Acta neuropath. (Berl.) 41, 145–155 (1978)

Acta Neuropathologica
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Histopathological Evaluation of Materials Implanted in the Cerebral Cortex

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Summary. Histopathological changes of the cerebral cortex in response to small, penetrating metal and non-metal implants were analyzed by means of light and electron microscopy. The needle-shaped implants were left in place during all stages of histological preparation and embedded in plastic together with the cortex. Changes of the brain-implant boundary were classified as non-reactive, reactive, or toxic, according to the reactive cellular constituents. Among the non-reactive materials were several plastics and metals such as aluminum, gold, platinum, and tungsten. The boundary of these implants displayed little or no gliosis and normal neuropile with synapses within 5 µm of the implant's surface. The boundary of reactive materials such as tantalum or silicon dioxide was marked by multinucleate giant cells and a thin layer (10 µm) of connective tissue. Toxic materials such as iron and copper were separated from the cortical neuropile by a capsule of cellular connective tissue and a zone of astrocytosis. Cobalt, a highly toxic material, produced more extensive changes in the zones of connective tissue and astrocytes. These results indicate that a variety of materials are well tolerated by the brain and could be used in the fabrication of neuroprosthetic devices.

Key words: Cerebral cortex – Brain implants – Reactivity – Toxicity – Biocompatability – Neuroprostheses.

Animal studies have demonstrated the feasibility of implanting electrodes into the brain for long periods to stimulate nerve cells or record electrical activity (e.g. Delgado et al., 1961; Hess, 1932). Penetrating electrodes implanted in humans to monitor electroencephalographic activity and to stimulate the brain to identify epileptogenic foci have been well tolerated (Dodge et al., 1955; Heath, 1954; Ramey and O'Doherty, 1960; Spiegel and Wycis, 1961; Walker and Marshall, 1961). Thus it has been assumed that penetrating electrodes produce a negligible amount of damage and that no appreciable histological alterations occur in nearby nerve cells when little or no electrical current is passed.

We undertook the current investigation to determine the long-term effects of a variety of materials that might be used to fabricate cortical stimulating electrodes constituting part of neuroprostheses for the blind (Brindley and Lewin, 1968; Dobelle et al., 1974, 1976; Dobelle and Mladejovsky, 1974) and deaf (Dobelle et al., 1973). Although surface electrodes will probably be used in these devices, we chose needle-shaped materials resembling penetrating electrodes for analysis because they can be apposed directly to parenchymal nervous tissue without meningeal intervention and because they represent a "worst case" situation; i.e., they are in direct contact with neurons and are not buffered by cerebrospinal fluid. The current study did not consider the effects of electrical stimulation, but we are now investigating this question.

Studies relying on conventional techniques have revealed an inconsistent pattern of reactive change related to mechanical trauma during implantation or to the materials used to fabricate the electrodes (Collias and Manuelidis, 1957; Robinson and Johnson, 1961). Although Collias and Manuelidis observed a cellular capsule, loose connective tissue, and a dense zone of astrocytes, it is unclear whether these changes were caused by trauma or by the materials used. When Fischer et al. (1957, 1961) and Delgado (1961) introduced metallic and plastic-coated implants into the brains of animals, they observed few changes near

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Table 1. Summary of Histopathological Changes Surrounding Cortical Implants

Reactivity	Material	Type and/or Composition	Number of needles implanted	Duration of implants (days)
Non-reactive	Aluminum	Trace of iron[b]	16	132–190
	Alumina ceramic[c]	Sintered aluminum oxide: 96% alumina, 4% silica	6	59–215
	Gold[d]	99.9%	23	89–134
	Platinum	100%[b]	14	56–196
	Polyethylene[e]	Hifax, high-density type	9	74–202
	Polypropylene[e]	Profax	10	102–223
	Silicon	Single crystals doped with phosphorus at concentrations of 10^{18} P atoms/cm^3; resistivity = 0.005 ohm-cm	19	88–421
	Teflon FEP[f]		9	104–211
	Teflon FEP[f]	Type C20, chemically bondable	6	67– 92
	Teflon FEP[g]	Modified Penntube II SMT	6	67– 92
	Teflon TFE[f]	High-purity sample	12	104–222
	Tungsten	100%[b]	12	61–190
Reactive	Araldite	Epoxy plastic resin Durcupan ACM, Fluka AG[h] containing 0.1% methylene blue dye, Ehrlich 671[i]	62	50–723
	Silicon dioxide	Pyrex	14	59– 62
	Teflon TFE[g]	Type I with sodium-ammonia surface etching for adhesion	6	72– 88
	Tantalum	100%[b]	18	63–418
	Gold-silicon dioxide passivated micro-circuit[j]		27	130–197
	Molybdenum	100%[b]	18	61–227
	Nichrome	80% nickel, 19% chromium, 0.5% iron[b]	12	105–221
	Titanium dioxide	100%[b]	4	104–190
	Teflon TFE [g]	Penntube I, shrinkable	9	67– 88
Toxic	Silastic RTV	Industrial grade, Type D for mold making (vulcanizes at room temperature) on gold wire. Dow Corning	3	88–210
	Germanium	Electrically active elements, less than one part per billion	6	139–220
	Silver	100%[b]	12	125–219
	Iron	95.5% iron, 0.5% manganese[b]	10	132–188
	Copper	100%[b]	12	133–192
	Cobalt	Cobalt powder, form 309[k], and gelatin, USP lot 3139x[l], mixed according to Fischer et al. (1967, 1968)	62	72–553

[a] 0 = absent, + = occasionally present, ++ = often present, +++ = usually present
[b] Method of analysis: ARL electron microprobe
[c] Stratamet Ceramic Corp., Redwood City, Calif.
[d] Wilkinson Co., Westlake Village, Calif.
[e] Hercules, Inc., Wilmington, Del.
[f] E. I. Dupont de Nemours & Co., Wilmington, Del.
[g] Penntube Plastics Co., Clifton Heights, Pa.
[h] Chemische Fabrik, 9470 Buchs, Switzerland
[i] Chroma Gesellschaft, Stuttgart, Germany
[j] Wise et al., 1970; Integrated Circuit Laboratory, Stanford University, Stanford, Calif.
[k] Matheson Coleman & Bell, Norwood, Ohio
[l] J. T. Baker Chemical Co., Phillipsburg, N. J.

the insulated implants but "noticeable damage and necrosis" in the vicinity of metals such as silver and copper. Other investigators (Baleydier and Quoex, 1975; Chusid and Kopeloff, 1967; Dymond et al., 1970; Wilder et al., 1972) subsequently confirmed these findings using conventional histological procedures and ultrastructural techniques to evaluate the effects of silver, cobalt, and other metals.

Schultz and Willey (1976) described a sheath containing foreign body giant cells around metal electrodes coated with Epoxylite. Their ultrastructural studies confirmed the lack of direct contact between passive electrodes and central nervous tissue but did not consider factors governing the development of the capsule. An investigation of histopathological changes in nervous tissue in the vicinity of small in-dwelling

Table 1. Continuation

Connective tissue capsule[a]					Reactive central nervous tissue[a]						
Calcification	Macrophages	Meningeal fibroblasts	Plasma cells	Boundary or giant cells	Hypertrophic astrocytes	Loss of neuropile	Astrocytes with granules	Abnormal neurons	Dark cells	Perivascular cuffing	Large blood vessels
0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	+	0	0	0	0	0	0	0
0	0	0	0	+	0	0	0	0	0	0	0
0	0	0	0	+	0	0	0	0	0	0	0
0	0	0	0	+	+	+	0	0	0	0	0
0	0	0	0	+	+	+	0	0	0	0	0
0	0	0	0	+	+	+	0	0	0	0	0
0	0	0	0	+	+	+	0	0	0	0	0
0	0	0	0	+	+	+	0	0	0	0	0
0	0	0	0	+	+	+	0	0	0	0	0
0	0	++	0	+	+	+	0	++	+	+	+
0	0	++	0	+	+	+	0	0	+++	++	0
0	+	+	++	+	+	+	++	0	+	+++	+
+	++	+	+	++	+	+	+	+	++	0	+
++	++	++	+	+	++	++	+	0	+	+	+
+++	+++	+++	+	++	++	++	+	+	+	+	++

plastic needles revealed no sheath, little gliosis and normal synapses within 5 μm of the implant (Stensaas and Stensaas, 1976). In that study, chronically implanted Araldite needles were left in place during histological preparation, and the tissue was embedded in the same plastic. Leaving the implant in situ preserved the tissue-implant boundary and permitted a detailed correlation of changes at the interface by light and electron microscopy. The fact that the boundary remained stable after an initial period of adjustment suggested that little damage would result if intra-cortical implants of inert materials were used to interface a therapeutic or prosthetic device with the brain.

In the current study, the materials also remained in situ during all stages of tissue preparation, and plastic sections were used to assess cellular changes. Light and electron microscopic analysis of implants that remained in place for as long as two years indicated that while many materials were non-reactive and produced virtually no cortical alterations, others induced varying degrees of reactive change through local toxic effects.

Materials and Methods

Twenty-seven materials available in the form of sheets or wire were used to form wedge- or rod-shaped implants that were pointed at one end, varied in length from 2–3 mm, and had diameters of 0.5–0.75 mm or less. (The composition and, when applicable, the source and method of analyzing each material are noted in Table 1.) After the implants had been sterilized in 95% ethanol and air dried for 10 min, they were inserted into the cortex through burr holes in the skull. Thirty days post-implantation, no additional changes (except in the case of cobalt) related to mechanical trauma occurred.

Young adult rabbits weighing 1800 g were anaesthetized with Innovar, and their heads were immobilized. Four to 6 burr holes were drilled in the skull at least 5 mm apart, the dura was opened,

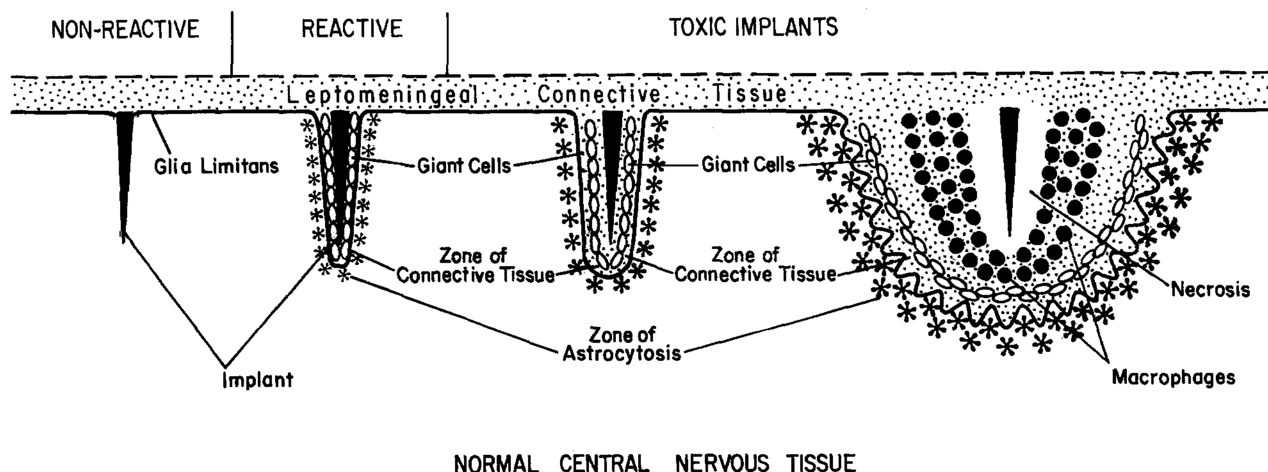

Fig. 1. Summary diagram illustrating the histopathological changes around non-reactive, reactive, and toxic implants. The zones of astrocytosis (asterisks) and connective tissue (stippled areas) vary in size in proportion to the implant's reactivity. Giant cells (white circles) and macrophages (black circles) are restricted to the zone of connective tissue

and needles of one material were carefully inserted into the brain with watchmaker's forceps (Fig. 1). The skin was then closed with wound clips, and the animals were allowed to survive from 50 to 723 days. Silicon dioxide and Araldite needles were also implanted in young adult rats weighing 150 g anesthetized with chloral hydrate and ether.

One hour before sacrifice, the animals were injected with 1000 units of heparin. They were then anaesthetized with Innovar and ether, respirated, and perfused through the heart with 0.12 M phosphate-buffered fixative (pH 7.4) containing 1% paraformaldehyde and 1% glutaraldehyde (Wuerker and Palay, 1969) or with 0.1 M cacodylate-buffered fixative (pH 7.4) containing 4% paraformaldehyde and 0.5% glutaraldehyde (Matthews and Kruger, 1973). Four hours after perfusion, the brain was partially exposed and the head was immersed in cold phosphate- or cacodylate-buffered fixative for 18–24 h.

Elongate blocks of tissue with the implants in the center were carefully removed without damaging the brain-implant boundary. A rim of cortex 0.5 mm wide surrounded each implant, yielding a block with final dimensions of approximately 4 × 1.5 × 2.0 mm. The blocks were washed in buffered sucrose solution, immersed in 2% osmic acid for 4–5 h, dehydrated in ethanol and acetone, and embedded in Araldite (Fluka). The boundary was then sampled using one of the following techniques. 1. Relatively soft materials such as aluminum and gold were left in place and sectioned together with the cerebral cortex. 2. The exposed surface of harder materials was carefully trimmed to a narrow strip along the boundary with either a stainless-steel razor blade or a high-speed dental drill. Although the glass knife was often damaged during sectioning, the boundary containing the tissue usually remained intact. 3. Extremely hard materials were partially exposed by removing portions of the tissue and then breaking the implant away from the block with fine forceps. In well-polymerized blocks, this procedure left an intact brain-implant boundary that could be cut with a glass or diamond knife.

Sections were taken from all blocks approximately 1 mm beneath the pial surface and, when necessary, from deeper and more superficial levels as well. Semithin (1.0 μm) sections were mounted on glass slides and stained with a 1% methylene blue-1% borax solution. Ultrathin (0.06 μm) sections were mounted on formvar film in one-hole (1 × 2 mm) grids and stained with uranyl acetate and lead citrate. Thirteen materials – aluminum, Araldite, cobalt, copper, germanium, iron, molybdenum, platinum, polyethylene, silastic RTV, silver, Teflon TFE, and Teflon FEP – were examined with the electron microscope.

Histopathological changes visible in plastic sections by light microscopy at high magnification (1000 ×) and by electron microscopy of companion sections were evaluated with reference to each type of reactive cell in both central nervous tissue and the connective tissue capsule. Estimates of the degree of change in each of these elements in the vicinity of implants with reactive alterations were based on comparison with boundary conditions of non-reactive implants. The changes that occurred were arbitrarily assigned a value on a three-point scale according to the degree of change visible in areas of minimal reaction. The findings from such evaluations, which involved several implants of the same material, were then compiled and used to prepare Table 1. The spectrum of reactive change apparent in Table 1 was used to classify implants as non-reactive, reactive and toxic and the general pattern characteristic of each was depicted qualitatively in a summary diagram (Fig. 1).

Results

Table 1 ranks the materials in order of increasing reactivity, according to the cellular constituents of the connective tissue capsule and changes in central nervous tissue. This classification is based on observations of semithin and ultrathin sections in which the implant remained in contact with the cortex during all preparatory procedures. The variability encountered at the brain-implant boundary of a particular material was attributable primarily to mechanical trauma during implantation (Stensaas and Stensaas, 1976) and, to a lesser extent, to ongoing damage caused by differential movement of brain and implant when the implant extended beyond the cortical surface and contacted the dura mater. To rule out the effect of this variability on the grading system used for histopathological analysis, only areas of minimal

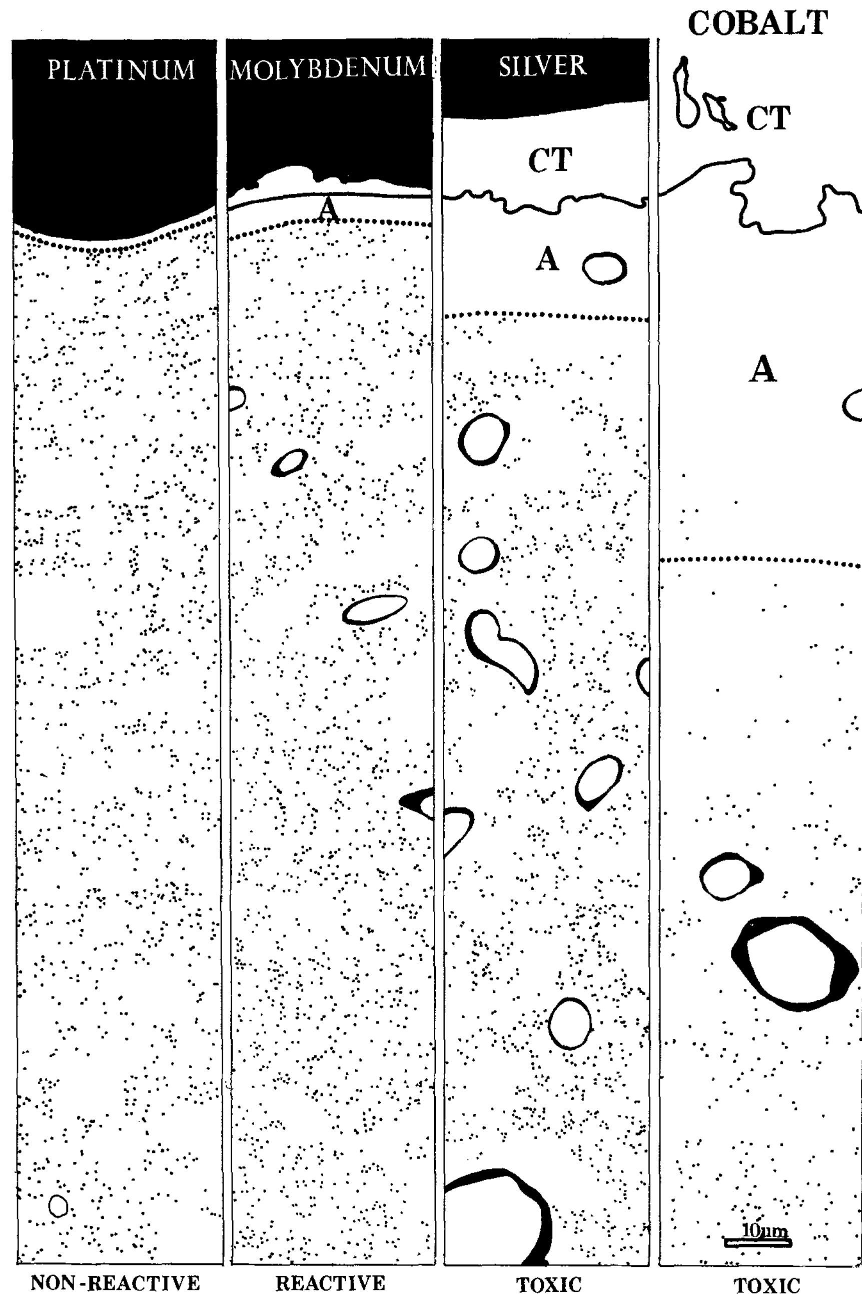

Fig. 2
Schematic representation of synapses (small black dots) and blood vessels (circles) in cortex surrounding non-reactive, reactive, and toxic implants (solid black). The solid line marks the boundary between the zone of connective tissue (*CT*) and the cortex. Note the reduction of synapses in cortex surrounding toxic implants; this is correlated with an increasingly wider zone of astrocytosis (*A*). Left to right: platinum (196 days), molybdenum (227 days), silver (219 days), and cobalt (72 days)

histological change were analyzed. Thus the data in Table 1 represent *minimal* reactive alterations observed around each type of implant. It should be emphasized that all implants of a particular material showed a consistent pattern of change.

The principal changes in cortex surrounding non-reactive, reactive and toxic implants are summarized schematically in Figure 1. Whereas normal central nervous tissue extended to the surface of non-reactive implants, zones of astrocytosis and connective tissue surrounded reactive and toxic implants. Although the width and complexity of these zones varied, the same basic pattern was typical of viable tissue around all reactive and toxic materials. In addition, however, a zone of necrosis surrounded cobalt.

Figure 2 illustrates the distribution of synapses in neuropile around the different types of implants, based on an analysis of EM photomontages. The gray matter within 10 µm of non-reactive and reactive implants showed a normal incidence of synapses. However, the cortex surrounding toxic implants showed a reduced incidence of synapses and an increased number of blood vessels. Similar patterns of synaptic distribution were observed in ultrathin sam-

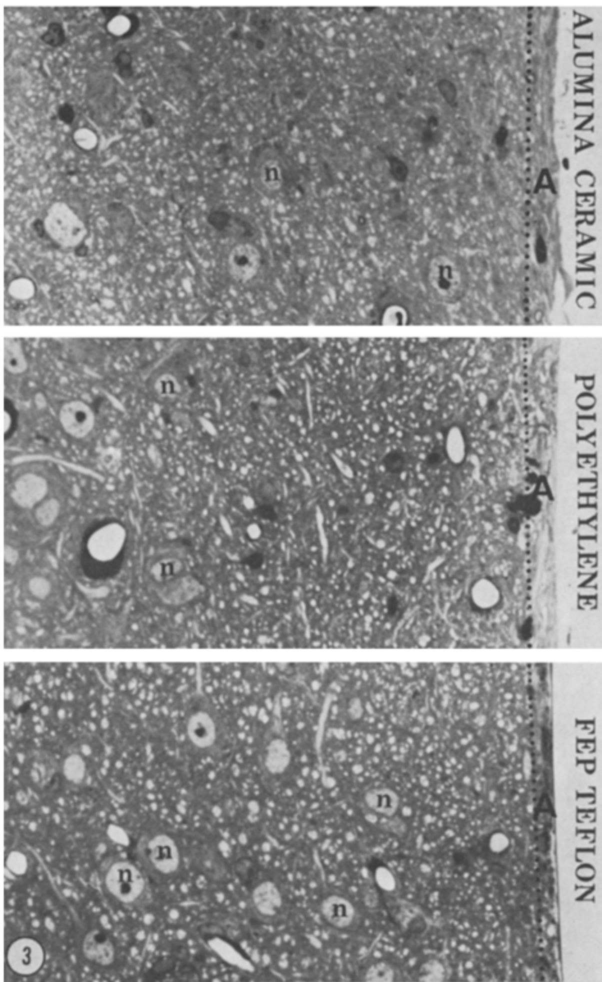

Fig. 3. Brain-implant boundary of non-reactive ceramic and plastic implants. Cerebral cortex containing apparently normal neurons (*n*) and neuropile is separated from the implant by a narrow zone of astrocytosis (A). Alumina ceramic (196 days), polyethylene (196 days), and Teflon FEP C20 (92 days). ×400

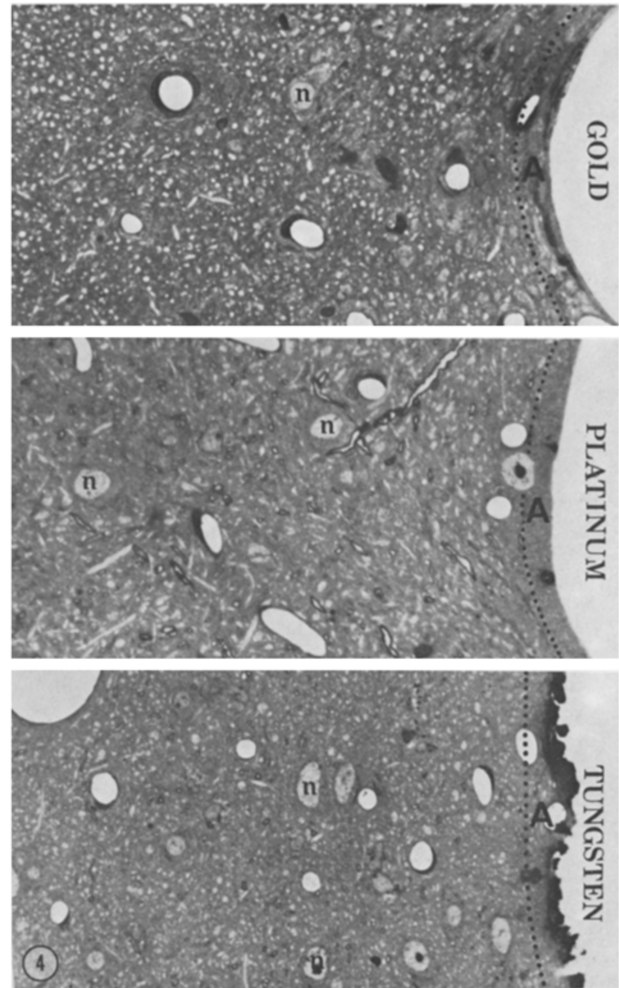

Fig. 4. Brain-implant boundary of non-reactive metal implants. The dotted line separates apparently normal cerebral cortex with neurons (*n*) from a narrow zone of astrocytosis (*A*). Gold (134 days), platinum (196 days), and tungsten (190 days). ×400

ples of other materials and could be correlated with the characteristics of neuropile in semithin sections examined by light microscopy.

The brain-implant boundary of the three non-reactive, non-metallic implants shown in Figure 3 was surrounded by cortical neuropile with a normal texture. Unstained profiles of dendrites extended to within a few micrometers of the implant, and nerve and glial cells of the gray matter appeared to be normal. The narrow zone of astrocyte processes at the implant surface resembled the zona limitans at the pial surface of the cerebral cortex. The non-reactive metallic implants illustrated in Figure 4 showed a similar pattern. However, the reactive metal implants shown in Figure 5 were surrounded by a thin layer of boundary cells and an abnormally wide zone of astrocytic processes. Apparently normal neuropile, neurons, and glial cells extended to within 50 μm of the implant, and a small quantity of collagen was visible between the boundary cells and the cortical surface in electron micrographs of the boundary.

Moderately toxic implants were surrounded by a concentric zone of connective tissue with distinctive cellular constituents (see Fig. 6). Electron microscopy revealed that the dark, multinucleate giant cells apposed to the implant's surface contained numerous lysosomal dense bodies, were apposed to one another by numerous microvillar projections, and rested on a layer of collagen. Hypertrophic astrocytes were commonly observed in the zone of astrocytosis that forms the new cortical surface. The texture of neuropile in the adjacent gray matter was altered and often

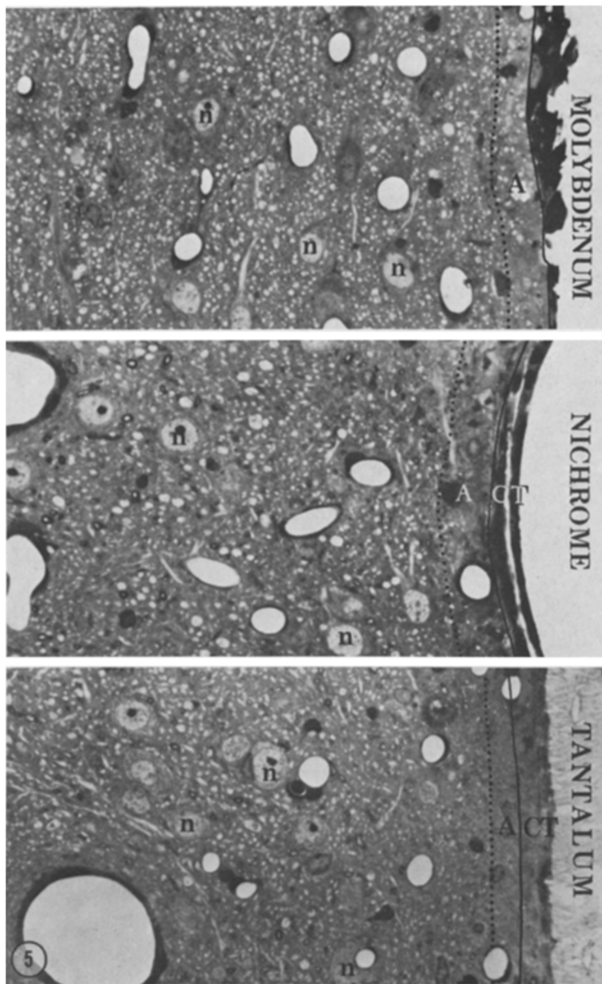

Fig. 5. The brain-implant boundary of reactive metal implants is marked by astrocytosis (*A*) and connective tissue (*CT*). Cerebral cortex with neurons (*n*) surrounds the zone of astrocytosis. Molybdenum (227 days), nichrome (197 days), and tantalum (196 days). ×400

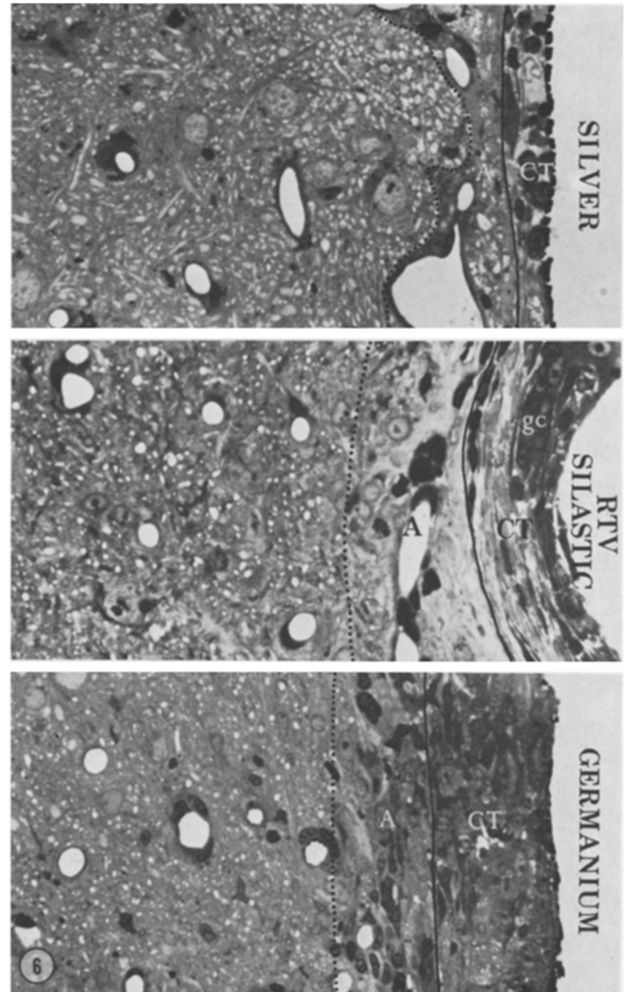

Fig. 6. The brain-implant boundary of moderately toxic implants is marked by a zone of astrocytosis (*A*) and connective tissue (*CT*) containing giant cells (*gc*). Altered cerebral cortex with perivascular cuffing and an increased number of small dark cells surrounds the zone of astrocytosis. Silver (125 days), silastic RTV (188 days), and germanium (220 days). ×400

displayed fewer light dendritic profiles than normal. Perivascular cuffing was typical of some but not all moderately toxic implants; as shown in Figure 6, cuffing occurred in the vicinity of silver, silastic RTV and germanium. The plasma cells and macrophages of the cuff were similar to cells found in the zone of connective tissue and sometimes contained reactive dense bodies that resembled the material at the implant surface.

Increasingly wider zones of connective tissue and astrocytosis were observed around the more toxic materials, iron and copper (Fig. 7A and B), and contained areas of presumed calcification. Semithin and ultrathin sections could be cut only after dilute hydrochloric acid had been applied to the block's surface.

Cobalt, the most toxic material tested, was separated from the gray matter by a wide, complex zone of astrocytosis. This finding corroborated that of Fischer (1968). Patches of dark, needle-like material were observed in the outer, lightly staining portion of this zone (see Fig. 7C), which was continuous with wide areas along the boundary of connective tissue that presumably contained extracellular deposits of calcium (see Fig. 8). Since the two areas had similar staining properties and looked similar under the electron microscope, we assumed that the material in the outer zone also probably represented some form of calcium. Concentric layers or subdivisions were consistent features of the connective tissue surrounding the central acellular necrotic core, and well-defined

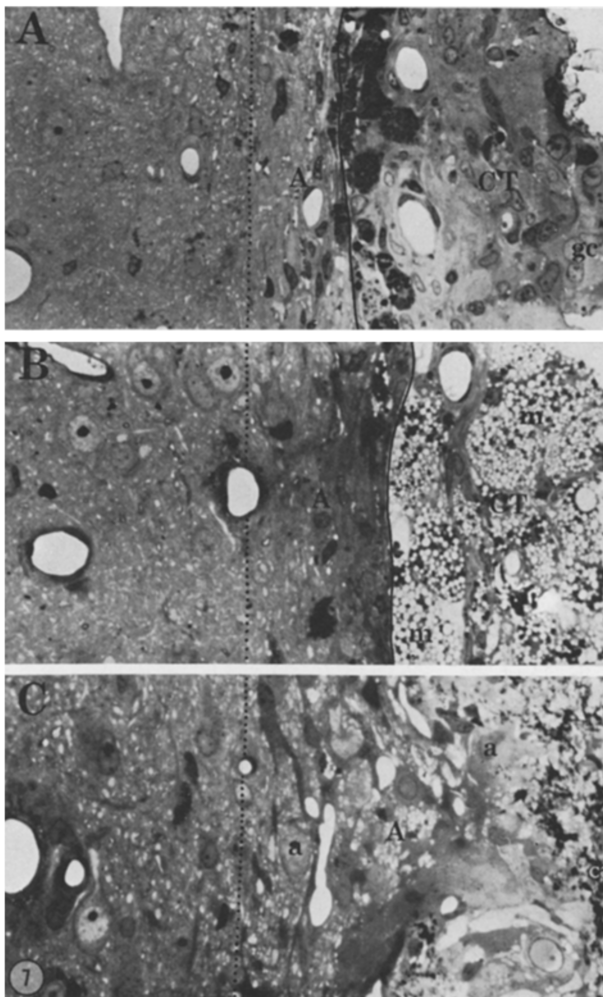

Fig. 7. The complex boundary surrounding toxic implants: iron (*A*), copper (*B*), and cobalt (*C*). Altered cerebral cortex surrounds the zone of astrocytosis (*A*). Macrophages (*m*) and giant cells (*gc*) are situated in the zone of connective tissue (*CT*) near iron and copper implants. Calcium (*ca*) and hypertrophic astrocytes (*a*) occur in the zone of astrocytosis near the cobalt implant. Iron (188 days), copper (192 days), and cobalt (270 days). × 400

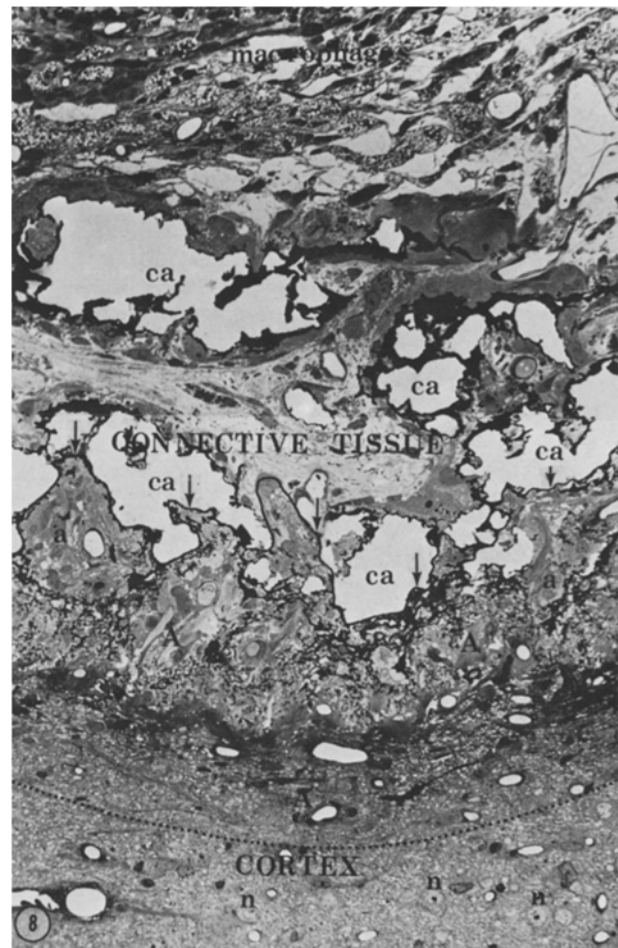

Fig. 8. Cobalt implant at low magnification illustrating the concentric zones of reactive tissue. Note the complex border (arrows) between the connective tissue and the zone of astrocytosis (*A*). Although macrophages and areas of calcification (*ca*) predominate in the zone of connective tissue, hypertrophic astrocytes (*a*) are also common. Neurons (*n*) occur near the zone of astrocytosis. The zone of necrosis adjacent to the implant is not shown because of the extensive width of the zone of connective tissue. (270 days.) × 200

areas of giant cells and macrophages always occurred in the same relation to the implant.

Discussion

Precise histopathological determinations of the compatability or toxicity of materials implanted in the brain are contingent upon the following: 1. the brain-implant boundary must remain intact, 2. the cellular constituents along the boundary must be identifiable, and 3. the observed changes must be distinguishable from those caused by mechanical trauma.

Detection of changes that occur near non-reactive or reactive materials depends on observations of the actual brain-implant boundary. Thus, loss of portions of the boundary adhering to the implant during its removal from the brain for frozen or paraffin histological procedures prevents the examination of precisely that tissue which is most important for detailed histological analysis. We avoided this problem by leaving the implant in place during all stages of tissue preparation and by cutting plastic sections that included the brain-implant boundary. Because semithin sections allow a greater degree of optical resolution than do frozen or paraffin section, it was possible to identify subtle changes in the neuropile. Furthermore, the features observed with light microscopy were directly comparable to those observed with

electron microscopy. Coordinated use of semithin and ultrathin sections from the same block of material thus allowed positive identification of all reactive cellular and subcellular constituents and eliminated the need for the selective heavy-metal strains traditionally used for neuropathological analysis.

Variability in the characteristics of the boundary surrounding a given implant was typical of the pattern of response to all implanted materials. This was apparently the result of mechanical disruption of nervous tissue during implantation and differential movement of the brain with respect to the implant. We ruled out these changes by evaluating the reactivity or biocompatability of each material on the basis of *minimal* histological changes at more than one level in individual specimens and by analyzing sections from several implants of the same material.

Non-Reactive and Reactive Implants

The brain-implant boundary of non-reactive implants was composed of a thin layer of astrocyte processes similar to the glia-limitans that normally forms the pial surface of the brain. In the absence of inflammation or trauma, there was intimate apposition between the implant and cortex with normal-appearing synapses within 5 μm of the implant. Implants surrounded by high incidence of apparently normal gray matter indicated that displacement of tissue during its surgical introduction left the neuropile and vasculature intact. Nerve and glial elements thus withstand direct apposition to non-reactive material for long periods in the absence of ongoing mechanical trauma. That central nervous tissue can tolerate direct contact with a foreign body with virtually no reactive cellular changes confirms the findings of an earlier study (Stensaas and Stensaas, 1976), based on the analysis of a single type of epoxy plastic (Araldite).

Reactive materials showed varying degrees of biocompatability. Although the boundary conditions were similar to those of non-reactive implants, more extensive change was indicated by the consistent presence of boundary or giant cells. These giant cells were similar to the epithelioid cells surrounding foreign bodies in the brain (Schultz and Willey, 1976) and in other tissue (Black and Epstein, 1974; Papadimitriou et al., 1973; Sutton and Weiss, 1966). The tendency of such cells to form a sheet and to be united by numerous small interdigitating processes suggests the possibility that these cells may impede the free exchange of material when interposed along the surface of the implant. However, cerebrospinal fluid in the layer of collagen interposed between boundary cells and astrocytes of the cortex also may permit attenuation of the noxious effects of the various reactive materials. The cytological characteristics of boundary cells with prominent lysosomal constituents suggests a third possibility: namely, that these cells modify the effects of noxious agents arising from the implant by the uptake of material. An analytical electron microscopic investigation of the degree to which boundary cells engage in endocytosis and intracellular breakdown of material from the implant is now in progress.

Toxic Implants

Although our results indicate that central nervous tissue is vulnerable to the toxic effects of metals such as copper, iron, and cobalt, the character of reactive changes over long-term exposure to noxious agents suggests a common response pattern. The development of a capsule results from the concomitant development of meningeal connective tissue and gliosis. The extent of encapsulation presumably depends on local levels of toxicity. Whereas relatively modest zones of connective tissue are interposed between cortical gray matter and implants of substances such as copper, a complex capsule with calcification forms around extremely toxic materials such as cobalt. Other reports of mineralized tissue in the central nervous system (Mascherpa and Valentino, 1959; Bignami and Appicciutoli. 1964) indicate that mineralization is a consequence of changes which occur in extracellular fluid. Deposition of hydroxyapatite in metal-induced calcification probably occurs by the binding of cations with phosphate. According to Gabbiani et al. (1970), "the formation of apatite may constitute an effective means of fixing a potentially toxic compound". However, iron and other cations can react in vivo with collagen and may modify the structure of collagen so that it favors the precipitation of apatite. In the current study, we observed crystalline material not only in the extracellular space but in macrophages, astrocytes, and fibroblasts. Chou and Fukuhara (1973) saw membrane-bound "calcospherites" in glial cells following chronic methyl mercury poisoning. Thus, when evaluating an implant's toxicity, the presence of mineralization in the extracellular space or in macrophages, astrocytes, or fibroblasts should be investigated.

The connective tissue components of the capsule probably reduce local levels of toxicity by titration or spatial buffering. Thus the distance required for substances to reach the brain by diffusion through the interposed layer of connective tissue and cerebrospinal fluid would attenuate their effects. Continual turnover of fluid within the subarachnoid space may also serve to reduce the concentration of toxic by-products. A second, and qualitatively distinct

line of defense is provided by the complex feltwork of reactive astrocytes that forms around toxic implants. Although these astrocytes are intrinsically less capable of withstanding toxic products than are giant cells and meningeal elements, they are far better suited than neurons to tolerate these effects. The extensive necrosis of neuropile after implanation may be the primary stimulus for the reactive changes of astrocytes. Accordingly, the death of neuronal constituents would be followed by proliferation of the glial elements and better able to withstand changes produced by the implant (Cavanagh, 1970).

Acknowledgements. This research was supported by the Surdna Foundation and contributions to the Artificial Organs Development Fund, University of Utah. Early experiments were funded by NIH contract 70-2278. We wish to thank Dr. Wm. H. Dobelle for his continued encouragement and support. We also thank Barbara Gilson, Jill Jones, Barbara Heindel, Garry Hanson, Corwin Edwards, and Glen Tonneson for their technical assistance.

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Received July 26, 1977/Accepted September 24, 1977