

## **Histological Reaction to Various Conductive and Dielectric Films Chronically Implanted in the Subdural Space**

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### **Summary**

Thirty different test patches of various thin film materials were chronically implanted in the subdural space of cats to determine their suitability as components for proposed neuroprosthetic devices. In particular, materials employed by the microelectronics industry were screened, and reactions were found to be quite dependent on specific formulations or surface preparations of otherwise similar materials. A nonspecific but severe complication of pressure necrosis under thin films that spontaneously roll and curl *in vivo* was noted.

### **INTRODUCTION**

Sophisticated neural prosthetic devices currently being developed call for placement of complicated multi-electrode arrays on the pial surface of the cerebral cortex for multichannel recording and/or stimulation.<sup>1</sup> To achieve the necessary physical properties and component densities, consideration is being given to thin film laminates and photolithographic (microelectronic) fabrication, often involving new or unusual materials or treatments of materials whose biocompatibility is untested. Previous subdural implantation testing (recently reviewed<sup>2</sup>) has been confined to bulk samples of metals

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for electrodes<sup>3-8</sup> and a limited number of polymers for dural substitutes.<sup>9,10</sup> However, for long-term implants, readily fabricated, high-quality dielectrics may be a limiting design factor,<sup>11</sup> and many candidate materials remain essentially untested. Also, as Coleman, King, and Andrade<sup>12</sup> point out, the tissue reaction to a given material may vary widely depending on surface treatment, texture, and impurities, all of which constitute aspects frequently manipulated in microelectronic fabrication techniques.

In this series of experiments, 30 different test patches were fabricated from 6 different metals and 14 different dielectrics, using various combinations and surface treatments of these materials customarily employed in microelectronic and biomedical devices. In some cases, they are formulations which might be intended for contact with subdural tissues; in others, they are materials frequently used in microelectronic fabrication which might come into contact with tissue as residues or through encapsulation failures. In most cases, histologic evaluation with light microscopy was made for 3-7 samples of each material implanted subdurally in cats for 8-30 weeks.

### GENERAL METHODS

The fabrication of each test patch is briefly described in the Results section along with a summary statement of the nature of the observed tissue reactions. Materials for these patches were all obtained as standard commercially available products used in compliance with the manufacturer's recommendations on handling and shelf life. Where dip-coating, evaporating, or electroplating steps were employed, they were carried out using standard microelectronic clean-room techniques, including filtered air, deionized water, and nonreactive vessels and electrodes. Flexible substrate films were handled on "carrier substrates" of Corning Microsheet #0211 glass during fabrication. All fabrication steps described apply only to the "front," exposed surface of the substrate films which was implanted facedown on the pia-arachnoid membranes. The back surface of each patch was the untreated, virgin substrate material which rested against the glass carrier during fabrication.

After completing fabrication steps, if any, each sheet of test material was individually rinsed according to a standardized procedure

by holding it with stainless steel forceps under streams of deionized water for 30 sec, fresh reagent-grade acetone for 30 sec, fresh glass-distilled water for 30 sec, and then force-drying each in filtered compressed Freon gas (acetone omitted for patches #6, #19, #27-29). Sheets were then cut with surgical instruments into test patches measuring  $6 \times 8$  mm with an orientation notch in one corner to assure that the fabricated surface was placed in contact with the pia-arachnoid membrane during implantation. Each patch was stored submerged in glass-distilled water in individual Pyrex tubes. The patches were sterilized in their tubes by wet-cycle steam autoclaving just prior to implantation.

Forty-two adult cats were implanted with four different patches each. Midline craniotomies were performed under sterile conditions. The patches were introduced through slits in the dura, sliding two patches into each hemisphere's subdural space, anterior and posterior to the margins of the craniotomy site. The results reported are from 32 cats surviving the predetermined test periods (8-30 weeks). Causes of mortality were scattered among anesthesia and postoperative hemorrhage and infection.

The animals were sacrificed by deep ether anesthesia and perfusion with 10% formalin and 2% gum acacia. The entire brain was removed, keeping the dura intact until it was carefully dissected off after fixation. Twenty-eight brains were embedded in celloidin and serially sectioned  $20 \mu$  thick. At 100 section intervals, hematoxylin and eosin, cresyl violet, and myelin stains were done. At the site of each test patch, the dura mater and pia-arachnoid membranes were each rated on a 0-4+ ascending scale for both fibrosis and inflammation. Cerebral cortex was rated on a similar scale for compression damage, neuronal loss, and gliosis. The underlying white matter was similarly evaluated for gliosis. Four brains containing a total of 16 different patches of particular interest were processed by frozen sections with Cajal gold staining for astrocytes.

## MATERIALS AND RESULTS

For each of the numbered test patches in Table I, we have given a short name describing its composition followed by the number of samples evaluated and the average ratings for the following histologic

TABLE I  
Summary of Materials Tested

ID #	Surface Composition <sup>a</sup>	Samples	Reaction <sup>b</sup>							Rating <sup>c</sup>
			DF	DI	AF	AI	NL	CG	WG	
# 1	Teflon A	5	1.8	1.2	0	0	0	0.2	0.2	S
# 2	Teflon C2	4	1.2	1.0	0.5	0.2	0	0.2	0.5	S
# 3	Chemgrip Teflon	4	3.5	2.3	1.0	0.2	0.2	0.7	0.7	X
# 4	Epotek #301 Epoxy	4	1.7	1.5	0	0	0	0	0	S
# 5	Epoxy Varnish	2	1.5	0.5	0.5	0.5	0	0.5	1.0	S
# 6	Isonel Varnish	2	2.5	2.0	0.5	1.0	0	0	1.0	D
# 7	Titanium	5	2.0	1.4	0.8	0.2	0	0.6	1.0	S
# 8	Gold (Evaporated)	6	2.5	1.4	1.2	1.0	0	0.6	1.0	S
# 9	Parylene-C	5	2.5	1.7	1.0	1.3	0.3	1.3	1.0	D
# 10	Stainless Steel	2	2.0	1.0	0.5	0	0	0.5	0.5	S
# 11	Chromium	3	1.0	0.7	0	0	0	1.0	0	S
# 12	Nickel	7	2.3	1.2	0.8	0.3	0	0.8	1.0	S
# 13	Gold (Electro- plated)	3	2.0	0.8	1.0	0.3	0	0.3	1.0	S
# 14	Platanex Platinum	7	1.7	1.1	1.0	0.7	0	0.8	1.0	S
# 15	Platinum (Evaporated)	1	1.0	1.0	1.0	0	0	1.0	1.0	S

(continued)

reactions in the order shown (0 = no reaction, 4 = most severe reaction):

- Dural fibrosis (DF)
- Dural inflammation (DI)
- Arachnoid fibrosis (AF)
- Arachnoid inflammation (AI)
- Cortical neuronal loss (NL)
- Cortical gliosis (CG)
- White matter gliosis (WG)

A summary assessment of the material as probably safe (S), doubtfully safe (D), and unsafe (X) based on a neuropathologists'

TABLE I (continued)  
Summary of Materials Tested

ID #	Surface Composition <sup>a</sup>	Samples	Reaction <sup>b</sup>							Rating <sup>c</sup>
			DF	DI	AF	AI	NL	CG	WG	
# 16	Engelhard Platinum	1	3.0	3.0	2.0	1.0	2.0	1.0	1.0	X
# 17	Platinum Black	1	3.0	3.0	3.0	1.0	1.0	1.0	1.0	D
# 18	AZ-1350 Photo-Resist	5	3.0	1.7	1.0	1.2	0.2	0.7	1.0	D
# 19	KPR Photo- Resist	2	2.5	2.0	0.5	1.0	0	0	1.0	D
# 20 )	Silastic <sup>d</sup>	6	2.0	1.0	0.8	0.3	0	1.0	1.0	S
# 21 )										
# 22 )										
# 23	Kapton	4	2.7	1.0	1.2	0.7	0	0	1.0	S
# 24	Mylar-S	4	2.0	0.7	1.0	0.2	0	0.5	0.7	D
# 25	Aclar 33-C	2	4.0	1.0	1.0	0	0	0.5	1.0	S
# 26	Transmount 70G <sup>e</sup>	2	1/3	1/3	0/3	0/2	4/2	0/1	1/1	D
# 27	Polyurethane	4	1.5	0.7	0.5	0.2	0	0	0.7	S
# 28 )	Hydron <sup>d</sup>	9	1.1	0.1	0.2	0.1	0	0.2	0.5	S
# 29 )										
# 30	Alumina Ceramic	3	1.3	0.3	0.7	0	0	1.0	1.0	S

<sup>a</sup> Substrates #1-8 were variously treated Teflon; #9-19 were Parylene; #20-30 formed their own substrates.

<sup>b</sup> Reaction key: DF = dural fibrosis; DI = dural inflammation; AF = arachnoid fibrosis; AI = arachnoid inflammation; NL = neuronal loss; CG = cortical gliosis, WG = white matter gliosis.

<sup>c</sup> Ratings: S = Safe, D = Doubtfully Safe, X = Unsafe

<sup>d</sup> Similar formulations and reactions grouped together.

<sup>e</sup> Inconsistent reaction, both results given.

(B. W. K.) survey of the slides is given last. Similarly numbered paragraphs below further describe the fabrication of each patch as well as including unusual findings noted by the neuropathologist.

Figures 1-5 show typical reactions for several materials. The dura mater reactions were generally similar to that provoked by a subdural hematoma with a proliferation of fibroblasts encapsulating the test patch with a capsule thicker on its parietal than visceral

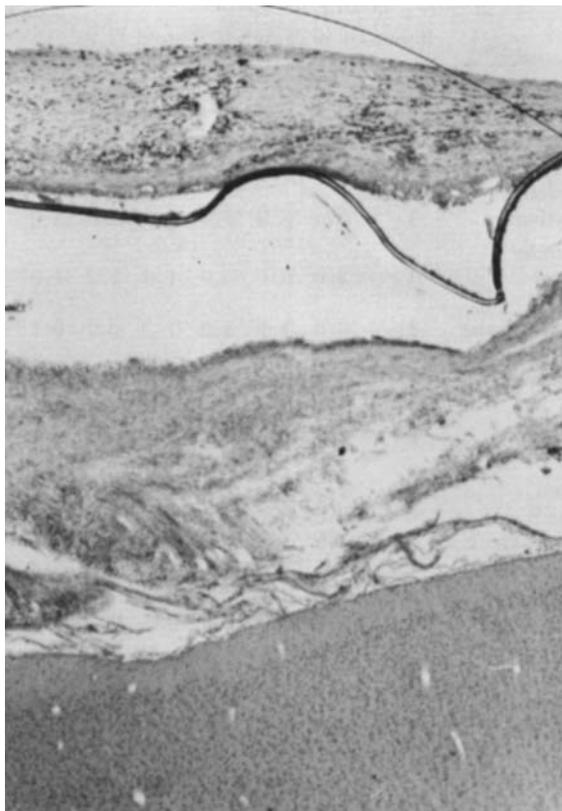


Fig. 1. Photomicrograph 13 weeks after implantation of epoxy on Teflon (test patch #4, "safe"). This section shows marked thickening of both visceral and parietal capsular walls with mild inflammatory reaction (++) . The reaction was apparently secondary to compression, as other implants and other areas of this implant showed much less reaction. Hematoxylin and eosin (30 $\times$ ).

surface. The dural membrane always formed at least a thin layer between the visceral surface of the test patch and the pia-arachnoid membrane. Thus, the dural reaction is often a significant factor, and the overall assessment takes into consideration the ability of the dura to form a stable, protective layer between the implant and underlying cortex.



Fig. 2. Photomicrograph 13 weeks after implantation of evaporated titanium on Teflon (patch #7, "safe") showing encapsulation with mild lymphocytic reaction (+). Hematoxylin and eosin (120 $\times$ ).

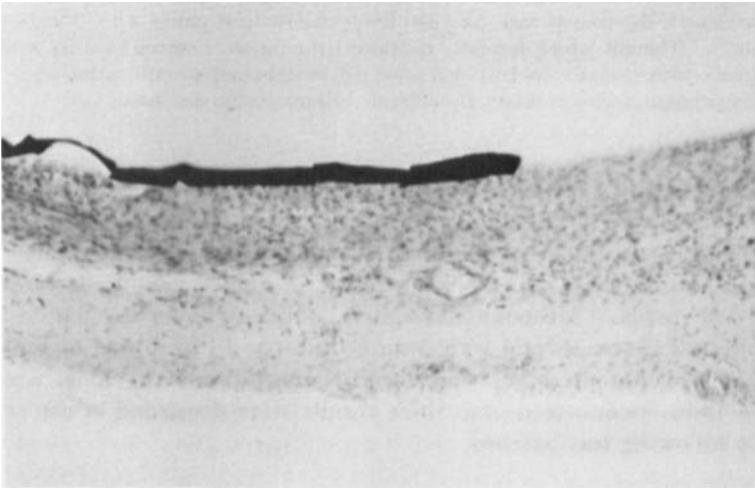


Fig. 3. Photomicrograph 13 weeks after implantation of evaporated platinum on Parylene (patch #15, "safe") showing encapsulation with mild lymphocytic reaction (+). Hematoxylin and eosin (120 $\times$ ).

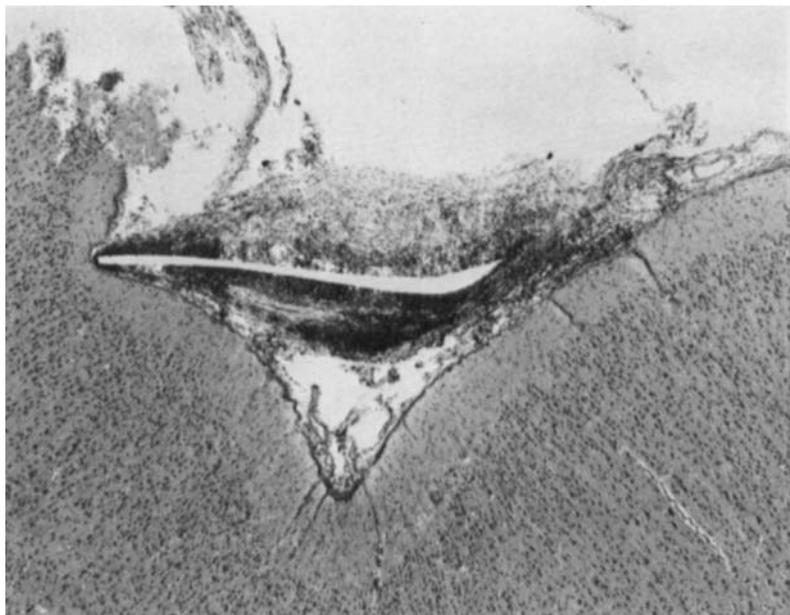


Fig. 4. Photomicrograph 10 weeks after subdural implantation of a sheet of Parylene-C dip-coated with AZ-1350 Photo-Resist (test patch #18, "doubtfully safe"). The slit which formerly contained the patch is surrounded by a thick capsule with a small round cell and some polymorphonuclear infiltration (+++). The adjacent cortex is relatively normal. Hematoxylin and eosin (43 $\times$ ).

In general, reactions tended to be consistent for each material tested with no clear differences with duration of implantation. Significant exceptions were, however, encountered with a number of thin film implants which folded, rolled, or angled into the substance of the cortex. Although the materials all originally lay flat in the subdural space, several were seen at autopsy to be curled or folded. The resulting pressure necrosis often constituted the most severe reactions encountered, and these results were discarded in assessing the following test patches.

#1 *Teflon A (S)*: 0.5 mil DuPont Teflon FEP, surface A (un-etched).

#2 *Teflon C2 (S)*: 2.0 mil DuPont Teflon FEP, surface C20,



Fig. 5. Photomicrograph 14 weeks after implantation of Silastic sponge (patch #22, "safe") showing arachnoidal thickening and fibrosis (++) . Hematoxylin and eosin (120 $\times$ ).

surface etched on both sides by DuPont's proprietary ion bombardment process to make a wettable, bondable surface.

#3 *Chemgrip Teflon (X)*: Patch #1 surface etched in commercial sodium naphthalene preparation (Chemgrip, Epoxy Technology, Wayne, N.J.) and washed in butanol as recommended by the manufacturer. The tissue reaction was described as a marked encapsulation with granulations.

#4 *Epoxy on Teflon (S)*: Patch #3 further fabricated by dip-coating a thin layer of two-component, amine-cured transparent epoxy (Epotek #301, Epoxy Technology) and curing in a hot air oven at 65°C for 1 hr (see Fig. 1).

#5 *Epoxy lite on Teflon (S)*: Patch #3 further fabricated by dip-coating a thin layer of epoxy varnish (Epoxy lite 6001-M, Epoxy lite Corp., Columbus, Ohio) and baking in a hot air oven at 65°C for 1 hr. This is a xylol-dissolved, acid-cured bisphenolate resin frequently used to dip-coat insulate tungsten microelectrodes.<sup>13</sup>

#6 *Isonel on Teflon (D)*: Patch #3 further fabricated by dip-coating a thin layer of varnish (Isonel 31, Schenectady Varnish Co., Schenectady, N.Y.) and baking in a hot air oven at 65°C for 1 hr.

This is a tough, heat-resistant, flexible varnish coating frequently used on tungsten microelectrodes.<sup>14</sup>

#7 *Titanium on Teflon (S)*: 1 mil substrate of Teflon FEP surface C (ion bombardment etched on fabricated surface only), vacuum-metallized by vapor-depositing 700 Å titanium metal from alumina ceramic-coated molybdenum boat source in liquid nitrogen trapped, oil diffusion pumped vacuum system. Titanium can be used as an undercoat to provide adhesion between evaporated gold films and plastic substrates (see Fig. 2).

#8 *Gold on Teflon (S)*: Patch #7 further fabricated by vapor-depositing 2000 Å gold metal from a tungsten filament source during the same pump-down as the titanium metallization.

#9 *Parylene (D)*: Approximately 0.7 mil thick vapor-condensed film of Parylene-C deposited on temporary glass carrier substrates in a proprietary process at Union Carbide Co., Bound Brook, N.J., peeled off carrier substrate to make patches. This is a unique spontaneously polymerizing plastic film which conformally coats complex objects at room temperature under vacuum and has low water vapor transmission and high chemical resistance to degradation.<sup>15,16</sup>

#10 *Stainless Steel on Parylene (S)*: Patch #9 further fabricated by sputtering 1000 Å of stainless steel from a #304 alloy target in nitrogen atmosphere. Severe loss of adhesion of metal film to substrate noted at autopsy.

#11 *Chromium on Parylene (S)*: Patch #9 further fabricated by vacuum deposition of 1000 Å chromium metal from tungsten basket source. Chromium is a frequently used thin-film electrical resistor element and undercoating to promote adhesion of gold films.

#12 *Nickel on Parylene (S)*: Patch #9 vacuum-metallized with 700 Å titanium followed by 2000 Å gold. The composite is then electroplated with 5 μ of nickel from a nickel sulfamate bath (Harstan Chemical Corp., Brooklyn, N.Y.) at 40°C at 30 ASF (amps/ft<sup>2</sup>) against a nickel anode.

#13 *Gold Electroplate on Parylene (S)*: Same metallization layer as in #12, electroplated with 24 kt gold 1 μ thick instead of nickel, from a cyanide-based bath with gold anode (Orotemp 24 kt, Technic, Inc., Cranston, R.I.).

#14 *Platanex on Parylene (S)*: Same metallization layer as in #12, electroplated with 1 μ thick layer of bright platinum from an

acid bath (Platanex III, Selrex Corp., Nutley, N.J.) at 80°C at 10 ASF against a platinum anode.

#15 *Evaporated Platinum on Parylene (S)*: Same metallization layer as in #12, further vacuum metallized with approx. 1000 Å platinum from tungsten filaments electroplated with the Platanex bath described in #14 (see Fig. 3).

#16 *Alkaline Platinum on Parylene (X)*: Patch #15 further fabricated by electroplating a 1 μ thick layer of bright platinum from an alkaline bath (Engelhard Industries) at 85°C at 10 ASF against a platinum anode.

#17 *Platinum Black on Parylene (D)*: Patch #15 further fabricated by electroplating a 5 μ thick layer of platinum black from a 1% chloroplatinic acid solution at 10 ASF against a platinum anode.

#18 *Baked Photo-Resist on Parylene (D)*: Patch #9 dip-coated with 3–5 μ of AZ-1350 positive-working photo-resist (Shipley Co., Newton, Mass.), and baked on a hot plate in air at 375°F for 5 min without light exposure or chemical developing. This is a photolithographically formable insulation coating which in very thin, high-resolution coatings is a low-grade but stable electrical insulation which acts as a nontoxic substrate for tissue culture of heart muscle and nerves.<sup>17</sup> In this study, marked leukocytic infiltration was noted in the dural capsule adjacent to the implant (see Fig. 4).

#19 *KPR on Parylene (D)*: Patch #9 dip-coated with KPR negative-working photo-resist (Kodak), stabilized by exposure to high-intensity white light. This is a standard photo-resist used in manufacturing high-resolution microcircuits.

#20, #21, #22 *Silastic (S)*: Various samples of Silastic 372 Elastomer sheet and fine sponge (Dow Corning) which reacted quite uniformly (see Fig. 5).

#23 *Kapton (S)*: 0.5 mil Kapton polyimide film (DuPont).

#24 *Mylar (D)*: 0.25 mil thick Mylar Type S polyester film (DuPont). Dural reaction described as moderately granulomatous.

#25 *Aclar (S)*: 1.0 mil thick Aclar 33-C fluorohalocarbon heat-sealable film (Allied Chemical Corp.).

#26 *Transmount (D)*: 2 mil thick heat setting thermoplastic adhesive (Transmount 70G, USM Corp., Rutherford, N.J.). Since results in the two patches tested were quite different, both sets of ratings are given. Both reactions were, however, moderately severe.

#27 *Polyurethane (S)*: Approximately 5 mil thick film of polyurethane precipitated from a dimethylformamide solution, supplied courtesy of the University of Utah Division of Artificial Organs.

#28, #29 *Hydron (S)*: Various pieces of poly(glycol methacrylate) gel sponge, supplied courtesy of the University of Utah Division of Artificial Organs. Reactions were quite uniformly benign.

#30 *Alumina (S)*: 5 mil thick chips of alumina ceramic used for hermetically sealed microcircuit packages.

## DISCUSSION

These experiments were intended to serve as an initial screening for a large number of materials formulations of interest to researchers considering the construction of implantable microelectronic devices. It would be difficult to draw firm, general conclusions from these data, since the number of samples of each material was quite limited and the details of fabrication were often arbitrarily selected to be simply representative of typical microelectronics techniques. However, a number of results were both unexpected and consistent enough to bear some preliminary hypothesizing. It should be emphasized that the designation "probably safe" is based on the overall pattern of the tissue reaction, individual components of which might make a "safe" material quite unsuitable in a given application (e.g., severe dural fibrosis without inflammation seen in #25).

There appears to be a significant histopathologic difference between Teflon FEP surfaces etched by ion bombardment (#2) and sodium naphthalene (#3). Since the former process is performed on the plastic film at the factory and the latter conveniently employed in the laboratory for selective area etching, the apparent tendency of the laboratory process to leave a toxic surface residue despite the recommended washing procedure is unfortunate. Further attempts to improve the washing procedure for biomedical applications would seem justified in view of the usefulness of the etching procedure. Interestingly, both the Epoxylite varnish (#5) and Epoxy encapsulant (#4), which were coated on sodium-etched Teflon, formed nontoxic barriers which prevented toxic materials from escaping and causing any significant tissue reaction.

The reactivity of bare Parylene-C films was at first surprising in view of its successful use in endothelial tissue cultures,<sup>19</sup> and our own

extensive experience with Parylene-C as a substrate for microcircuits implanted in the brain.<sup>20</sup> Furthermore, metal thin films using Parylene-C as a substrate were quite unreactive (#10-15), even when the metal film lost adhesion *in vivo* (#10), exposing the underlying Parylene. Subsequent discussions with persons familiar with the deposition process indicate that small temperature fluctuations during the pyrolysis step, which converts the dimer raw material to an activated divalent radical prior to condensation and polymerization, can cause inclusion of hydrochloric acid and other breakdown products within the normally homogeneous polymer film. We theorize that this may have happened to the Parylene batch we tested, and that these relatively volatile contaminants either out-gassed or were passivated during the pump-down, substrate heating, and metallization steps employed in patches #10-15.

The relative reactivity of Mylar film was surprising since it is virtually the same chemical formulation as that of Dacron fiber, a commonly used material in vascular prostheses and as a core to strengthen Silastic dural substitutes.<sup>10</sup> As others have pointed out,<sup>21</sup> the frequently proprietary fabrication steps whereby raw chemicals are transformed into their final physical form may be critical to the biocompatibility of the finished product.

Two industrial-grade materials (#18, baked photo-resist; #26, Transmount) eliciting moderately severe reactions here were tested because of the surprisingly low toxicity previously noted in tissue culture (unpublished, G. E. L.). These results support the contention of others that tissue culture, while usually sensitive, can completely miss certain kinds of foreign-body reactions (e.g., antigenic, thrombotic, mechanical, etc.).<sup>12</sup>

The rather impressive lack of reaction to alumina ceramic (#30) is encouraging since such ceramic materials are generally considered essential to long-term hermetic sealing of electronic circuits destined for immersion in salt water.

Chromium (#11) and nickel (#12) have both been thought to be relatively toxic implants based on experience in rabbit muscle,<sup>22</sup> although they are frequent constituents of nontoxic steel alloys. In this series, exposed bright evaporated chromium films elicited minimal reactions, while the somewhat grainier electroplated nickel was only moderately reactive. While neither material is likely to be used directly in contact with tissues, they would be difficult to

replace as undercoatings and internal conductors in microelectronic devices. Their relatively low toxicity here would indicate that they would cause little damage if passively exposed through encapsulant failure, although such failure in the presence of electric currents might release considerably more ions and thus result in much greater toxicity.

The markedly different results obtained with different platinum formulations (# 14-17) should serve as a warning despite the unfortunately small numbers of patches tested in this study. Platinum is frequently mentioned as an ideal material for electrode surfaces designed to be in direct contact with tissues because of its extreme corrosion resistance and nonpolarizing surface.<sup>23,24</sup> As expected, evaporated platinum was least reactive, although this particular method of evaporation from tungsten filaments probably produces a significant alloying of the platinum film with tungsten metal which, by itself, is quite reactive in brain.<sup>2</sup> The Platanex III bright platinum electroplate was also minimally reactive and would appear to be an acceptable way to build up thick films of inert metal on more easily photolithographically fabricated thin films. The severe reaction elicited by the Engelhard alkaline-bath platinum would seem to indicate significant inclusions of toxic materials in the otherwise bright, smooth electroplated surface. The severe reaction to platinum black is surprising since the only potentially toxic species in the chloroplatinic acid bath is platinum ions. Platinum black coatings are frequently applied to small surface area biomedical electrodes because the very rough surface so generated has a high real surface area and lowers the junction impedance.<sup>25</sup> It may be that this rough surface and/or the possible inclusion and gradual leaching of platinum salts is, in fact, a significant central nervous system irritant when applied over large areas.

The nonspecific observation of severe damage from pressure necrosis under thin films that became rolled and folded has been seen by others.<sup>26</sup> Very thin, flexible printed circuits can be readily manufactured, and their ability to conform to the convoluted cortical surface and move freely with the brain during motion in the skull would seem desirable. However, we are quite certain that most, if not all, of the rolling and folding of the very thin flexible films implanted in the study occurred gradually after implantation. Among the mechanisms which might be hypothesized are differentially

contracting dural and arachnoid adhesions, simple relative transverse rubbing motion between dura and pia-arachnoid, and gradual curling of the implant itself as a result of differential adsorption and absorption of water, lipids, and protein on various parts of the surface. In each of these mechanisms, the flaccidity of the thin film would actually contribute to the tendency of an implant to cause pressure necrosis rather than avoid it. In the overall design of any such thin film subdural implant, attention will have to be given to providing some form of anchoring or structural support at the perimeters to prevent this complication.

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