debris in vivo.

Retrieved implants and associated tissue are an important source of material for the study of the biological reaction to particulates [3, 7, 14, 15]. The histology of the foreign body reaction in hip arthroplasties is well documented [5, 8, 15]. Along with routine light microscopy, a limited amount of ultrastructural work has been performed in this area [17]. Up to now, no attempt has been made to correlate size, shape and composition of particles to cell response at both the histological and the ultrastructural level.

In this study we have employed several methods of light microscopy and electron microscopy in an attempt to achieve this.

Offprint requests to: U. E. Pazzaglia

Materials and Methods

The material for this work was obtained from 12 cemented hip prostheses removed following aseptic loosening. Case reports are not included because the study concerns exclusively the cell response to foreign materials. Femoral components included stainless-steel and cast Co-Cr alloy prostheses of different designs. The cups were all of high-density polyethylene. Radiopaque cement had been used in all cases. The main data on these prostheses are summarized in Table 1.

Tissue specimens were obtained from the capsule surrounding the head of the prosthesis and from the bone-cement interfaces of the stem and the cup. For light microscopy, specimens of tissue were fixed in 10% formaldehyde buffered at pH 7.4 before embedding in paraffin. Sections 5–7 μm thick were stained with haematoxylin-eosin. Other specimens were fresh frozen to −70°C and sections were then prepared with a cryotome. These sections were stained for lipids and acid phosphatase [2]. Scanning electron microscopy and X-ray microanalysis was performed on routine histology sections; the coverslip was removed with xylene and the sections were coated with a thin layer of carbon or gold. For transmission electron microscopy specimens were fixed in 4% buffered glutaraldehyde and post-fixed in 1% osmium tetroxide solution. They were dehydrated in alcohol and embedded in Epon 812 resin. Some of the thin sections prepared by ultramicrotomy were stained with uranyl acetate and lead citrate before examination in a Philips 300 TEM.

Table 1. Data on implants which supplied tissue specimens for the study

Patient	Prosthesis	Alloy	Removed after	Stem surface signs[a]
CGB	Charnley	Stainless steel	5 years 1 month	Corrosion
NE	Charnley	Stainless steel	2 years 1 month	Breakage, corrosion and wear
EG	Müller	Co-Cr	9 years 6 months	Wear
CW	Müller	Co-Cr	2 years	Wear
MP	Charnley	Stainless steel	5 years 2 months	Corrosion
BR	GR (Rizzoli)	Co-Cr	11 years 3 months	Wear
RA	Charnley	Stainless steel	6 years 8 months	Corrosion
PM	Charnley	Stainless steel	11 years 5 months	Breakage, corrosion and wear
AP	Müller	Co-Cr	6 years 3 months	Breakage, wear
SF	Charnley	Stainless steel	6 years 10 months	Breakage, corrosion and wear
FP	Charnley	Stainless steel	7 years 5 months	Breakage, corrosion and wear
PF	Charnley	Stainless steel	11 years 1 month	Breakage, corrosion and wear

[a] No sign of abnormally high wear was observed on the sockets

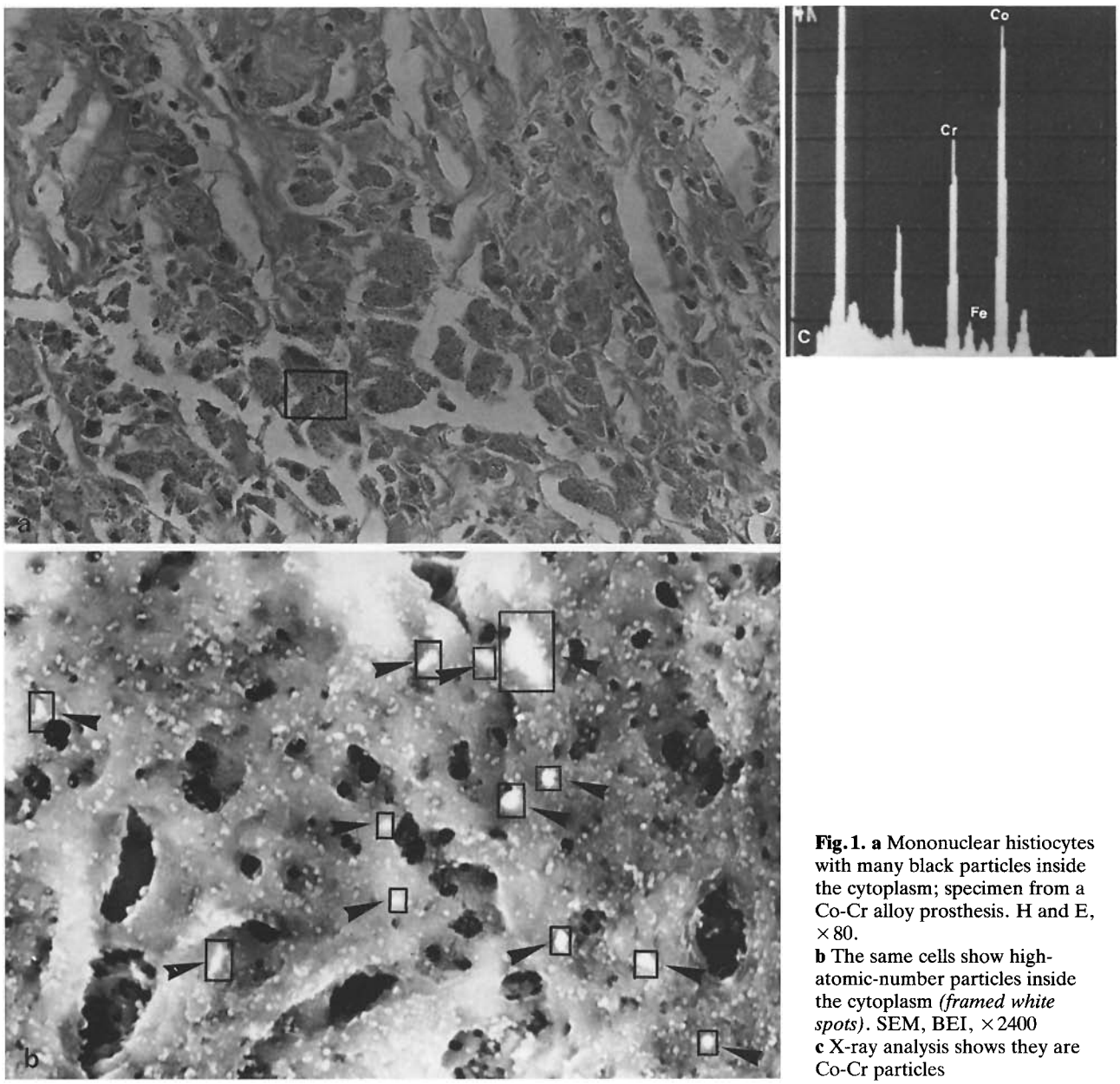


Fig. 1. a Mononuclear histiocytes with many black particles inside the cytoplasm; specimen from a Co-Cr alloy prosthesis. H and E, ×80.
b The same cells show high-atomic-number particles inside the cytoplasm *(framed white spots)*. SEM, BEI, ×2400
c X-ray analysis shows they are Co-Cr particles

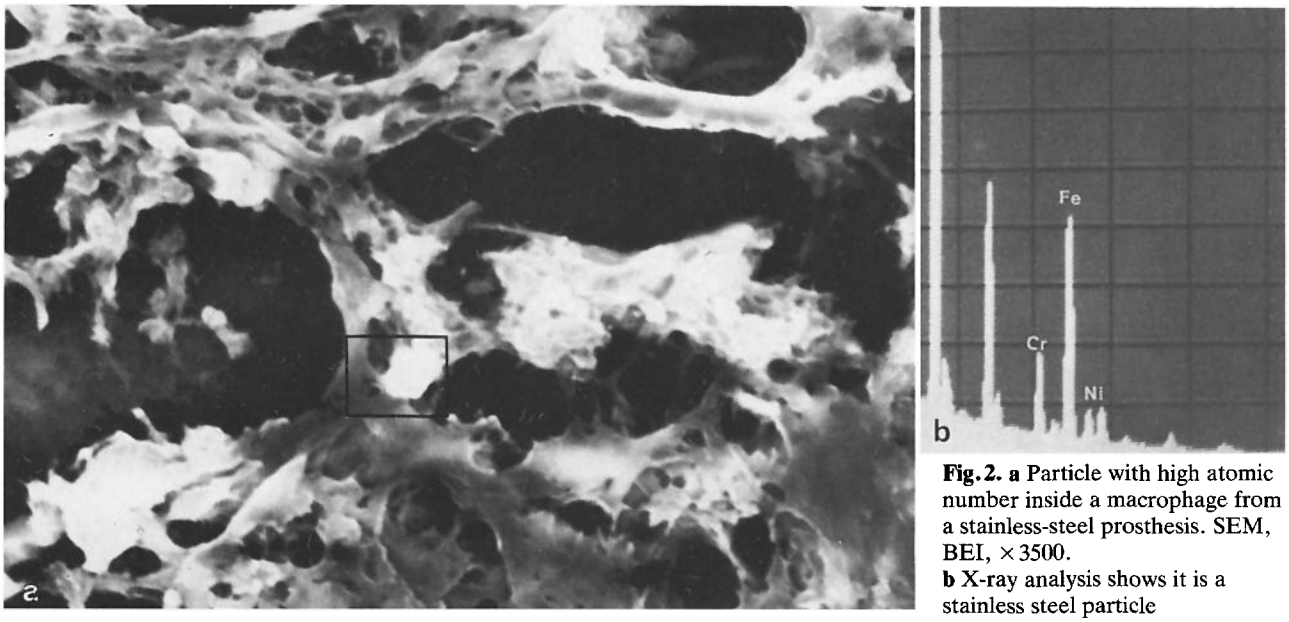


Fig. 2. a Particle with high atomic number inside a macrophage from a stainless-steel prosthesis. SEM, BEI, ×3500.
b X-ray analysis shows it is a stainless steel particle

Results

Three classes of material in particulate form produced in vivo by hip prostheses were observed in this study: metal particles, polyethylene fibres and methylmethacrylate globules. Each class is well characterized, not only by the chemical composition but also by the shape and size range. In these respects all cases were similar.

Metal particles were always observed inside the cytoplasm of cells; only where an acellular and not yet organized biological material (fibrin-like material) was present were the particles cell free.

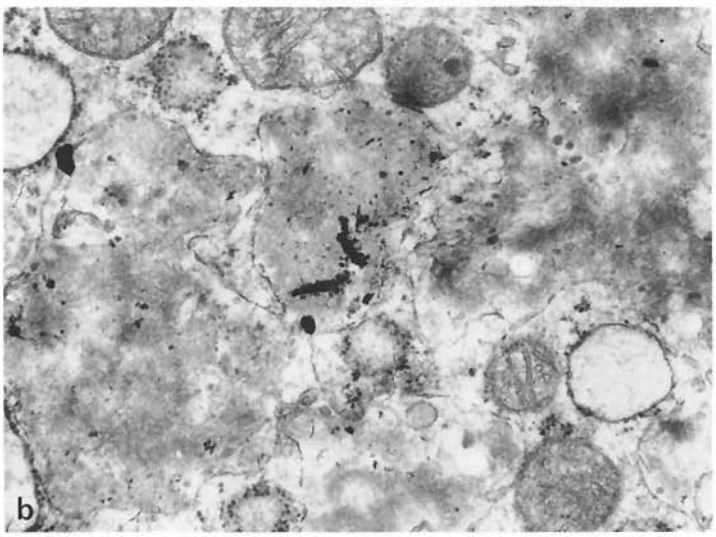
The metal particles were phagocytosed by mononuclear histiocytes, which exhibited a foamy cytoplasm. The particles appeared black when viewed by transmitted light microscopy and had an irregular shape. They were not larger than 1 μm (Fig. 1). Metal particles are not birefringent in polarized light; indeed, they are opaque to the light, but the smallest refract the light on their edges, so they appear weakly luminous. The same refraction is evident when they are observed in a dark field.

Acid phosphatase and lipid staining showed a very positive reaction in the cells which phagocytosed metal particles.

A scanning electron microscope with a backscattered electron detector revealed the particles as bright spots, and simultaneous X-ray analysis confirmed their elemental composition: Ni, Cr, Mn and Fe were detected in particles from stainless-steel prostheses, Co, Cr and Mo from Co-Cr alloy prostheses (Fig. 2). In ultrathin sections, both stained and unstained, electron-opaque particles were contained in numerous secondary lysosomes, which dominated the cytoplasm. X-ray analysis by TEM was used to confirm the metallic nature of this opaque material (Fig. 3). While some cells had uninterrupted cytoplasmic and lysosomal membranes, other cells exhibited disruption of these structures, having suffered various degrees of cellular damage, and in some cases appeared frankly necrotic (Fig. 4). Such macrophages were observed both in soft tissue specimens and in bone specimens, where they had penetrated the haversian canals of diaphyseal cortical bone and the medullary spaces of cancellous bone.

Polyethylene particles are transparent and therefore cannot be directly observed by bright-field light microscopy. In polarized light they are birefringent; their shape is that of elongated, irregular fibres or flattened chips; the size range is wide, but they are never less than 3 μm. The smallest particles are phagocytosed by mononuclear cells, but as the size increases they are engulfed by multinucleated giant cells or surrounded by a fibrous tissue capsule.

Polyethylene fibers inside the cells cannot be detected by scanning electron microscopy because their low atomic number gives rise to a poor backscattered electron signal. Larger particles, which lie outside the cells, may be observed directly by the SEM operated in the secondary electron mode. They are elongated like stripes or look like flattened chips; their surface is rough and frayed (Fig. 5). In TEM polyethylene fibres inside the cells look like electron-transparent areas, rounded or elongated in shape according to the plane of the section, the smallest reaching



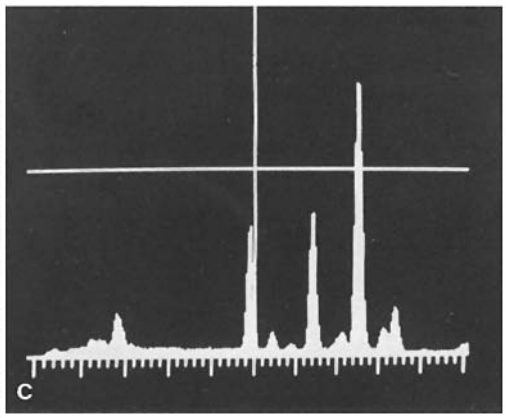


Fig. 3. a A fibroblast with normal morphology and a mononuclear histiocyte with many lysosomal cisternae which contain highly electron-dense particles. There are electron-transparent holes where the largest particles tore the slice under the microtome blade. There are no electron-dense particles in the intercellular matrix. TEM, ×9000.
b Large secondary lysosomes of a mononuclear histiocyte containing highly electron-dense particles. TEM, ×46000.
c X-ray analysis shows electron-dense particles to be Co-Cr alloy

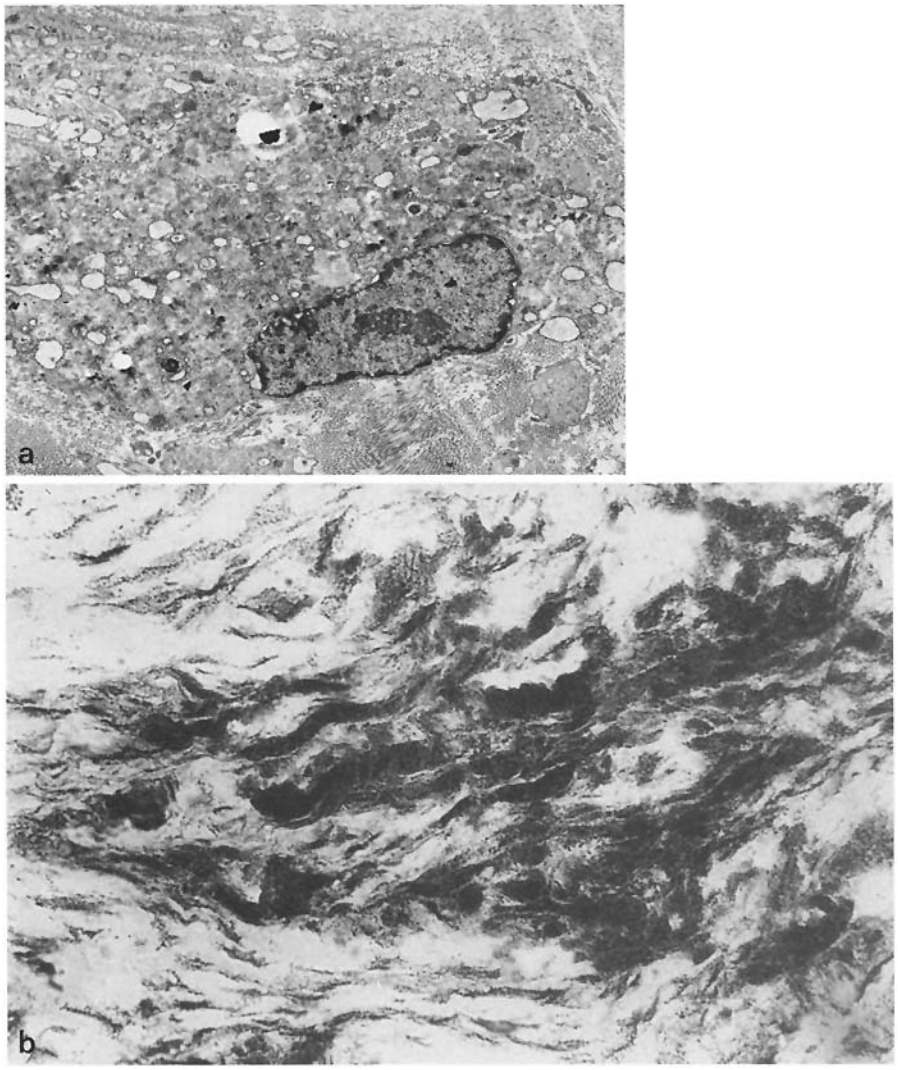


Fig. 4. a A mononuclear histiocyte in very poor condition with many large lysosomes, widespread myelinic figures and discontinuous plasma membrane. TEM, × 4000. **b** Mononuclear histiocytes show a strongly positive reaction for acid phosphatase. × 175

30000 Å. The edges may be irregular, with deep gaps where cytoplasmic substance penetrates. No evidence of membrane structure is observable around the particles, and they appear to be in intimate contact with the cytoplasm. The cells have well-developed cytoplasmic organelles and appear healthy.

Often, it is possible to observe cells which have phagocytosed both small polyethylene particles and metal particles. In this case, metal particles are always observed inside secondary lysosomes, while polyethylene particles do not exhibit any definite relation with the cytoplasmic membranes (Fig. 6).

Methylmethacrylate particles are solubilized by solvents used in tissue processing. Their presence is implied by rounded, empty holes in the section. These are surrounded by large multinucleated giant cells or by a fibrous connective capsule. The size range is wide, the smallest being about 50–100 μm in diameter and engulfed by a single giant cell, while the largest may be 3–5 mm in diameter surrounded by a fibrous capsule. Both giant cells and fibroblasts of the capsule lack acid-phosphatase staining activity.

Some of the globules may contain a fine granular material which refracts the light in dark field and in polarized light. The corresponding SEM picture is of empty cavities inside one giant cell or between two or more giant cells. Bright material looks like granular particles, 0.1 μm in size, and with a high atomic number if observed in BEI and with the characteristic spectrum of barium in X-ray analysis (Fig. 7).

The same granular material may be observed in the general vicinity of the acrylic globule and is present only on the surface of the adjoining cells, never inside the cells. This is due to the fact that Ba particles become dislodged during processing of the tissue.

Transmission electron microscopy of thin sections showed the cells surrounding the acrylic globule to

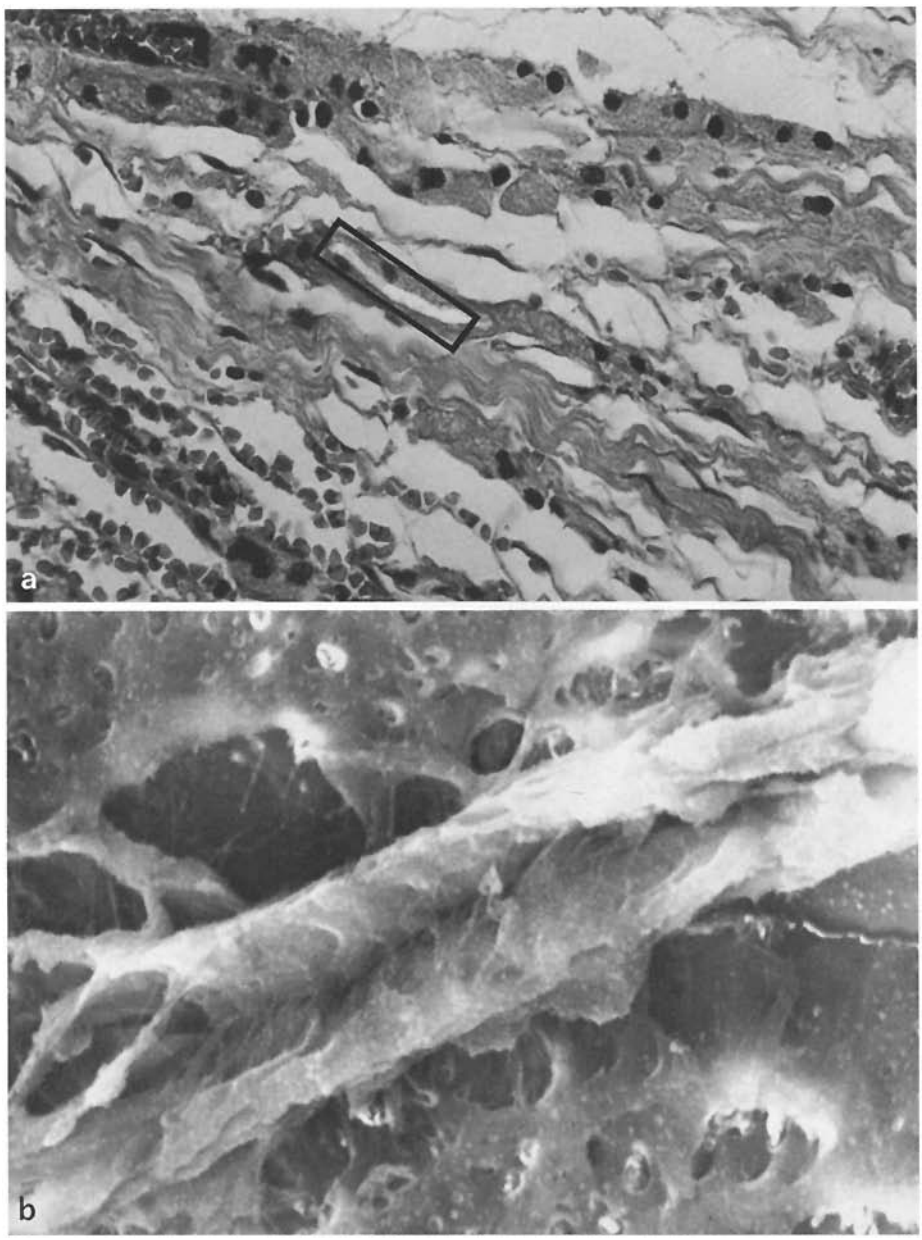


Fig. 5. a A large polyethylene fibre surrounded by histiocytes; double exposition in polarized light and bright field. H and E, ×80.
b The same fibre in scan. SEM, SEI, ×1600

have a well-developed endoplasmic reticulum, free ribosomes, mitochondria and a well-developed Golgi apparatus. The plasma membrane adjacent to the methylmethacrylate was complete, with a thin layer of filamentous material (fibrin-like) interposed between the cell surface and the acrylic cement. Thin sheets of the same material appeared inside what could have been gaps in the mass of the acrylic globule. The cells had a healthy appearance (Fig. 8).

Discussion

Three types of foreign bodies are considered, which are produced by hip prostheses comprising a metal stem with a high-density polyethylene cup and fixed by acrylic bone cement. Identification of particles by routine light-microscope histology is easily achieved [1, 8, 15], but little is known about the cellular response to each type of foreign material as it can be visualized by electron microscopy and histochemical methods.

Several factors influence the cellular reaction to foreign material:

The Chemical Composition of the Material

Toxic materials may produce intracellular damage and necrosis. Toxicity of metals used in orthopaedic

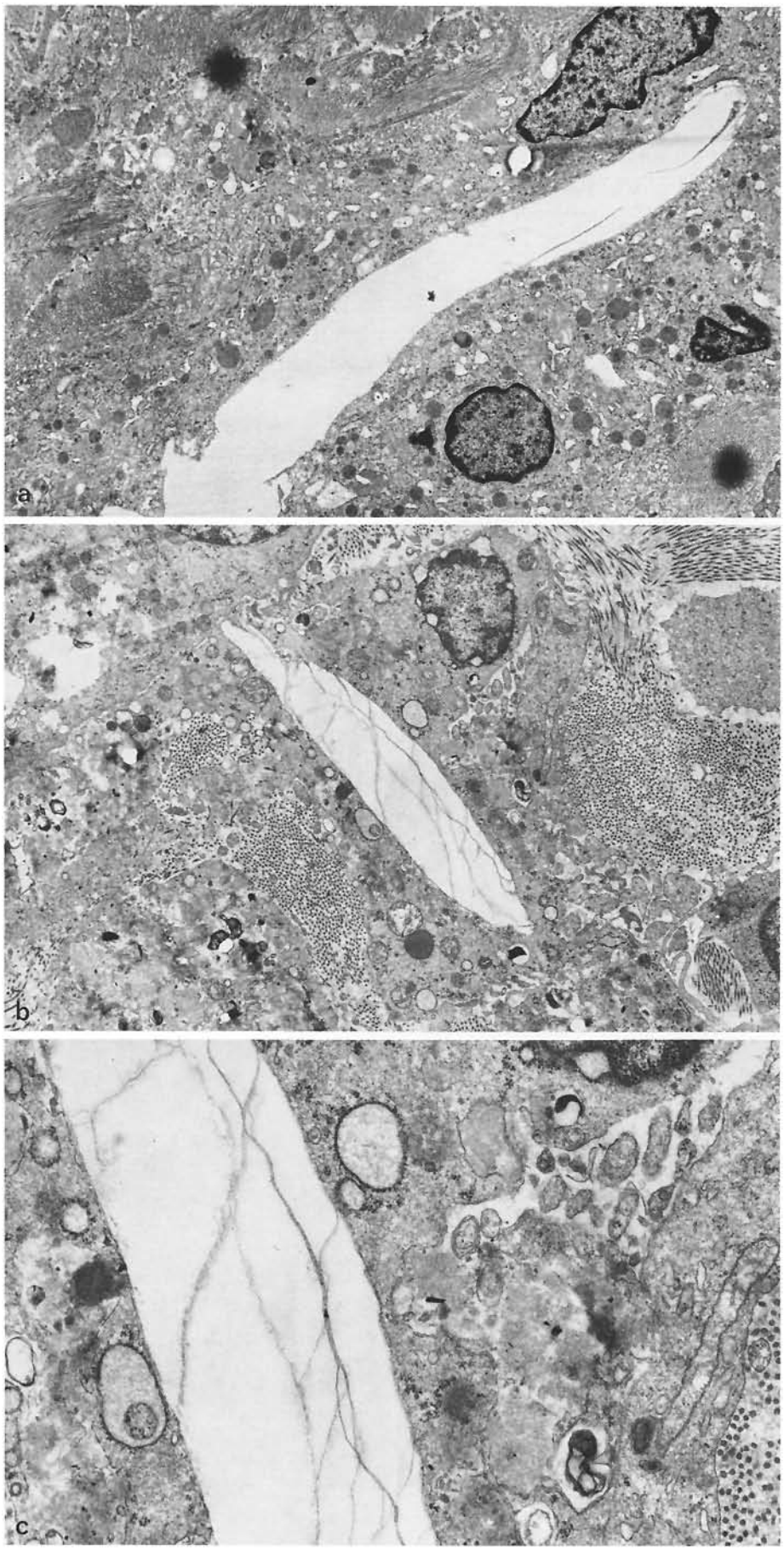


Fig. 6. a A large polyethylene fibre surrounded by several mononuclear histiocytes or giant cells. No lysosomes are observed inside the cells. TEM, ×9000.
b A small polyethylene fibre inside the cytoplasm of a mononuclear histiocyte. TEM, ×10200.
c Detail of **b**: The same cell has phagocytosed metal particles and they are observed inside lysosomes. TEM, ×26100

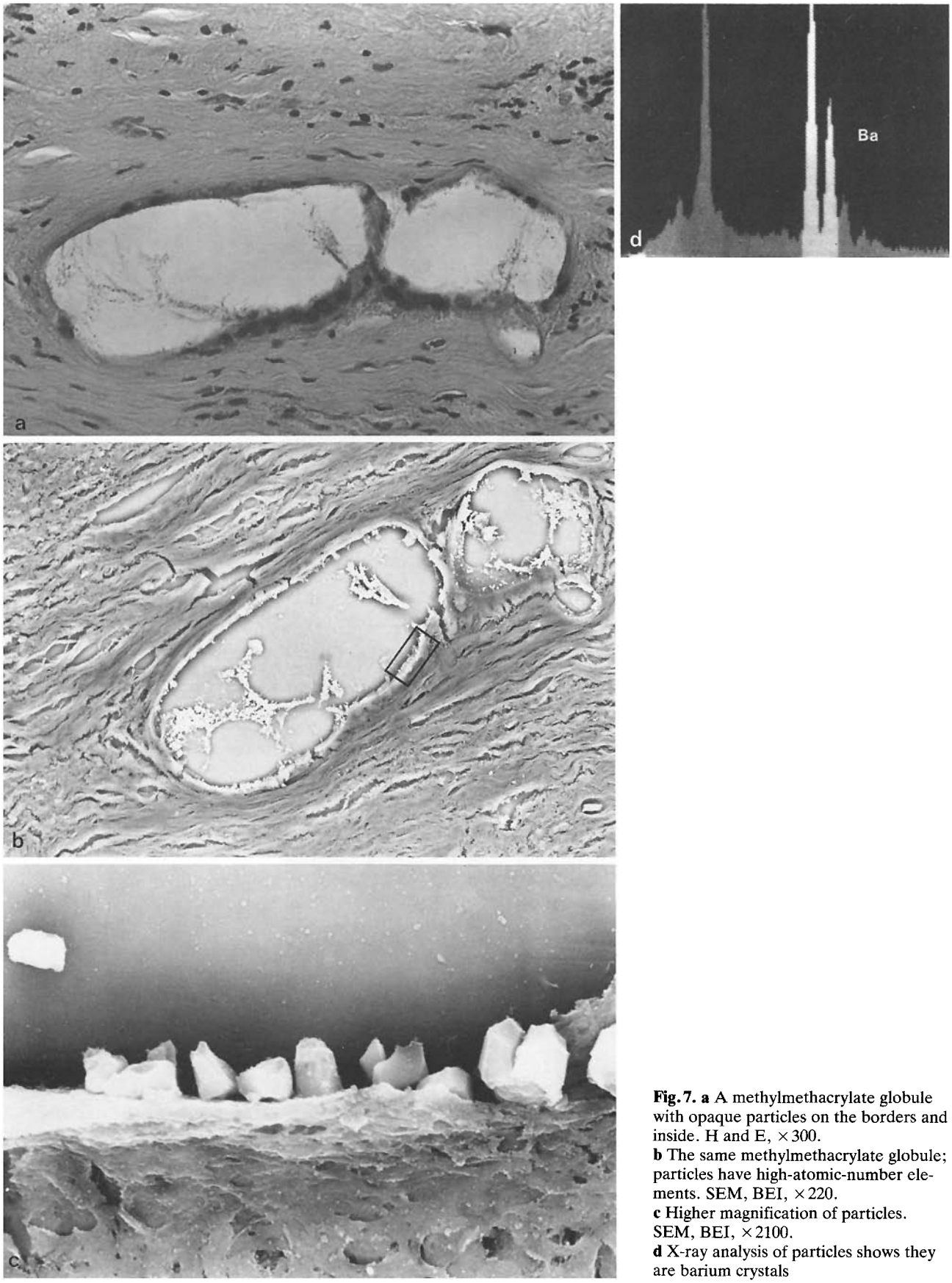


Fig. 7. a A methylmethacrylate globule with opaque particles on the borders and inside. H and E, ×300.
b The same methylmethacrylate globule; particles have high-atomic-number elements. SEM, BEI, ×220.
c Higher magnification of particles. SEM, BEI, ×2100.
d X-ray analysis of particles shows they are barium crystals

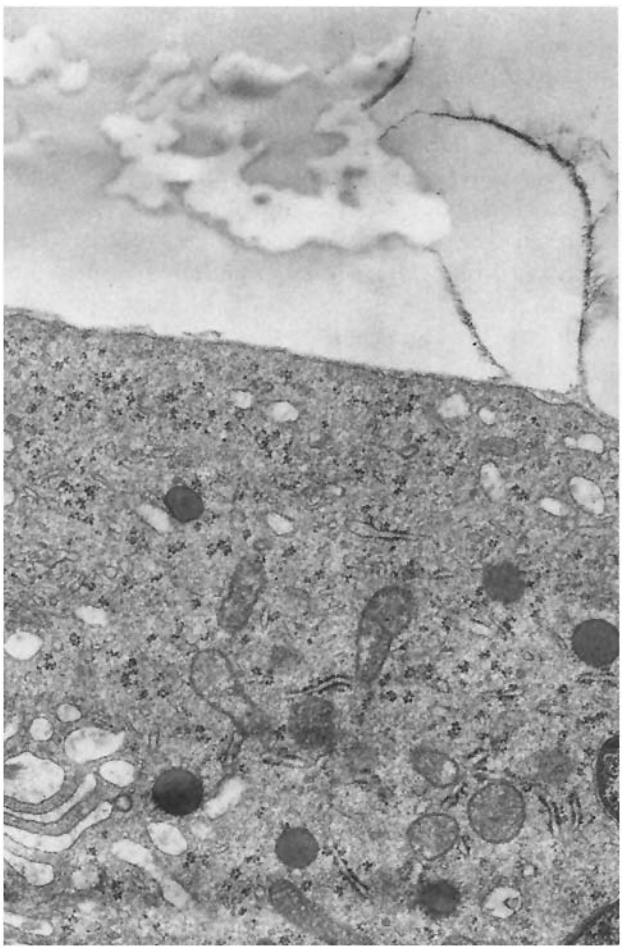


Fig. 8. Ultrastructural detail of a cell surrounding a methylmethacrylate globule. The cell shows a well-developed granular endoplasmic reticulum, ribosomes and mitochondria. The cell membrane is uninterrupted and a thin fibrin-like material is interposed between the cell membrane and the acrylic. Filaments of this material spread inside thin cracks in the acrylic. TEM, × 27000

implants has been observed for tissue culture cells (Co-Cr alloy being more toxic than stainless steel), but the metals seem to be well tolerated by human tissues [9,16].

The results of this study agree with the latter observation: cells which have phagocytosed or are in contact with particles of the studied materials do not show ultrastructural lesions of cytoplasmic structures. Necrosis was observed only in cells which had phagocytosed large amounts of metal particles either stainless steel or Co-Cr alloy), while small quantities of the same materials left the cells healthy.

Two explanations are possible: (a) It is necessary to accumulate large quantities of particles to release soluble ions sufficient to reach the threshold of toxicity, but in this case the behaviour of cells which phagocytosed stainless steel or Co-Cr alloy particles should have been different. (b) There is a mechanism of cellular damage other than direct poisoning by metal ions; this will be discussed later.

Also, barium particles were identified in contact with cells surrounding acrylic globules, but these were more likely an artefact related to processing of the specimens.

The Form, the Size and the Location of Particles

Methylmethacrylate particles are typically globular; polyethylene particles form fibres or chips; metal particles are very irregular in shape. The form of the particles is related to the mechanism of production. Methylmethacrylate particles are derived from free acrylic globules or from pieces of cement abraded by bone. Polyethylene particles are produced by processes of wear of the socket. Metal particles result from both wear and corrosion of the stem.

For each type, size shows a wide range of variation. Nevertheless, it is possible to characterize approximately the limits for each type, based on the structural properties of the original material and the mechanism of particle production.

Metal particles are the smallest, varying from 50–100 Å to a maximum of 1 μm. The size of polyethylene particles is difficult to evaluate in histological sections because of their fibre shape; they are randomly orientated in the tissue, and it is impossible to know if the section is cut perpendicular to the main axis of the fibre or parallel to it. Although with this limit the smallest polyethylene fibres observed in this work were about 3–5 μm long, while the longest reached 3–5 mm. The size of methylmethacrylate particles is easily evaluated on account of their globular shape with seriate sections: they vary from 50–100 μm to several millimeters.

The size of the particles is an important factor determining the behaviour of the cells; small particles (i.e. all the metal particles and the smallest polyethylene particles) are phagocytosed by mononuclear histiocytes, while larger particles are engulfed by multinucleated giant cells. When particles are very large they are surrounded by a fibrous capsule or by several giant cells.

This cellular behaviour was also observed in previous light-microscopy studies of the tissue reaction to foreign material [8,15]. Metal particles in the same size range but of different composition (stainless steel and Co-Cr alloy) have always been observed inside secondary lysosomes and appear to elicit the same intracellular response, i.e. development of the lysosomal system [6] and synthesis of lysosomal enzymes in an attempt to digest the foreign material. Small polyethylene particles have also been observed inside

the cell cytoplasm of mononuclear histiocytes, but they are not surrounded by any membrane structure. This is particularly evident in macrophages which have engulfed both metal and plastic particles.

The different reaction of the cells to the two types of material may be related to the chemical composition or to the different size; the smallest polyethylene particles are much larger than metal debris and well above the size of the lysosomal structures.

Neither large polyethylene fibres nor methylmethacrylate globules stimulate lysosome development or cytoplasmic organelle alterations in the phagocytosing or adjoining giant cells; indeed, lysosomes in multinucleated giant cells were observed to be not larger than those in mononuclear histiocytes. This leads to the hypothesis that for the material considered in this study the critical factor is size.

The Time Factor

It has been observed in experimental studies that small particles of metal debris implanted in the tissue of experimental animals are engulfed en bloc by a fibrous capsule [4]. Large masses of small particles presented to the cells at a rapid rate elicit a tissue reaction to the whole mass. Only if particles are released slowly in the tissue may the reaction develop through the phagocytosis processes, and this is the case with particles released from hip prostheses in vivo.

Cellular damage was observed to occur only in those cells which phagocytosed the smallest material particles, i.e. metal particles, while small polyethylene and acrylic particles were also phagocytosed by cells did not lead to lysosomal development. The following chain of events is suggested by the ultrastructural study of the foreign body reaction in periprosthetic tissues: In the attempt to digest the foreign material of suitable size, development of the lysosomal system and synthesis of lysosomal enzymes takes place; a single enzyme marker (acid phosphatase) was used here, but the result can be extrapolated to a wider range of lysosomal enzymes [10]. Because the material remains undigested, the cells become autolytic, and lytic enzymes, together with undigested particles, are ultimately released into the surroundings. More macrophages move in and so more lytic enzymes are produced, activating a self-perpetuating cycle.

The results of this study suggest that for materials currently in orthopaedic use the critical factors may be quantity, size and particle release rate; in the cases studied this critical combination was reached exclusively by metal particles (both stainless steel and Co-Cr alloy).

Previous papers concerning the failure of hip prostheses have emphasized the role of plastic wear particles in the foreign body reaction [1,5,11]. This is not in contrast with our results; we also observed a cellular reaction to these particles with stimulation of a granulation tissue, but in this case the mechanism of cellular damage is different from that of metal particles. As described by Buchhorn and Willert [1], an excessive proliferation of the granulation tissue tends to produce cellular necrosis if the blood supply cannot follow the expansion of the granulomas. In this case the critical factor becomes the quantity of wear particles when they exceed the capacity of transport and storage of the drainage system.

Conclusions

This study of the foreign body reaction in hip prostheses employing electron-microscopy methods has shown that metal particles are potentially more harmful at the cellular level than plastic or acrylic because of the factor of size. In this regard, differences between stainless steel and Co-Cr alloy particles were not observed.

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