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The histopathology of different foreign-body reactions in oral soft tissue and bone tissue*

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Summary. Foreign bodies may be endogenous or exogenous and provoke chronic inflammation of the foreign-body type. The reaction provides a mechanism for elimination of the foreign body and the reaction pattern depends on the kind of tissue involved. In soft tissues there is cellular inflammation and fibrous encapsulation with macrophages. In bone, during the healing period, biomechanical factors determine whether a fibrous encapsulation or a bony covering develops demarcating the foreign material. The particular characteristics of the foreign-body reaction in bone explain the success of dental and orthopaedic implants.

Key words: Foreign-body reaction – Soft tissue – Bone tissue – Implants

Introduction

Foreign bodies induce chronic inflammation. Depending on the kind of foreign material and its location, the reaction pattern of the connective tissue differs, but in every case the reaction provoked tends to eliminate the material by rejection, dissolution, resorption or demarcation. These materials may be endogenous or exogenous; endogenous materials include epithelial products such as mucin (mucoceles of extravasation type) or keratin (pilomatrixoma). Exogenous foreign material may be organic or inorganic in origin (Gardner 1987) and include the materials used as dental implants (biomaterials) which are titanium, tantalium or alumina ceramics. Calcium-phosphate ceramic is used for bone substitution in orthopaedics, dentistry and maxillofacial surgery.

Biomaterials are classified into three different groups according to their biocompatibility: biotolerated, bioinert, and bioactive. This grading is based on the tissue reaction to implant material in bone (Heimke 1990; Osborn 1979; Schroeder 1988). Implant reactions and foreign-body reactions are a problem with which a surgical pathologist is infrequently confronted and the preparation of histological slides with foreign material and adjacent soft or hard tissue requires special equipment.

The aim of this paper is to document the foreign-body reaction according to location (bone or soft tissue) and type of foreign material in biopsies. A comparison of the reaction pattern to different implant materials in human organs is made. A further factor investigated is into the classification of the biomaterial and its subdivision into biotolerated, bioinert and bioactive.

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Materials and methods

Biopsy specimens from buccal mucosa, mucosa of the vestibulum and jaw bone containing foreign material (amalgam, root filling material, calcium phosphate ceramics; Table 1) were fixed in buffered 4% formalin, dehydrated and embedded in light polymerizing resin (7200 VLC, Kulzer). Dental explants with surrounding hard and soft tissue and jaw bones with dental implants from autopsies and from animals in different experiments (Table 2) were fixed in buffered neutral 4% formalin and embedded in light polymerizing resin (7200 VLC, Kulzer) after dehydration. All the tissues were prepared without decalcification and without removing foreign material or implants using the "cutting-grinding" technique (Donath 1988).

For ultrastructural investigation implant replicas of epoxy resin with titanium coating of a thickness of about 90–120 nm were used. After a healing period of 3 months implants with parts of jaw bone from dogs were removed and fixed with Karnovsky (1965) fixative. Small slices were prepared by an Exact-cutting grinding unit (Donath 1988a) and post-fixed in 2% s-collidine-buffered osmic acid for 2 h, dehydrated through graded ethanol solutions, and embedded in epoxy resin (Luft 1961). Thin sections were collected on bare carbon reinforced formvar-coated grids and contrasted with uranyl acetate and lead citrate. The grids were examined and photographed with a Philips EM 300.

Results

Keratin provokes granulomatous inflammation in the connective tissue and is resorbed by multinucleate giant

Table 1. Type and number of biopsies containing foreign material

Material	Localization	
	Soft tissue	Bone
Catgut	84	–
Colatamp (collagen)	32	8
Keratin	6	2
Carbon	12	12
Calcium phosphate	38	162
Alumina ceramic	14	48
Bone sequestrum	8	14
Root-filling material	52	17
Amalgam	34	11
Shrapnel	1	1

Table 2. Jaw bones with dental implants (human autopsy and animal experimental material)

Type of implants	Human *n*	Animal *n*
Tübinger Sofortimplantate	7	38
Branemark	10	82
Bonefit	8	34
IMZ	28	60
Blade-Vents	12	40
Core-Vents	–	12

cells (Fig. 1a). The periphery of the granulomas is limited by fibrous tissue. There is a mild cellular inflammatory reaction with lymphocytes and plasma cells. Keratin in the bone marrow of an odontogenic keratocyst is in direct bone contact (Fig. 1b) but only on bone-free surfaces are multinucleate giant cells seen.

Carbon in muscle provokes the formation of multiple mono- and multinucleate giant cells on its surface and a small connective tissue wall around the adjacent muscle (Fig. 1c). The surrounding connective tissue shows macrophages with carbon particles in the cytoplasm; carbon in bone is surrounded by connective tissue if the carbon is in contact with the periosteum or muscle (Fig. 1d). Biomechanically stable carbon is in direct bone contact and its surfaces become bone-covered even when no bone is formed in these areas under normal circumstances (Fig. 1a). Bone-free carbon surfaces show mono- and multinucleate macrophages.

Calcium-phosphate ceramics in mobile soft tissues, which are used in alveolar ridge augmentation, are surrounded by bundles of collagen fibres running parallel to the implant surface. Between the ceramic surface and the fibres are spaces which contain multinucleate giant cells (Fig. 1e). The adjacent ceramic surface shows lacunae. The surrounding connective tissue is often infiltrated by macrophages with ceramic particles in the cytoplasm, and rarely by lymphocytes and plasma cells. Granules of calcium-phosphate ceramic under the mucous membrane of the alveolar ridge become surrounded by proliferating epithelium and particles in direct contact with the superficial layers of the covering epithelium are extruded by degeneration of superficial cell layers. Calcium-phosphate ceramics in bone provoke different reaction patterns which correlate with the calicum-phosphate ratio. Ceramics with a high calcium content are strongly alkaline in water, show less resorption on the ceramic surface and less bone contact over long distances. Calcium-phosphate ceramics with a low content of calcium have an acid reaction; bone binding occurs but the bone near the ceramic is hypomineralized. Hydroxyapaptite ceramics come into bone contact over long distances, but there are also bone-free surfaces which bear in mono- and multinucleate giant cells (Fig. 1f).

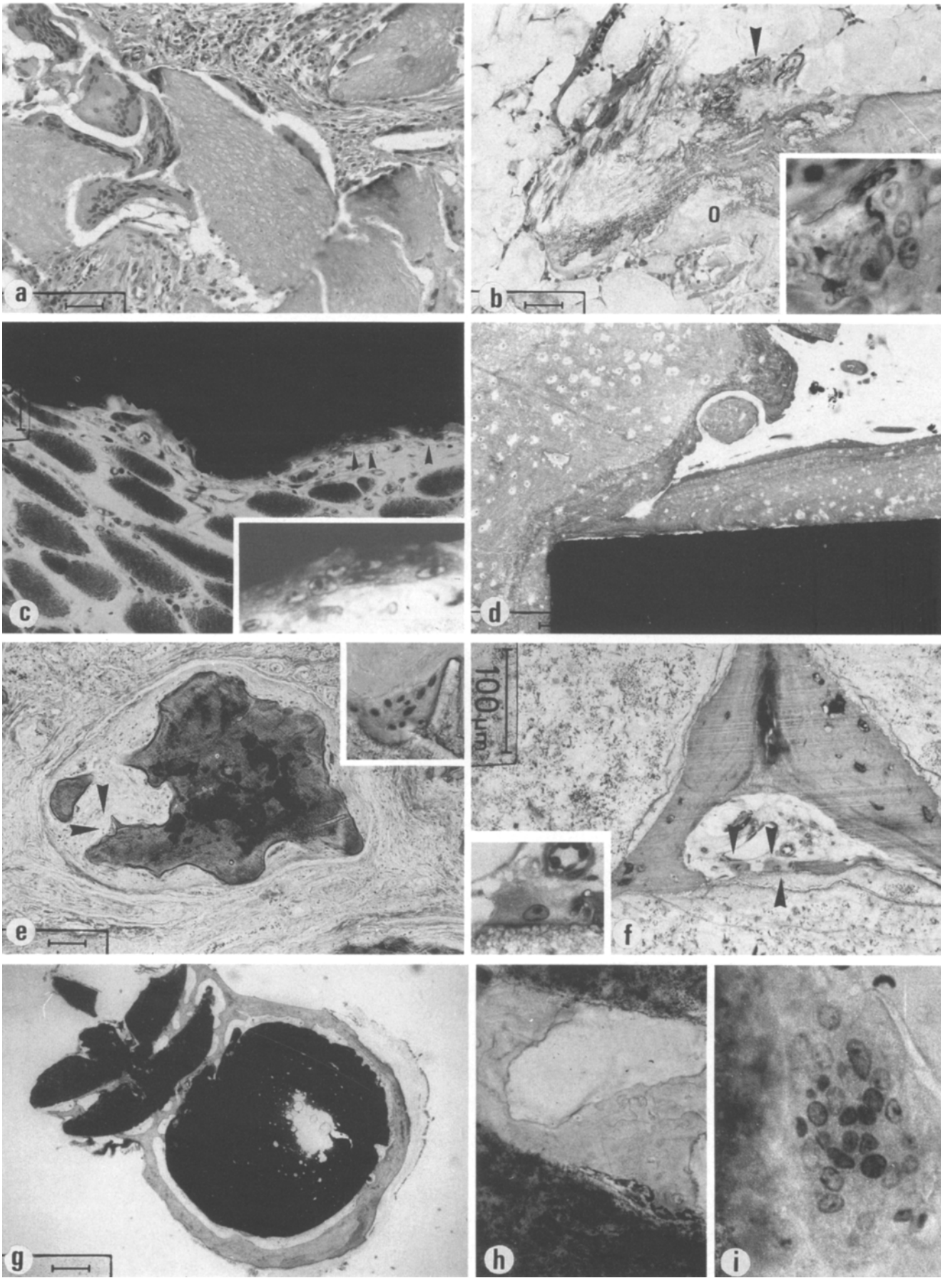
No bone bonding occurs on hydroxyapatite ceramic surfaces if the ceramic is in contact with the periosteum or muscle. Porous synthetic hydroxyapatite ceramic in an artificial cleft in the maxilla of a rat is surrounded by collagen fibres, with no bone on the implant surface, after 18 months.

Porous calcium phosphate ceramics in the bone marrow have a "wallpaper-like" bone layer on both surfaces and those in cortical bone which extend into the adjacent soft tissue become covered by bone at normally bone-free sites.

Root-filling material situated at the bottom of a maxillary sinus is surrounded by small bone lamella (Fig. 1g). In some parts the bone is in direct contact with the root filling material (Fig. 1h). Bone-free surfaces contain large mulinucleate giant cells (Fig. 1i) and the connective tissue shows no lymphocytes or plasma cells.

Amalgam is surrounded by multinucleate giant cells and peripherally by collagen fibres in the connective tissue of the buccal mucosa. Small amalgam particles are also situated in the cytoplasm of multinucleate giant cells (Fig. 2a). Collagen fibres around blood vessels are loaded with fine black granules. The connective tissue

Fig. 1a–i. Foreign-body reaction in soft and bone tissue. **a** Keratin from a pilomatrixoma is resorbed by polynuclear giant cells. Mild cellular inflammation, no fibrous capsule. H&E, ×150. **b** Keratin from an odontogenic keratocyst in the bone marrow surrounded by bone and osteoid (*O*), little resorption by polynuclear giant cells (*arrowhead*). Toluidine blue, ×140. *Inset*: polynuclear giant cell, ×560. **c** Carbon in the muscle is covered by polynuclear giant cells (*arrowheads*) and loose connective tissue. Toluidine blue, ×150. *Inset*: polynuclear giant cell, ×450. **d** Carbon in bone. Bone growing on carbon surface (bone conduction) when the carbon was immobile during the healing period. Toluidine blue, ×150. **e** Hydroxyapatite ceramic (Interpore 200) in soft tissue is encapsulated by fibrous tissue, some polynuclear giant cells on the ceramic surface (*arrowheads*). Toluidine blue, ×70. *Inset*: polynuclear giant cell, ×350. **f** Hydroxyapatite ceramic granulate in direct bone contact. Mononuclear macrophages on the bone-free ceramic surface (*arrowheads*). Macrophages with ceramic particles near to blood vessel. Toluidine blue, ×150. *Inset*: macrophage, ×450. **g** Root-filling material from the floor of the maxillar sinus below the mucosal membrane surrounded by a bone lamallae. Toluidine blue, ×18. **h** Part of **g**. Direct bone contact to the root-filling material. Toluidine blue, ×180. **i** Part of **g**. Polynuclear giant cell on the root-filling material. Toluidine blue, ×500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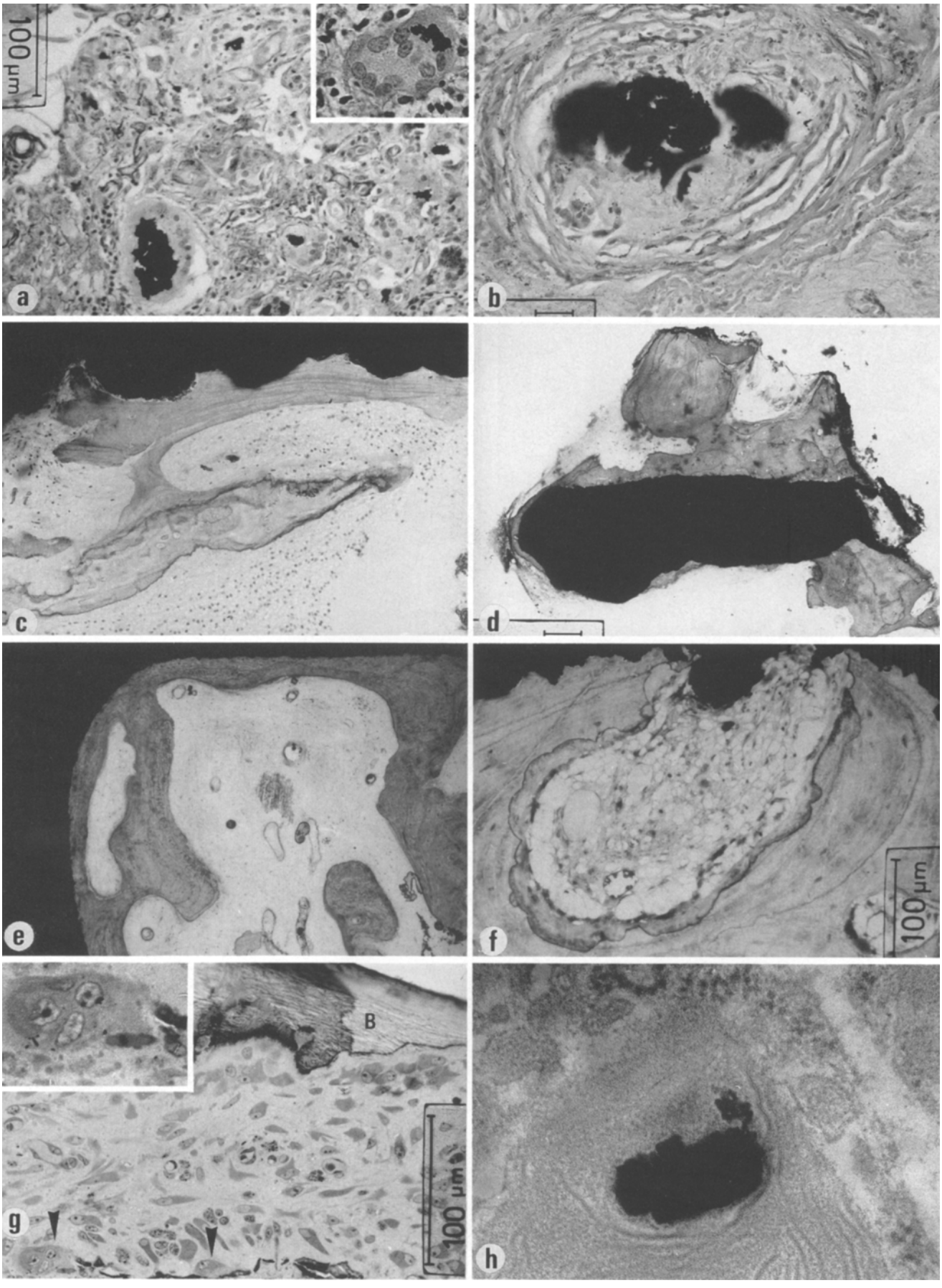
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is densely infiltrated by lymphocytes, histiocytes and plasma cells. Amalgam in bone after retrograde root canal filling is surrounded by collagen-rich connective tissue which is mostly hyalinized (Fig. 2b). Few multinucleate giant cells are seen on the amalgam surfaces under the collagen fibres. In the bone marrow amalgam is covered by bone over long distances and bone near to the corrosion zone of the amalgam is hypomineralized (Fig. 2c). Bone-free amalgam surfaces bear some mono- and multinuclear macrophages. In the minimal fibrous connective-tissue reaction few lymphocytes and macrophages are seen.

Shrapnel fragments from the frontal bone illustrated here were removed because of squamous cell carcinoma of the overlying skin. The shrapnel had lain in compact bone for 45 years. Histologically, large areas of the shrapnel are in direct bone contact (Fig. 2d). Only on the bone-free surfaces are there macrophages and corrosion products. Plasma cells or lymphocytes are not present.

Post-irradiation sequestra in the jaw bone are surrounded by connective tissue and the epithelium of the alveolar ridge often grows downwards and surrounds them. Within the epithelium they are lifted to the alveolar ridge and extruded.

Numerous dental implants of different designs are in use but most of them are made of titanium and several of tantalium and alumina ceramics. All kinds of implants come into bone contact if they are stable during the healing period (Fig. 2e, f). The implant surfaces are never completely covered by bone. Non-loaded implants are in contact with small bone lamellae, which are in turn in contact with the trabecular bone. The small bone lamellae are interrupted by areas of bone marrow or parts of the canal system (Fig. 2f). Between the bone marrow and the implant surface there are only two to three cell layers of fibrocytes with collagen, or the implant surface is in direct contact with fat. Bone-free surfaces of the implant of the canal system contain mono- or multinucleate macrophages. Macrophages on titanium implant surfaces occasionally contain small particles of titanium in the cytoplasm. Loaded titanium implants are covered by compact bone, which has only some bone-free areas near Haversian canals. Implants, loaded or unloaded, which extend into the nerve canal of the mandible have no bone contact in this part. They are covered by collagen fibres running parallel to the implant surface.

Titanium implants with calcium phosphate coatings have more bone contact than pure titanium implants with plasma flame-sprayed or sand-blasted surfaces. The calcium-phosphate coating of titanium implants is very often resorbed by multinucleate giant cells and membranous-like ceramic particles are enclosed in the newly formed bone.

Polycrystalline alumina ceramic implants have direct bone contact over long distances. Most of the implant surfaces show a zone with crystalloid particles, some of which are in the cytoplasm of adjacent mono- or multinucleate giant cells, and in the bone. There are often microscopically small spaces between implant surface and bone containing stainable homogeneous material. Bone-free implant surfaces are covered by a loose vascularized connective tissue or the fat of the bone marrow. A capsule of connective tissue develops around all implants which were not immobile during the healing period, independent of their material. Mono- and multinucleate giant cells are also seen on implant surfaces under the connective tissue.

In semi-thin sections mono- and multinucleate giant cells are in direct contact with the titanium coating on bone-free implant surfaces (Fig. 2g). Ultrastructurally there are metallic inclusions in membrane-rich lysosomes (Fig. 2h). On bone-covered implant surfaces hydroxyapatite crystallites from the bone matrix extend right up to the titanium surface to form an intimate contact between titanium and bone.

Fig. 2a–h. Foreign-body reaction in soft and bone tissue. **a** Amalgam in the connective tissue of the buccal mucosa with a cellular inflammation. Amalgam is enclosed in the cytoplasm of polynuclear giant cells. H&E, ×180. *Inset*: polynuclear giant cell with amalgam ×500. **b** Amalgam in soft-tissue in the jaw bone after retrograde root canal filling surrounded by fibrous tissue, single macrophages. H&E, ×280. **c** Amalgam in the bone marrow after root canal filling is covered by bone over long distances. Hypomineralization of the bone in contact with the amalgam. Toluidine blue, ×100. **d** Shrapnel 45 years in the os frontale. Large areas of the surface are in direct bone contact. Toluidine blue. ×62. **e** Basal part of an IMZ implant covered by bone. Toluidine blue, ×20. **f** Part of the surface of a TPS screw with direct bone contact and a Haversian channel with macrophages on the bone-free implant surface. Toluidine blue, ×180. **g** Tissue adjacent to an implant. Bottom: implant surface with mono- and polynuclear macrophages (*arrowheads*), loose connective tissue with macrophages, bone (*B*), Toluidine blue, ×380. **h** Metallic foreign body in a membrane-rich lysosome of a macrophage. EM, ×22000

Discussion

In a localized foreign-body reaction there is no noteworthy general response at all. The tissue response to endogenous and exogenous foreign material is complex and with the increasing use of so-called biomaterials such as calcium phosphate ceramics, plastics and metals in reconstructive surgery, it is a pathological problem of considerable importance. Most studies of foreign-body reaction have been concentrated on the soft tissue and little attention has been drawn to bone where the reaction differs.

Biomaterials used for repair and replacement of bone and as endosteal implants have been tested in bone (Albrektsson and Jacobsson 1987; Atkinson and Witt 1982; Branemark 1983; Branemark et al. 1969, 1977; Büsing and d'Hoedt 1981; Carlsson et al. 1986; Donath 1987, 1988a, b; Donath et al. 1985, 1987; Schroeder et al. 1978, 1981). Three different tissue reactions have been observed around the material tested: connective tissue formation, direct bone contact or bone bonding. Multinucleate giant cells are always present.

Bone tissue reaction to biomaterials is used as an indicator of their biocompatibility and the biomaterials are divided into categories of biotolerated, bioinert and bioactive (Breme and Schmid 1990; Heimke 1990; Osborn 1979). Heimke (1990) gives the following definitions of terms used for grading the degree of compatibility of bone replacement materials. *Biotolerated* materials show evidence of influence of material on adjacent tissue; ions or monomers leak into the surrounding tissue. The result is irritation and differentiation of precursor cells into osteoblasts (distance osteogenesis) and formation of a collagen-rich interlayer. *Bioinert* materials show no evidence of an influence of the material on local tissues. Leakage of ions and other matter from the implant into the surrounding tissue are apparently without effects on cells and without systemic effects. The result is an absence of biochemical influence on cell differentiation and proliferation; there is no biochemical response in the cells to the presence of an implant. An alternative hypothesis is that rapid and high affinity binding of molecules from the host covers the implant. The result is no enzyme reactions and the implant is "camouflaged" against the host's immune system. No foreign-body reactions develops. Contact osteogenesis may occur. *Bioactive* materials show deposition of collagen and/or hydroxyapatite from the surrounding bone onto the surface of the implant. It results in bone formation with a gluing effect (bonding osteogenesis) without the necessity for glue.

These definitions of biocompatibility describe the foreign-body reaction in bone, which is influenced by several factors. The number of multinucleate giant cells on the surface of biomaterial depends on its roughness (Donath et al. 1984) and the surface energy (Murray et al. 1989), not on the chemical nature of the material. The deposition of bone on the surface of biomaterial depends not on the kind of foreign material but on the primary stability during the healing period. (Donath and Kirsch 1986; Schroeder et al. 1978). Linder (1989) tested pure titanium, titanium-aluminium-vanadium alloy, chrome-cobalt alloy, and stainless steel in the tibia of adult rabbits. Under identical healing conditions, all metals were accepted by the bone in the same way. He concludes that osseointegration should be regarded not as an exclusive reaction to a specific implant material, but as the expression of a non-specific and basic healing response in bone.

The grading of biocompatibility of materials in bone as described by Heimke (1990) and others is flawed because their system is not based on fundamental bone reactions. Bone is a specialized connective tissue and corresponds to the fibrous capsule in connective tissue.

Foreign material which is resorbed very quickly in soft tissue is treated quite differently by bone. There is less resorption by micro- and macrophages. Most of the foreign-body surface in a mechanically stable zone of bone is covered by newly formed bone. This basic reaction pattern is found with all foreign material, like collagen (Collatamp; Osborn 1985), keratin, carbon, shrapnel, amalgam, root-filling material, ceramics and metallic biomaterial. This tissue reaction has been studied in transplantated devascularized bone, which is used as inert scaffolding to repair bone defects. The transplanted antigen-free bone is a splint on the surface of which the new bone grows. Surfaces without newly formed bone are covered by multinucleate giant cells with signs of resorption. All foreign materials in bone provoke an identical tissue reaction if they are immobile during the healing period and the mobility of the foreign body during the healing period affects the formation of collagen fibres running parallel to the foreign-body surface (fibrous capsule). The influence of mobility on bone growth is known from bone fractures where instability during the healing period leads to pseudoarthrosis. Connective tissue around foreign or biomaterial occurs also in large bone defects where regenerative tissue comes not only from the bone but also from the mucous membrane or nerve channel of the mandible. This regenerative tissue has no bone precursor cells or pre-osteoblasts; it produces collagen-rich connective tissue and ends as a fibrous scar.

Calcium phosphate ceramic is a bioactive material, mostly used as bone substitute material and as a coating on titanium implants. Its reaction in both soft and hard tissues is identical to other foreign material of organic or inorganic origin. No osteogenesis occurs on a calcium phosphate ceramic surface. Bone growth on ceramic surfaces is seen in other foreign materials as bone formation occurring at a slower rate than in the natural process (Donath et al. 1985). The main difference between other biomaterial and calcium phosphate ceramics is the border region between the bone and the ceramic. On calcium phosphate ceramic surfaces there is a bone-bonding comparable to bone formation on the enamel of impacted wisdom teeth (Schulz 1988), and the products of resorption go into the calcium-phosphate metabolism.

Endogenous and exogenous foreign material in soft tissue is capable of producing an inflammatory response: a foreign-body reaction. It is not possible to divide biomaterials into different grades of biocompatibility by their effects on soft tissue; a subdivision is only possible by examination of differences in biochemical stability (degree of solubility, resorption). Suture materials such as catgut produce a brisk acute pyogenic inflammatory reaction which is soon followed by the appearance of macrophages and giant cells. The strength of plain catgut is reduced to half within 2 days, whereas for chromic gut the time is 10 days (Gardner 1987). Collagen (Collatamp) is also resorbed by polymorphonuclear leucocytes. Granulomas with multinucleate giant cells are formed around keratin in connective tissue of epidermoid cysts and pilomatrixoma. Amalgam in the cheek provokes a chronic inflammation with lymphocytes and plasma cells. The amalgam itself becomes resorbed by mono- and polynuclear macrophages. Calcium phosphate, alumina ceramic and carbon provoke also a chronic inflammation with a granulomatous response. On the ceramic surfaces there are mono- and multinucleate macrophages. The ceramic surface adjacent to the resorbing cells contains lacunae as a sign of resorption.

The foreign-body reaction is a defence mechanism

to eliminate endogenous and exogenous foreign material and is different in soft and hard tissue. In soft tissue the reaction is of rejection, solution, resorption or fibrous encapsulation; in bone, by exclusion from other parts of the body through bone demarcation (immobile), fibrous encapsulation (mobile), or even by interposition of fat, as well as by resorption (Hillmann and Donath 1991). There are several other factors which determine the severity of the inflammatory response such as the chemical nature, physical state and electro-chemical potential of the material, but these do not change the basic tissue reaction pattern or foreign-body reaction to endogenous, exogenous or biomaterials. The numerous clinical, radiological and morphological studies in implants are specific investigations of the foreign body reaction. To our knowledge there is no biomaterial which is absolutely inert.

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