

Criteria for the Selection of Materials for Implanted Electrodes

L. A. GEDDES and R. ROEDER

Purdue University, Department of Biomedical Engineering, 500 Central Drive, West Lafayette, IN

(Received 23 April 2002; accepted 14 April 2003)

Abstract—There are four criteria that must be considered when choosing material for an implanted electrode: (1) tissue response, (2) allergic response, (3) electrode-tissue impedance, and (4) radiographic visibility. This paper discusses these four criteria and identifies the materials that are the best candidates for such electrodes. For electrodes that make ohmic contact with tissues: gold, platinum, platinum–iridium, tungsten, and tantalum are good candidates. The preferred insulating materials are polyimide and glass. The characteristics of stimulator output circuits and the importance of the bidirectional waveform in relation to electrode decomposition are discussed. The paper concludes with an analysis, the design criteria, and the special properties and materials for capacitive recording and stimulating electrodes. © 2003 Biomedical Engineering Society. [DOI: 10.1114/1.1581292]

Keywords—Implanted electrodes, Microelectrodes, Stimulating electrodes, Electrode arrays, Electrodes.

INTRODUCTION

In these days of nanotechnology techniques, small electrodes are implanted to stimulate excitable tissue, to detect bioelectric events, and to measure chemical substances. The choice of electrode metal and an insulation applied thereto have an important bearing on electrode performance and longevity. An ideal implanted electrode and/or its insulation should not provoke a vigorous local or generalized host response. It should establish a stable impedance contact with the tissue. The metal and its insulation should not produce an allergic response; this latter important factor has not been considered hitherto. The implanted electrode should be visible radiographically. Capacitive electrodes share the same requirements except for the low-impedance criterion.

CAPSULE FORMATION

When a metal, with or without insulation, is implanted into a tissue bed, two responses occur: (1) the tissue fluids try to dissolve it and (2) an inflammatory reaction occurs and the implant soon triggers a cascade

of events that results in the implant being encapsulated by inexcitable fibrous tissue. In the latter case, the capsule can be thick or thin, depending on the reactivity of the tissue to the implant and the implant's surface shape and condition. If the implant is an electrode, the capsule separates it from the tissue that it is designed to stimulate or record from. A capsule surrounding a stimulating electrode raises the threshold for stimulation in proportion to the capsule thickness and the fluid content within the capsule can also affect the stimulation threshold. A capsule surrounding a recording electrode effectively makes the electrode distant from the active tissue and reduces the amplitude available for recording.

For diagnostic purposes, Dodge *et al.*⁹ implanted electrodes in the brain of a patient who died 19 months later. Each electrode consisted of six strands of Formvar-insulated copper wire (97.5 μm in diameter). After the patient died, the brain was examined histologically. A well-defined capsule was found along the tracks of the electrodes. In later studies, they used stainless steel electrodes which they found to produce less tissue response.

Fischer *et al.*¹¹ studied the response of the brains of cats to 1 cm lengths of 24 gauge wires left *in situ* for periods up to 4 weeks. The wires employed were of chlorided silver, bare silver, copper, and stainless steel. Both bare and insulated wires were implanted. After 1 week, histological studies showed tissue response. Silver and copper wires proved to be the most toxic to brain tissue. After 3 weeks a narrow ring of necrotic tissue surrounded the silver wire. Around this ring was a circular edematous region, 2 mm in diameter. The reaction to the copper wire after 3 weeks was similar except that an increase in vascularity had also occurred. Necrotic tissue and an edematous region encircled the copper wire. The diameter of the capsule was determined partially by the extent of the mechanical trauma produced by its introduction into the brain. Fischer and co-workers concluded that the electrode material of choice for such studies is stainless steel.

Collias and Manuelidis,⁸ implanted bundles of six stainless steel electrodes (125 μm in diameter) into the brains of cats. Describing the histological changes that occurred over periods extending up to 6 months, they

Address correspondence to L. A. Geddes, Purdue University, Department of Biomedical Engineering, 500 Central Drive, West Lafayette, IN 47907-2022. Electronic mail: bmeoprogram@ecn.purdue.edu

found that an orderly sequence of changes took place in the tissue surrounding the electrodes. At the end of 24 h there was a zone of hemorrhage, necrosis, and edema extending to about 1 mm from the electrode. After 3 days there was less hemorrhage and necrotic debris; by the seventh day a 0.1 mm layer of capillaries occupied the necrotic zone. By the 15th day, the capillaries had almost completely replaced the necrotic region, and connective tissue had started to form. After the passage of a month, the necrotic debris had disappeared and a well-defined capsule surrounded the electrode track. Capsule formation was virtually complete after 4 months, at which time a thick, dense capsule completely encircled the electrode.

Robinson and Johnson³³ carried out studies similar to those just described. They implanted wires (125 μm in diameter) of gold, platinum, silver, stainless steel, tantalum, and tungsten into cat brains and studied the tissue responses at various times over a period extending to 6 months. Responses similar to those previously described were observed. After about a week the differences between the metals in regard to the reaction produced began to be detectable. Gold and stainless steel evoked the least tissue response; tantalum, platinum, and tungsten produced slightly more. Silver precipitated a vigorous tissue reaction. Encapsulation of all electrodes was evident at 15 days, with thicker capsules around the metals that provoked the greatest tissue response.

Dymond *et al.*¹⁰ implanted the following materials into cat brains and evaluated them histologically after 2 months: platinum, platinum–8% tungsten, platinum–10% rhodium, platinum–10% iridium, platinum–10% nickel, platinized platinum, a gold–nickel–chromium alloy, a gold–palladium–rhodium alloy, a chromium–nickel–molybdenum alloy (Vitallium), stainless steel, silver, rhenium, gold, and boron. They found that platinum–8% tungsten, platinum–10% iridium, platinum, gold–nickel–chromium alloy, stainless steel, and gold–palladium–rhodium alloys all had tissue reactions which were slightly less than those of platinum–10% rhodium, platinum–10% nickel, rhenium, and platinized platinum. Boron was found to be nontoxic. Interestingly they found that platinum black produced a denser capsule. Chlorided silver and bare silver were found to be toxic. From their study they ranked the materials as candidates in the following order: gold, platinum–8% tungsten, platinum–10% iridium, platinum, gold–nickel–chromium, stainless steel, titanium, gold–palladium–rhodium, nickel–chromium–molybdenum, platinum–10% rhodium, platinum–10% nickel, platinized platinum, tantalum, zirconium, rhenium, and tungsten. The materials found to be unsatisfactory were: silver, silver–silver chloride, copper, and iron.

Stensaas and Stensaas³⁹ implanted 27 materials (metals and insulators) into the cortices of rabbits. The im-

plants were rod-shaped, 5 mm long, and 500–750 μm in diameter. Histological examination at 30 days revealed no reaction, i.e., no gliosis in response to aluminum, gold, platinum, and tungsten. There was a mild response to tantalum and Pyrex glass, a severe response to iron, copper, and cobalt, which were highly toxic.

Babb and Kupfer,² implanted metals and insulators in the brains of rats and studied the responses at 11–63 days. They stated that silver and copper were unsuitable as electrodes because of the strong tissue response. They recommended the use of stainless steel and nichrome (80% Ni 20% Cr) as electrodes. Among the insulators, polyimide was better than epoxy, the former produced little tissue response.

Agnew and McCreery²⁷ summarized the published literature prior to that time; they stated that the following were relative innocuous: aluminum, beryllium, chromium, iron, lead, tin, and tungsten. Magnesium and manganese produced local necrosis. Bismuth, cadmium, copper, cobalt, and nickel produced more severe local necrosis. Zinc produced prominent lymphocytic cuffing.

INTEGRATED-CIRCUIT TECHNOLOGY ELECTRODES

Wise and Starr⁴² appear to have been the first to fabricate a three-electrode array occupying 50 μm using silicon technology. Since then the technology has advanced and it is now possible to produce many micro-electrodes on a silicon chip.

Campbell *et al.*⁷ described a fabrication technique to create an array of 100 pointed conical needle electrodes of silicon, each 1.5 mm long, and 0.09 mm at the base; the array projected from a 4.2 \times 4.2 mm monocrystalline silicon chip. Because silicon oxidizes readily, the electrodes were coated with platinum. The electrodes were designed for cortical stimulation. In commenting on their electrodes, the authors stated, "The impedance characteristics of these arrays have been measured and found to be well suited for stimulation of cortical tissue (very low impedance along the needle, very high impedance between electrodes). Some drawbacks do exist in the thermomigration method used to create these electrical characteristics. Oftentimes electrodes are shorted together, and the nature of the isolating *p-n* junction pairs is such that surface condition is critical to the effectiveness of the isolation. Also, the electrode tips should be coated with iridium oxide rather than platinum which will enhance the charge transfer capabilities of each electrode." No data were given on the effective electrode area or the magnitude of the electrode-tissue impedance.

An improved silicon-based 10 \times 10 needle-electrode array, similar to that reported by Campbell *et al.*⁷ was described by Jones *et al.*²⁰ The technique used to manufacture these Utah electrode arrays differed from the pre-

vious method in that glass provided electrical isolation between the individual electrodes in the array. The new electrode arrays exhibited superior electrical properties. The interelectrode impedances were at least 10 T Ω , and interelectrode capacitances of approximately 50 fF. The authors stated that their array was adequately strong for cortical insertion. However, they did not measure the effective electrode area, but provided one data point on electrode-tissue impedance, namely 10,000–20,000 Ω at 1 kHz for a current of 1 μ A. Maynard²⁵ described the electrodes in more detail.

Schmidt *et al.*³⁶ reported on the biocompatibility of phosphorous-doped monocrystalline silicon electrodes implanted in cat brains. Uncoated silicon, silicon coated with polyimide, silicon coated with an aluminum-chelating agent, then insulated with polyimide were prepared. Fifteen arrays remained implanted for 24 h to determine early tissue reaction to the implantation procedure, and twelve arrays remained implanted for 6 months to determine structural and material biocompatibility. Edema and hemorrhage were present around the short-term implants that involved less than 6% of the total area of the tissue covered by the array. With the chronic implants, leukocytes were rarely present and macrophages were found around roughly one-third of the tracks. Remnants of foreign material from the electrodes could be identified in less than 10% of the tracks. Gliosis was found around all tracks, forming an annulus between 20 and 40 μ m thick. A capsule was not always present and never exceeded a thickness of 9 μ m. These results suggest that the implantation procedure produced a limited amount of tissue damage and that the arrays are biocompatible. However, the arrays insulated with polyimide indicated a reaction due to aluminum oxide in the primer. These silicon electrodes provoked only a mild tissue response. No data were given on the electrode-tissue interface impedance or effective area. Interestingly, epoxy, which can be used as an insulator, produced a tissue response. Pyrex glass produced some response, but polyimide produced very little tissue response.

At this point, it is possible to identify the metals that should not be used for implanted electrodes because of vigorous tissue reactivity. These pure metals are iron, copper, silver, cobalt, zinc, magnesium, manganese, and aluminum which oxidizes. Agnew and McCreary²⁷ advise against bismuth, cadmium, and nickel.

SIGNIFICANCE OF A TISSUE CAPSULE

The significance of a tissue capsule surrounding a stimulating electrode is well known to those who implant cardiac pacemakers. The procedure at the time of implantation involves determining the threshold current for stimulation (capture). Then the output of the pulse generator is doubled to accommodate the increase in thresh-

old current as the electrode becomes encapsulated with inexcitable fibrous tissue. Typically platinum-iridium electrodes are used.

The growth of an inexcitable tissue capsule is due to the inflammatory response of the tissue. To reduce this response and minimize the increase in pacing current threshold that it engenders, Radovsky *et al.*,²⁸ used platinum-iridium pacemaker electrodes that incorporated an anti-inflammatory steroid (dexamethasone) as described by Stokes *et al.*⁴⁰ The study was as follows.

A pair of endocardial pacemaker leads, identical except for the presence or absence of dexamethasone in the distal stimulating electrode, was implanted into the right ventricle of each of 12 dogs for either 3 weeks (n =six pairs) or 6 weeks (n =six pairs). Fibrous connective tissue capsules formed around all of the distal porous-surfaced stimulating electrodes. Connective tissue capsules were composed of fibroblasts with an abundant collagen matrix and contained scattered macrophages, lymphocytes, plasma cells, and mast cells. Connective tissue sheaths around dexamethasone-coated leads were thinner (p <0.03), less cellular (p <0.10) and had fewer mast cells (p <0.10) than corresponding nonsteroid leads. Threshold voltages for electrical stimulation of the myocardium were consistently lower (p =0.005) for pacing leads with dexamethasone-eluting electrodes than for leads without dexamethasone. The electrode-tissue impedance was lower (p =0.1) for the steroid-eluting electrodes. This study gives clear evidence that reducing the inflammatory response to an implanted electrode with an anti-inflammatory agent is highly desirable.

Obviously it is desirable to achieve the thinnest capsule surrounding an implant. In addition to the species of metal being important, there is evidence that the size of the implant is a factor. For example, when Dodge *et al.*⁹ used smaller electrodes, they found less tissue response; however, the smaller diameter electrodes were of stainless steel rather than copper, thereby making it difficult to attribute the thinner capsule to size. However, the study by Campbell *et al.*⁷ gives evidence that very small diameter implants are associated with a thin capsule.

ALLERGENIC CONSIDERATIONS FOR IMPLANTED METALS AND ALLOYS

An implanted electrode should not produce an allergic response. Hitherto, this factor has been largely overlooked when considering an electrode metal or alloy or insulation for implantation. Some metals and alloys

are highly allergenic and are not candidates for an implant. The following discussion will elaborate on this issue.

An allergic response reflects a hypersensitive state acquired through prior exposure to a particular substance (allergen) and re-exposure produces an enhanced capability of the immune system to react. An allergen is any substance capable of producing a specific type of susceptibility. One may view an allergic response as an exaggeration of the body's defensive mechanisms.

It is not generally known that if an alloy contains an allergenic element, implantation of the alloy will produce an allergic response. The following case illustrates this point in which a stainless steel screw was implanted.

Barranco and Soloman³ reported a case of nickel dermatitis in a lady who had her ears pierced prior to a surgical implant; they reported: A 20-year-old white woman had her ears pierced in 1967. In July 1968, a Hauser procedure was done on the left knee for a chronically dislocated patella. A stainless steel screw was used to secure a transferred tendon in its new location. The patient experienced no difficulty with this procedure. The same procedure was done on the right knee in June 1969; again a stainless steel screw was used to reattach the transferred tendon. This time the procedure was complicated by a wound dehiscence and secondary closure.

In October 1969, an extensive eruption on the chest and back developed. This was a subacute eczematous dermatitis involving the skin of the shoulders, midback, buttocks, abdomen, and breasts. She was treated with both topical and systemic corticosteroids with only minimal improvement. She then disappeared from follow-up until November 1970, when the dermatitis was noted to be widespread as before, but also in areas of contact with jewelry such as the earlobes, neck, and ring fingers. It was thought that she had a contact dermatitis, most likely nickel.

Patch testing with nickel sulfate gave a 4+ result and Barranco continued: Out of sheer desperation, the stainless steel screws were considered a possible cause of the dermatitis, and the orthopedic surgeon begrudgingly removed them. The day following removal of the screws, the erythema had markedly subsided with very little itching present. 72 h later, she was essentially clear of her dermatitis, with no itching. Her treatment continued to be only topical corticosteroids.

Five days following removal of the screws, closed patch testing was done with pure nickel, nickel sulfate, pieces of the stainless steel screw recently removed from the patient and a current routine chemical patch-testing tray. All tests were negative except for a 4+ reaction to nickel, nickel sulfate, and the stainless steel screw. The orthopedist still doubted that the stainless steel screw

could be the cause of her dermatitis and reapplied the screw to the skin of the back. In a period of 4 h, generalized pruritus and erythema again developed.

The foregoing case clearly demonstrates that a subject can respond to a single element in an alloy; stainless steel in this case, which contains nickel, chromium, iron, and other elements. Note that the patient developed an allergy to only the nickel in the stainless steel.

There is a hierarchy of allergenic metals. Heading the list are nickel, chromium, and cobalt, followed by beryllium, mercury, copper, gold, and silver. Obviously, these metals, or alloys containing them, are not candidates for implanted electrodes in all subjects. If a response results from their implantation, the implant must be removed even if it is still functioning. Although allergy has been reported to result from contact with gold and platinum jewelry, it is important to note that these elements do not appear in pure form in jewelry; other elements are used to form more durable alloys. If an allergic response is suspected with an electrode, the patch test will give the evidence sought. The addition of a nonallergenic criterion for selection of an electrode metal reduces the list of eligible metals for an implanted electrode. Additional information on allergenic responses to metals and alloys can be found in Chapter 8 of *Medical Device Accidents* authored by Geddes.¹⁶

ELECTRODE IMPEDANCE

The impedance of an electrode-electrolyte interface depends on the species of metal, the type of electrolyte it contacts, the surface area, and the temperature. The impedance decreases with increasing area and surface roughness. It also decreases with increasing frequency and increasing current density used to make the measurement. The simplest equivalent circuit for the interface consists of a half-cell potential, a series capacitance and resistance (Warburg model), in parallel with the Faradic impedance; the latter accounts for the very low frequency and direct-current properties (see Refs. 14 and 15). The Warburg components account for the alternating-current impedance; all of these components are frequency and current-density dependent (see Refs. 37 and 13); because of this fact they are designated polarization elements.

The best single descriptor for comparing the impedance of various electrode metals is the Warburg, low current-density capacitance (C_w) which takes the form B/f^β , where B and β are dependent on the metal species and f is the frequency of the current used to make the measurement. It is the reactance ($1/2\pi f C_w$) that is an important component of the interface impedance; therefore the Warburg capacitance per unit area, for which

TABLE 1. Warburg capacitance ($\mu\text{F}/\text{cm}^2$) of metals in contact with 0.9% saline.

Metal type		Reference
Platinum black heavy (PtB) (estimated)	$149,700f^{-0.366}$	38
Platinum-iridium black (PtIrB)	$8619f^{-0.299}$	30
Platinum black medium (PtB)	$4950f^{-0.366}$	38
Platinum-iridium (PtIr)	$2696f^{-0.79}$	30
Copper (Cu)	$705f^{-0.518}$	29
Rhodium (Rh)	$112f^{-0.210}$	29
Silver (Ag)	$103f^{-0.259}$	29
Stainless steel (SS)	$161f^{-0.525}$	13
Platinum (Pt)	$21.6f^{-0.143}$	29
Stainless steel (SS)	$17.2f^{-0.266}$	29
MP35N (Ni Co Cr Mo)	$8.4f^{-0.127}$	29
Palladium (Pd)	$7.3f^{-0.113}$	29
Aluminum (Al)	$2.94f^{-0.126}$	29

there are values for some metals, should be considered. The higher the Warburg capacitance, the lower the electrode-tissue impedance. Table 1 presents the capacitance/cm² for many metals in contact with 0.9% saline at room temperature. Figure 1 is a log-log plot of the low-current density Warburg capacitance versus frequency for the materials shown in Table 1. The closer to the top of the figure, the lower the impedance of the electrode. Note that platinum black represents the lowest impedance. Some of the materials shown in Table 1 have not been qualified for use as implanted electrodes. In addition, for many metals that have been used for implants, there are no data on the Warburg capacitance. Therefore there are gaps in our knowledge; for example, there are no such data for chromium, tin, tungsten, nichrome, titanium nitride, lead, and gold, some of which have been used for implanted electrodes. However, some of these (lead and chromium) are not good candidates for implanted electrodes.

Although the Warburg model in which $C_w = B/f^\beta$ is useful for comparing electrode materials, it predicts an ever increasing impedance as the frequency is decreased. At direct current (dc), i.e., $f=0$, the impedance is infinite. However, when the frequency is below about 10 Hz, the Faradic impedance starts to dominate and there is a finite direct-current resistance. The highest impedance that an electrode-electrolyte interface can attain is the zero-current-density, dc (Faradic) resistance. A technique for making this measurement was reported by Geddes and Roeder.¹²

ELECTRODE SURFACE CONDITION

In addition to the species of metal and the electrode area in determining the low current-density electrode-tissue impedance, the condition of the electrode surface is equally important. Roughening an electrode surface increases its effective surface area without increasing its

geometric size. Roughening can be achieved by chemical etching, electrolytic etching, or mechanical abrasion (sand blasting). Sputtering a material on an electrode is also a way of obtaining a large effective area.

The first and the classical example of chemically preparing an electrode surface to reduce its impedance is due to Kohlrausch²¹ who faced the problem of measuring the resistivity of electrolytes. To do so required the availability of a low electrode-electrolyte impedance which he created by blackening a platinum electrode by electrolytically depositing finely divided platinum, i.e., platinum black. Schwan³⁸ optimized the method by the following technique. The platinum electrode to be blackened is first sand blasted; then it is placed in a solution of 0.025N HCl that contains 3% platinum chloride and 0.025% lead acetate. The platinum electrode to be blackened is made the cathode with respect to a large-area platinum anode in the solution. A current density of 10 mA/cm² and a deposit of 30 A-s/cm² produce the lowest impedance. The resulting electrode has an impedance about 30 times lower than that of a bare platinum surface. Such electrodes are still used for measuring the resistivity of electrolytes.

Platinum is often alloyed with iridium to create a platinum-iridium electrode. Such an electrode is widely used with cardiac pacemakers. It has a lower impedance than bare platinum but it is higher than that of platinum black. However, platinum-iridium has been blackened to reduce its impedance (see Fig. 1). Brummer and Robblee⁶ state that iridium is better than platinum for making very small microelectrodes because it is a harder material. They also reported that IrO₂ (an insulator) has 100 times the charge transfer capability than iridium.

Another electrode with a large rough surface is due to Schaldach³⁴ who described a method for preparing titanium nitride (TiN) by sputtering. He reported that it has an impedance that is six-fold lower than that of bare platinum and used it for cardiac pacing. It provided a lower stimulation threshold and larger sensed voltage.

RADIOGRAPHIC VISIBILITY

Implanted electrodes are usually small because they are designed to stimulate or detect bioelectric signals from small populations of excitable cells. After implantation it is highly desirable to be able to view them radiographically over time to monitor their integrity, especially if an abnormal response is encountered. Because of their small size it is prudent to select a metal that absorbs x rays strongly; this directs the choice of metals to those that have a high atomic number, being the number of protons in the nucleus. However, if the implant is large, the atomic number becomes less important.

Table 2 lists the atomic numbers of electrode materials that are candidates for implanted electrodes that do

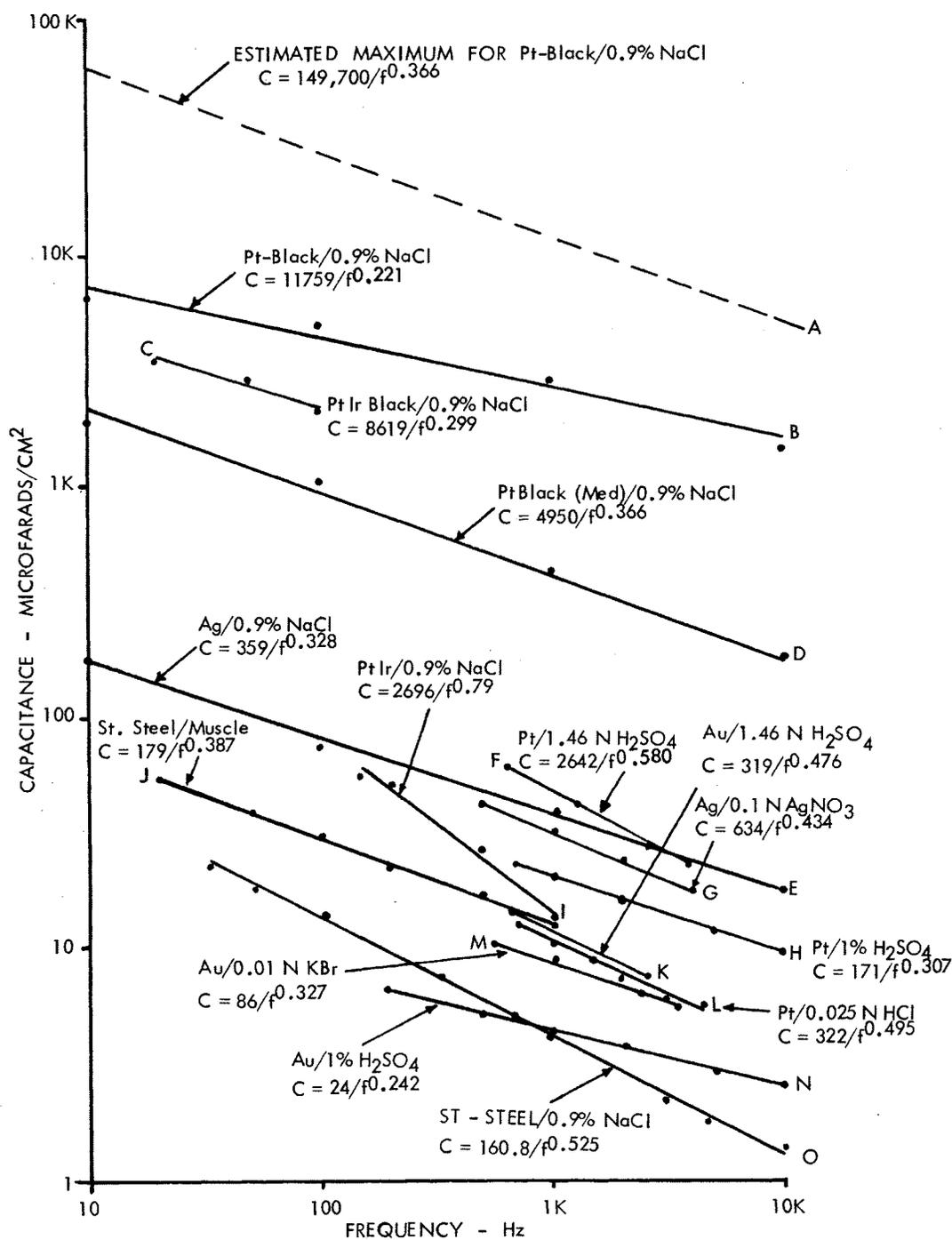


FIGURE 1. Warburg capacitance ($\mu\text{F}/\text{cm}^2$) of metals in contact with various electrolytes. (Redrawn from *Electrodes and the Measurement of Bioelectric Events* by L. A. Geddes, New York: Wiley-Interscience, 1972) (see Ref. 18).

not produce a vigorous tissue response. In the case of alloys, it is possible to estimate an equivalent atomic number by scaling according to the percentages of the elements in the alloy; this was the method used for Table 2 and is identified by (eq).

The materials included in Table 2 were drawn from the literature cited. To this list titanium nitride has been added because it was shown by Schaldach³⁴ that it has six-fold lower electrode-electrolyte impedance than bare platinum. Tungsten (W) was added because it was found

TABLE 2. Properties of materials. eq=equivalent.

Material	Atomic No.	Expansion coefficient	Melting point
Gold (Au)	79	13.2	1063
Platinum (Pt)	78	8.99	1773
Platinum-Iridium (PtIr)	78 (eq)	7.5-8.8	1815-1935
Iridium (Ir)	77	4.4-14.7	2716
Tungsten (W)	74	4.2	3370
Tantalum (Ta)	73	6.5	2996
Tin (Sn)	50	2.2	232
Rhodium (Rh)	45	8.2	1964
Nichrome	27 (eq)	8.5	1395
Stainless steel (316)	26 (eq)	10-20	1400-1450
Titanium nitride (TiN)	14 (eq)	9.4	2930

by Hubel¹⁹ to be an excellent material for cortical recording.

Although all of the metals and alloys shown in Table 2 are eligible for implanted electrodes, only a few have high enough atomic number (or equivalent) to be visualized radiographically. Among the most visible are gold, platinum, platinum-iridium, tungsten, and tantalum. Although the remainder will be less visible radiographically, if this is not a requirement, many of the materials in Table 2 are candidates. However, nichrome and stainless steel contain nickel, which is an allergen for some subjects.

INSULATION EXPANSION-COEFFICIENT MATCHING

When a hard insulation is applied to an electrode, attention must be given to the coefficient of expansion of the material that constitutes the electrode and that of the applied insulation. This is especially important if the insulation is applied at a higher temperature and the temperature at which the electrode is used is lower. For example, when glass is melted on to an electrode, if the electrode material has a different thermal coefficient of expansion than the insulation, during cooling the insulation will crack. Table 3 lists the thermal coefficients of expansion of many electrode materials and insulating materials. However, if the insulation is applied at room temperature (20 °C), the increase in temperature to body temperature (37 °C) may not strain the insulation, especially if it is a plastic.

Two other factors related to insulators merit consideration: (1) the dielectric constant and (2) the dielectric strength; Table 3 presents such data. The former determines the capacitance of the electrode with respect to its electrolytic environment; the latter is important only for stimulating electrodes. All dielectrics have a finite ability to withstand a voltage without breakdown. The dielectric strength of an insulator is expressed in terms of the voltage that it can sustain per 1/1000th in. (V/ml). Table

TABLE 3. Properties of insulating materials.

Material	Dielectric strength (V/ml)	Dielectric constant	Expansion coefficient ($\times 10^{-6}$)	Melting point (°C)
Polyimide	550	3.5	30-60	400
Pyrex glass	335	3-6	3.3	1245
Vycor glass	...	3.8	0.8	1550
Soda glass	...	4.8	12.0	1000
Quartz crystal	...	4.2	5.21	1410
Quartz fused	410	3.78	0.256	1500
Aluminum oxide	365	4.8	1.0	2000
Formvar	...	8.4
Ta Pentoxide	...	18-25	...	1785
Epoxy	400	3.6	62	...
Titanium dioxide	100-210	14-110	6.5-11.0	1843
IrO ₂	1100

3 lists the dielectric strengths of many insulating materials used to cover electrodes. Exceeding the dielectric strength makes the electrode conductive. The thinner the insulation, the lower the breakdown voltage for any insulation.

In situations when an insulating material needs to be heated for application to an electrode, in addition to matching thermal coefficients of expansion, it is necessary that the melting point of the insulation be below that of the metal that constitutes the electrode. Table 2 lists the melting points and expansion coefficients of several metals. Table 3 lists the melting points and expansion coefficients for many insulating materials.

An electrically heated circumscribed coil can provide heating to melt an insulator. A flame can also be used. The flame temperature for natural gas and air is 1950 °C, that for acetylene and air is 2325 °C and that for acetylene and oxygen is 3000 °C.

ELECTRODE-AREA MEASUREMENT

Because electrode impedance depends on the area of the electrode exposed to tissues and fluids, it is useful to obtain a measurement of the electrode area. Using a light microscope to make such a measurement is difficult because the insulation is very thin near the electrode tip and the end of the insulation is not visible. Hubel¹⁹ described a simple method that involves placing a drop of saline on a glass slide that is viewed with a microscope. A small wire is then placed in the drop and connected to the positive pole of a battery; the other pole is connected to the microelectrode which is advanced into the drop, and the tip is viewed in the microscope. The active area can be estimated by observation of the area from which hydrogen gas bubbles are evolved. This method is very convenient to apply and has been used successfully to measure the area of a variety of large and small needle electrodes.

BIMETAL JUNCTION CORROSION

If the conductor that contacts the microelectrode is of a different metal, this bimetal junction must be fluid proof. If this junction comes into contact with tissue fluids, there exists a short circuited galvanic cell and current will flow in the electrolytic environment with the production an unstable potential that will turn up as noise if the electrode is used for recording (see Ref. 1). With the passage of time this electrochemical action will erode the junction and produce an open circuit.

STIMULATING ELECTRODES

When small-area electrodes are used to stimulate excitable tissue, despite the fact that the current is low, the current density is high and two new considerations arise: (1) stimulus waveform distortion and (2) electrochemical decomposition. The former is associated with the Warburg capacitive nature of the electrode-electrolyte interface and the type of stimulator output circuit (constant-voltage or constant-current). Electrolytic decomposition results when there is a direct-current component in the stimulus train.

STIMULATOR OUTPUT CIRCUITS

Basically there are only two types of stimulator output circuits: (1) constant-voltage and (2) constant-current. In both cases they are connected to the stimulating electrodes, which have complex resistive and reactive components, due to the nature of the electrode-electrolyte interface. With the constant-voltage stimulator, if the stimulus wave form is a rectangular voltage pulse, the current pulse will not be rectangular; it will have a spike on the rising phase, an exponential decay during the pulse, and an undershoot spike at the end of the pulse. This is the characteristic of a typical functional electrical stimulator in which the peak current depends on the stimulus voltage and inversely with the electrode-tissue impedance.

With the constant-current stimulator, which is typically used for research, the amplitude of the current pulse is independent of the electrode-tissue impedance. If a rectangular current pulse is delivered to stimulate the tissue, the voltage wave form across the electrodes will not be rectangular; it will have a small step, followed by an exponential rise that is terminated by the end of the pulse.

In practice, stimulators are neither true constant-voltage nor constant-current types. The typical stimulator has a low output impedance with respect to that of the tissue-electrode circuit; therefore it resembles a constant-voltage source. Consequently, the current

waveform will not be the same as the voltage waveform owing to the complex impedance of the electrode-electrolyte interface.

ELECTRODE DECOMPOSITION

When an electrode is implanted for recording a bioelectric signal, the size of the encircling capsule is the focus of interest. However, when a stimulating electrode is implanted, capsule thickness and electrode decomposition are important factors in choosing the best metal species. Of equal importance is the type of stimulus waveform and the type of stimulator output circuit. These factors will be discussed now.

Faraday's law of electrochemical decomposition states that for a monovalent element, 1 g equivalent of an element is removed (or deposited) by the passage of one Faraday, i.e., 96,500 C (A s) of charge transferred. Therefore, if a stimulus waveform has a dc component, electrolytic decomposition will occur.

There are two techniques that can be used to minimize the presence of a dc component in the stimulus: (1) use capacitive coupling in the output circuit of the stimulator; this method is used in cardiac pacing, (2) use what is called the balanced waveform, introduced by Lilly *et al.*²² in 1955. With this waveform the charge in the first phase is equal to the charge in the second, oppositely directed phase. There are two methods of satisfying this requirement: (1) use a bidirectional pulse in which the amplitude and duration of both pulses are the same, i.e., a reciprocal pulse. (2) The amplitude of the first pulse is higher and the duration is shorter than that of the second inverted pulse, the areas under both pulses being equal. However, use of the balanced pulse does not guarantee elimination of electrode decomposition due to the nonlinearity of the electrode-electrolyte interface. Nonetheless, when long-term (chronic) stimulation is to be employed, use of the bidirectional (incorrectly called biphasic) wave is the best choice along with use of a constant-current stimulator.

In 1955, Lilly *et al.*²² pointed out that in the late 1940s, chronic brain stimulation in monkeys and man was associated with neural damage at the electrodes. They postulated that this damage is due to the use of a monophasic stimulating waveform and they introduced the bidirectional wave, consisting of two identical 40 μ s oppositely directed pulses separated by 88 μ s. They studied the cortex response to this waveform and stated:

"From the results, it is concluded that this form of electric current does not detectably injure cellular function or structure when it is passed through the cortex near threshold values for 4-5 h per day for 15 weeks."

White and Thomas⁴¹ carried out an important study to

determine the decomposition of various metal wires (0.010 in.) used as electrodes in saline. They employed a 0.5/0.5 ms bidirectional wave with a frequency of 50/s delivered from a constant-current stimulator. The metals investigated were stainless steel, platinum, iridium, palladium, rhodium, rhenium, gold, tantalum, titanium, tungsten, zirconium, and some conducting oxides. Current densities ranged from 100 to 2000 mA/cm² (the latter is in excess of stimulation threshold). The electrodes were weighed before and after current flow. Current was passed for 24 h a day for periods up to 9 months. They concluded that iridium, rhodium, platinum, and palladium are very resistant to corrosion. They stated:

“Even microelectrodes 5 μm thick, made of such materials should have lifetimes on the order of decades. Gold is somewhat poorer but probably acceptable; all the other materials tested, including tungsten and stainless steel, are unacceptable as chronic microelectrode material.”

An interesting *in vitro* study on the ability of the bidirectional balanced wave to reduce the decomposition of 316 stainless steel microelectrodes (0.08 cm²) was reported by McHardy *et al.*²⁶ A bidirectional pulse (2 \times 0.5 ms) with a frequency of 50/s was delivered to the electrodes via a 3 μF capacitor (to block dc) for 1–3 days. They quantitated the electrode decomposition by measuring the iron deposited in the saline. They found that use of the balanced bidirectional wave permitted delivery of triple the charge density for the same electrode decomposition.

The foregoing study by White and Thomas merits special attention because the method used a balanced bidirectional waveform and a constant-current output circuit to deliver the pulse of current. Both guarantee that a minimum of dc will flow through the electrodes. This being so, it is seen that some electrode materials were decomposed, judged by weight loss, and others were resistant to decomposition. The method used by White and Thomas is the best for testing the suitability of an electrode metal for stimulation.

Brummer and Turner⁵ analyzed the possible electrochemical reactions, notably pH shift and electrolytic decomposition products that could occur at a platinum microelectrode-electrolyte interface. They stated that neural stimulation parameters range from 0.1 to 5 mA applied to electrodes ranging from 0.0005 to 0.08 cm². Pulse durations range from 10 to 100 μs with frequencies from 10 to 200/s. They conducted *in vitro* studies and recommended the use of a balanced bidirectional wave and to limit the charge density (C/cm²).

THE INSULATED (CAPACITIVE) ELECTRODE

It is possible to record bioelectric events and stimulate excitable tissues with an insulated electrode, i.e., one that does not make ohmic contact with tissues or body fluids. A capacitor consists of two conducting materials separated by an insulator (dielectric). With the insulated electrode, one conductor is the metal electrode; the dielectric is the insulation thereon and the other conducting material is the tissue fluids. The capacitance $C = kA/t$, where k is the dielectric constant of the insulator; A is the area of the electrode, and t is the thickness of the dielectric. It is desirable to achieve the highest capacitance for a given area; therefore a thin layer of dielectric is needed. However, the thinner the dielectric, the lower the dielectric breakdown voltage. The dielectric breakdown of an insulator is specified in terms of volts per 1/1000th in. (ml) of thickness.

CAPACITIVE RECORDING ELECTRODES

The first insulated recording electrodes appear to be due to Richardson *et al.*^{31,32} and Lopez *et al.*²⁴ of the US Air Force. The electrodes consisted of an aluminum plate (2.5 \times 2.5 cm) that was anodized on the surface placed in contact with the skin. On the back of the electrode was mounted a field-effect transistor (FET) with the gate terminal connected to the electrode. Surrounding the anodized electrode was an insulating block of potting compound surrounded by a circular metal ring that acted as an electrostatic shield; the FET was connected as a source follower. To protect the FET from acquiring a high electrostatic voltage, a high-resistance leakage path was provided by using two diodes (IN3600) in series opposition.

Following Richardson's lead, Wolfson and Neuman⁴³ described a small-area insulated electrode for general purpose bioelectric recording. The electrode measured 6 \times 6 mm and was fabricated from an 0.01 Ωcm , 0.23-mm-thick *N*-type silicon wafer. The circular region, 4.5 mm in diameter, was the active detecting portion of the surface and had an oxide 0.2 μm thick. The surrounding region, a 1.5- μm -thick oxide, minimized electrical leakage over the surface of the electrode, and extended down the sides and over the back of the disk except for a small region where an ohmic contact was made to the silicon and photomask; an etch process provided a tenacious insulating layer that is highly reproducible and can be maintained to close tolerances.

Wolfson and Neuman stated that a metal-oxide-semiconductor (FET) source follower was mounted to the back of the electrode. They reported a low-frequency cutoff of 0.005 Hz and the high-frequency cutoff was well above that for electrophysiological signals.

The desiderata for a capacitive recording electrode are a high dielectric constant and a thin dielectric to achieve a high capacitance. However, the breakdown voltage is not a consideration, but the thin dielectric coat must be free of pinholes. If radiographic visibility is required, a metal with a high atomic number is selected. In addition, the dielectric should not be allergenic.

Although capacitive electrodes are routinely used with diathermy and sometimes as electrosurgical dispersive electrodes, they have seldom been used as stimulating electrodes. Because their operation is associated with no net charge transfer, they merit consideration. In addition, the charge transfer density distribution thereunder is more uniform than that with electrodes that make ohmic contact with the subject. However, some dielectrics deteriorate with time, especially those in contact with conducting fluids, and the dielectric becomes conductive thereby changing the character of the electrode to become a conductive one.

CAPACITIVE STIMULATING ELECTRODES

An unusual type of capacitive stimulating electrode is described in a patent issued to Batrow and Batrow.⁴ Schaldach³⁵ reported the use of a catheter-tip capacitive cardiac pacing electrode.

The Batrow electrode was designed for transcutaneous phrenic-nerve stimulation to contract the diaphragm to produce artificial breathing. The electrode consisted of a flattened glass chamber containing argon gas at a low pressure. When it was placed on the skin and a high-voltage pulse was applied, the gas ionized and emitted light, becoming one plate of the capacitor electrode; the other plate was the subject. The remarkable feature of this capacitor electrode (and the very-short-duration pulses that were applied to it), was that it provided motor-nerve stimulation with very little skin sensation.

The capacitor electrode described by Schaldach,³⁵ used for cardiac pacing, consisted of a metal-oxide formed on the surface of a catheter-tip titanium electrode to create the dielectric which was titanium nitride. Schaldach reported that cardiac pacing could be accomplished with two-thirds less energy compared with a conventional pacing electrode of the same size. Importantly, he stated that stimulation was the result of charge rearrangement, there being no transfer of charge at the electrode surface.

Geddes *et al.*¹⁷ described a capacitor electrode suitable for human motor-point stimulation that was constructed from No. 7740 fused silica tubing (13 mm outer diameter, 11 mm inner diameter). The dielectric constant is 5.1. The tubing was heated in a flame to close the end and blown to form the end chamber, 25 mm in diameter and 1 mm thick. The chamber was filled with conducting

silver paint that captured a bare stranded wire and constituted one plate of the capacitor; the other plate was the subject.

The stimulator consisted of an autotransformer of the ignition-coil type. Into the primary was discharged an 8 μ F capacitor. The maximum open-circuit voltage was variable to 60 kV. The current wave form was a slightly underdamped sine wave, a fraction of a millisecond in duration.

Stimulation of the motor points of the forearm produced finger twitches and tetanic contractions with ease, causing little skin sensation. Even less sensation was perceived when a thin, 25 mm diameter gauze pad, lightly moistened with tap water, was placed between the skin and the capacitive electrode. The combination of a capacitive electrode and a short-duration pulse is ideal for transcutaneous motor-nerve stimulation with very little cutaneous sensation.

Loeb and Richmond²³ described a tantalum capacitive electrode for neural stimulation. The tantalum electrode was sintered with tantalum powder, then anodized to produce a small-area tantalum pentoxide electrode with a capacitance of 4 μ F. The reference electrode was an electrically conducting porous oxide of indium; these constituted the BION implantable stimulating system.

The capacitive stimulating electrode presents unusual design requirements. The dielectric constant of the insulation should be high to achieve a high capacitance. The dielectric should possess a high breakdown voltage (V/ml). The thinner the dielectric, the higher the capacitance, but the lower the breakdown voltage. The metal on which the insulation is placed should have a high atomic number to be visible radiographically. Finally, the insulation should be free of pinholes, nonallergenic, and not deteriorate in the presence of conducting fluids.

IMPEDANCE OF CONDUCTIVE ELECTRODES

Establishing a stable, low-impedance contact with tissue is the primary requirement of an implanted electrode. From Fig. 1, the choices are platinum black, platinum-iridium black, platinum-iridium, copper, rhodium, silver, stainless steel, MP35N, palladium, and aluminum in that order. However, platinum black induces a thick tissue capsule, as do copper and silver. There are no data on platinum-iridium black, but it is likely that it also stimulates a thick capsule. Stainless steel contains nickel, which is a potent allergen. MP35N has not been used as an electrode as yet. This leaves only platinum, rhodium, and palladium for which there are impedance data.

Table 2 lists other metals that have been used as electrodes and contains some that must be rejected on the basis of provoking a thick tissue capsule. If radiographic visibility is a requirement, those with the highest atomic number are the candidates, they are gold, plati-

num, tungsten, tantalum, tin, rhodium, palladium, and titanium nitride, the latter having a rough surface to obtain a large surface area; there are no data for a tissue response. Tin is a soft metal that is chlorided when used as a recording electrode. Chloriding will probably stimulate the growth of a thick tissue capsule. However, bare tin is smooth and flexible and is used by one manufacturer as a defibrillating electrode. Gold, platinum, tungsten, and titanium have all been used as surgical implants without allergenic response. There are no implant data on rhodium and palladium.

Selecting the best candidate from Tables 1 and 2, provides gold, platinum, tungsten, rhodium, palladium, and titanium. All of these metals can be deposited on a silicon substrate and can be used as implants with suitable insulation. However, White and Thomas⁴¹ does not recommend palladium, rhenium, tantalum, titanium, tungsten, and zirconium as stimulating electrodes due to their decomposition characteristics.

INSULATING MATERIALS

Table 3 lists the dielectric strengths, dielectric constants, expansion coefficients, and melting points of many insulating materials used for implanted electrodes. Polyimide appears to produce the least tissue response. If glass or fused quartz is used, the coefficient of expansion must match that of the electrode that it covers; otherwise cracking will result when cooling takes place.

As stated earlier, metals such as aluminum, indium, and tantalum can be anodized to produce a thin oxide coat that is an insulator. Of the two, tantalum appears to produce an oxide coat that has the highest capacitance per unit area.

INSULATORS FOR CAPACTIVE ELECTRODES

Three of the metals (aluminum, tantalum, and iridium) have been anodized to produce an oxide coat which is a dielectric; these oxides have a reasonable dielectric constant. The magnitude of the capacitance depends on the electrode area and inversely with the thickness of the oxide layer. The capacitance can be increased by first etching the surface before anodizing. The breakdown voltage depends on the thickness of the oxide layer. With a moderately thick layer, breakdown voltages of several hundred are attainable.

Both aluminum oxide (Al_2O_3) and tantalum pentoxide (Ta_2O_5) are used in commercially available capacitors. If radiographic visualization is a requirement, tantalum is the choice because of its higher atomic number (73), compared to that of aluminum (13). An implantable Ta_2O_5 capacitive electrode was reported by Loeb and Richmond (2001).²³ Neither Al_2O_3 or Ta_2O_5 have been reported to be allergenic.

CONCLUSION

Based on the four criteria (tissue response, allergenicity, impedance, and radiographic visibility), it is necessary to distinguish between stimulating and recording electrodes. From the study by White and Thomas (1974),⁴¹ the best metals are platinum, iridium, and rhodium, the latter being less visible radiographically. Gold is also a candidate for recording (noncurrent-carrying) electrodes. The choice for stimulating electrodes are platinum, platinum-iridium, gold, tungsten, and rhodium, the latter being a little less visible radiographically. For capacitive stimulating electrodes, tantalum pentoxide has the highest dielectric constant, followed by iridium oxide. Aluminum oxide is a candidate with a lower dielectric constant.

REFERENCES

- ¹Aronson, S., and L. A. Geddes. Electrode potential stability. *IEEE Trans. Biomed. Eng.* 32:85, 1987.
- ²Babb, T. L., and W. Kupfer. Phagocytic and metabolic reactions to chronically implanted metal brain electrodes. *Exp. Neurol.* 86:171-184, 1984.
- ³Barranco, V. P., and H. Soloman. Eczematous dermatitis in nickel. *J. Am. Med. Assoc.* 110:1244, 1972.
- ⁴Batrow, J., and P. Batrow. Electro-physiotherapy apparatus. US Patent No. 3,077,884 (19 Feb. 1963).
- ⁵Brummer, S. B., and M. J. Turner. Electrochemical considerations for safe electrical stimulation of the nervous system with platinum electrodes. *IEEE Trans. Biomed. Eng.* 24:59-63, 1977.
- ⁶Brummer, S. B., and L. S. Robblee. Criteria for selecting electrodes for electrical stimulation: Theoretical and practical. *Ann. N.Y. Acad. Sci.* 0077/8923:159-170, 1983.
- ⁷Campbell, P. K., K. F. Jones, R. J. Huber, K. W. Horch, and R. A. Normann. A silicon-based, three-dimensional neural interface. *IEEE Trans. Biomed. Eng.* 38:758-768, 1991.
- ⁸Collias, J. C., and E. E. Manuelidis. Histopathological changes produced by implanted electrodes in cat brains. *J. Neurosurg.* 14:302-328, 1957.
- ⁹Dodge, H. W., C. Petersen, C. W. Sem-Jacobsen, P. Sayre, and R. G. Bickford. The paucity of demonstrable brain damage following intracerebral electrography: Report of a case. *Proc. Staff Meet. Mayo Clin.* 30:215-221, 1955.
- ¹⁰Dymond, A. M., L. E. Kaechele, J. M. Jurist, and P. H. Crandall. Brain tissue reaction to some chronically implanted metals. *J. Neurosurg.* 33:574-580, 1970.
- ¹¹Fischer, G., G. P. Sayre, and R. G. Bickford. Histologic changes in the cat's brain after introduction of metallic and plastic coated wire used in electroencephalography. *Proc. Staff Meet. Mayo Clin.* 32:14-22, 1957.
- ¹²Geddes, L. A., and R. Roeder. Measurement of the direct-current (Faradic) resistance of the electrode-electrolyte interface. *Ann. Biomed. Eng.* 29:181-186, 2001.
- ¹³Geddes, L. A., C. P. DaCosta, and G. Wise. The impedance of stainless-steel electrodes. *Med. Biol. Eng.* 9:511-521, 1971.
- ¹⁴Geddes, L. A. Evolution of circuit models for the electrode-electrolyte interface. *Ann. Biomed. Eng.* 25:1-14, 1997.
- ¹⁵Geddes, L. A., and L. E. Baker. Principles of Applied Bio-

- medical Instrumentation, 3rd ed. New York: Wiley, 1989.
- ¹⁶Geddes, L. A. Medical Device Accidents. Boca Raton, FL: CRC Press, 1998.
 - ¹⁷Geddes, L. A., M. Hinds, and K. S. Foster. Stimulation with capacitive electrodes. *Med. Biol. Eng. Comput.* 25:359–360, 1987.
 - ¹⁸Geddes, L. A. Electrodes and the Measurement of Bioelectric Events. New York: Wiley-Interscience, 1972.
 - ¹⁹Hubel, D. H. Tungsten microelectrode for recording from single units. *Science (Washington, DC, U.S.)* 125:549–550, 1950.
 - ²⁰Jones, K. E., P. K. Campbell, and R. A. Norman. A glass/silicon composite intracortical array. *Ann. Biomed. Eng.* 20:423–437, 1992.
 - ²¹Kohlrausch, F. Über platinirte Elektroden und Widerstandsbestimmung. *Ann. Phys. (Leipzig)* 60:315–332, 1897.
 - ²²Lilly, J. C., J. R. Hughes, E. C. Alvord, and T. W. Gallin. Brief, noninjurious electrical stimulation of the brain. *Science (Washington, DC, U.S.)* 121:468–469, 1955.
 - ²³Loeb, C. E., and F. J. R. Richmond. BION Implants for Therapeutic and Functional Electrical Stimulation in Neural Prosthesis for Restoration of Sensory and Motor Function, edited by J. K. Chapin and K. A. Moxon. Boca Raton, FL: CRC Press, 2001.
 - ²⁴Lopez, A., and P. Richardson. Capacitive electrocardiographic and bioelectric electrodes. *IEEE Trans. Biomed. Eng.* 16:99, 1969.
 - ²⁵Maynard, E. M., C. T. Nordhausen, and R. A. Normann. The Utah intracortical electrode array. *Ann. Biomed. Eng.* 20:423–437, 1992.
 - ²⁶McHardy, J., D. Geller, and S. B. Brummer. An approach to corrosion control during electrical stimulation. *Ann. Biomed. Eng.* 5:144–149, 1977.
 - ²⁷Neural Prostheses, edited by W. F. Agnew and D. B. McCrery. Englewood Cliffs, NJ: Prentice Hall, 1990.
 - ²⁸Radovsky, A. S., and J. S. Van Vleet. Effects of dexamethasone elution on tissue reaction around stimulating electrodes of endocardial pacing leads in dogs. *Am. Heart J.* 117:1288–1298, 1989.
 - ²⁹Ragheb, T., and L. A. Geddes. The polarization impedance of common electrode metals operated at low current density. *Ann. Biomed. Eng.* 19:151–163, 1991.
 - ³⁰Ray, C. D., R. G. Bickford, L. C. Clark, R. E. Johnston, T. M. Richards, D. Rogers, and W. E. Russert. A new multicon-tact, multipurpose brain depth probe. *Proc. Staff Meet. Mayo Clin.* 40:771–804, 1965.
 - ³¹Richardson, P. C., F. K. Coombs, and R. M. Adams. Some new electrode techniques for long-term physiologic monitoring. *Aerosp. Med.* 39:745–750, 1968.
 - ³²Richardson, P. C., and F. K. Coombs. New construction techniques for insulated electrocardiographic electrodes. *Proc. 21st Ann. Conf. Eng. Med. Biol.* 10:13A.1, 1968.
 - ³³Robinson, F. R., and M. T. Johnson. Histopathological studies of tissue reactions to various metals implanted in cat brains, ASD Tech Rept. 1961, pp. 61–397. USAF Wright-Patterson AFB, Ohio p. 13.
 - ³⁴Schaldach, M., M. Hubmann, R. Hardt, and A. Weikl. Pacemaker electrodes made of titanium nitride. *Biomed. Technik.* 34:185–190, 1989.
 - ³⁵Schaldach, M. S. New pacemaker electrodes. *Trans. Am. Soc. Artif. Intern. Organs* 17:29–35, 1971.
 - ³⁶Schmidt, S., K. Horch, and R. Norman. Biocompatibility of silicon-based electrode arrays implanted in feline cortical tissue. *J. Biomed. Mater. Res.* 27:1393–1399, 1993.
 - ³⁷Schwan, H. P., and J. G. Maczuk. Electrode polarization: Limits of linearity. *Proc. 18th Ann. Conf. Eng. Biol. Med.*, 1965.
 - ³⁸Schwan, H. P. Determination of biological impedances. In: *Physical Techniques in Biological Research*. New York: Academic, 1963, Vol. VIB.
 - ³⁹Stensaas, S. S., and L. J. Stensaas. Histopathological evaluation of materials implanted in the cerebral cortex. *Acta Neuropathol. (Berl)* 41:145–155, 1978.
 - ⁴⁰Stokes, K. B., G. A. Bornzin, and W. A. Weabusch. A steroid-electing, low-threshold, low polarizing electrode. In: *Cardiac Pacing*, edited by D. Steinkoff. Verlag: Darnstadt, 1983, p. 369.
 - ⁴¹White, R. L., and T. J. Gross. An evaluation of the resistance to electrolysis for metals for use in biostimulation microprobes. *IEEE Trans. Biomed. Eng.* 21:451–487, 1974.
 - ⁴²Wise, K. D., and J. B. Angell. An integrated circuit approach to extracellular microelectrodes. *Proc. 8th Int. Conf. Med. Biol. Eng.*, 1969, paper No. 14-5.
 - ⁴³Wolfson, R. N., and M. R. Neuman. Miniature $S_i-S_1O_2$ insulated electrodes based on semiconductor technology. *Proc. 8th Int. Conf. Med. Biol. Eng.*, Chicago, IL: Carl Gorr, 1969, paper No. 14-6.