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Function of implanted cathodes in electrode-induced bone growth

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Abstract—*The application of microampere direct current (d.c.) to electrodes implanted in bone results in a proliferative response that has been found useful in the treatment of certain types of fracture. The mechanism of this response is unknown. In this investigation, the d.c. polarisation properties of 11 implantable cathode materials were measured,* in vitro *and* in vivo, *and then related to the conditions known to produce the osteogenic response. From these data, limiting parameters for clinical use of the various electrodes can be determined. Nitrogen purge experiments showed the dependence of the current on molecular oxygen and suggested that the products of oxygen reduction (H_2O_2, O_2^-, $OH\cdot$, OH^- etc.) may mediate the proliferation of bone by appropriate cells in the region of the electrode. The presence of these intermediates, some of which are free radicals, and their possible side effects needs further study.*

Keywords—*Bone proliferation, Direct current, Electrode reactions*

1 Introduction

WITHIN the last few years there has been increasing interest in the implantation of low current-density electrodes to induce bone growth in nonunited fractures and other circumstances (BRIGHTON, 1977; SPADARO, 1977; HERBST, 1978). For the most part, continuous direct current (d.c.) has been used for this, although pulsed currents, both biphasic and uniphasic, have also been tried. This is in contrast to most other forms of electrical stimulation (neuromuscular, central nervous system, cardiac) in which short high-current pulses (0·1 to 1 A/cm^2) are required to produce a physiological effect. Although there have been several studies published on the electrochemical aspects of the pulsed techniques, relatively little attention has been paid to the low-current d.c. electrode in the biological milieu. Certainly, the optimisation and safe use in osteosynthetic applications would seem to depend on a knowledge of the electrode interface and its reactions under these circumstances. The selection of an electrode material and its operating conditions should properly rest on such a knowledge.

Despite numerous reports of clinical success (60–80%) for surgically resistant nonunions (BRIGHTON, 1977), the mechanism of action of electrode-induced bone growth remains obscure. Indeed, there is likely to be more than one mechanism operative, even with a single technique and especially so with differing techniques. As has been noted before, however (SPADARO, 1978; CORDEY, 1978), the following generalisations are tenable:

(*a*) stimulation of osteogenesis is more successful with the electrode directly located in the fracture site

(*b*) cathodes are more effective than anodes

(*c*) continuous (d.c. supply) current is at least as effective, if not more so, than alternating (a.c. supply) or pulsed current

(*d*) current densities that are too high at the electrode produce necrosis rather than osteogenesis for either polarity

(*e*) necrosis is usually associated with anodic corrosion.

These observations are consistent with the idea that electrochemical reactions at or near the implanted cathode are mainly responsible for the osteogenic response *in vivo*, although the simultaneous effects of bulk electric fields or charge flow cannot be eliminated. The involvement of electrode reactions *per se* is also supported by a previous study in which metal-specific relative-population shifts were found in bone marrow cells *in vitro* after the application exposure to d.c. electrodes (SPADARO *et al.*, 1977),

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and also by the oxygen depletion measurements of BRIGHTON *et al.* (1975).

Of particular interest, especially with noble metal cathodes, are reactions involving the reduction of molecular oxygen (DEROSA and BEARD, 1977; HOARE, 1968; GREATBATCH *et al.*, 1969). Such reactions may occur in the current transduction process at all implanted cathodes and are a natural subject of inquiry in the search for mechanisms of bone stimulation.

The nature and extent of reactions at an electrode in the body can be determined, in part, from its electrical properties under various conditions. With this in mind, the purpose of the present experiments was to

(*a*) study the d.c. supply current-potential behaviour (polarisation curves) of a number of 'implantable' cathodes *in vitro* and *in vivo*

(*b*) seek limits for their safe operation

(*c*) explore the possible contribution of their electrochemical reaction products to their biological activity, particularly the elaboration of bone tissue.

The metals and alloys studied were chosen for their past or potential use as bone stimulation electrodes. Such studies of low-current d.c. electrodes should also be relevant to other therapeutic or diagnostic applications of direct current and pulsed currents with sufficient pulse width to permit similar reactions to occur (e.g. 1 ms or longer).

2 Methods

In vitro and *in vivo* measurements of current against potential were taken potentiostatically, i.e. by controlling the potential of the electrode under study with respect to a reference electrode (calomel in saturated KCl), as in Fig. 1. Potentials and currents were measured using battery-operated electrometers with high input impedances (Keithly 602, $10^{14}\ \Omega$). After each potential increment of 100 mV, 5 min were allowed for equilibration to occur before recording the currents. *In vitro* studies were made at 37°C in unstirred culture medium (Dulbecco's with Hepes buffer) with 10% foetal calf serum added. A spectrographic graphite counter electrode served as the anode (Fig. 1*a*). *In vivo* measurements were made by inserting the test electrode in the paraspinal muscles of an anaesthetised (chloral hydrate) mature rat, via a small skin incision. The wire was slid through a 1 mm diameter hypodermic needle into the muscle body and the needle withdrawn. A 50 cm coiled stainless-steel 316L, 0·41 mm wire around the base of the tail, coated with electrode paste, made an excellent counter electrode. The calomel reference electrode was connected, via a small polyethylene tubing filled with isotonic saline, into the subcutaneous tissue about 2 cm from the test electrode site (Fig. 1*b*). A 15 min resting time and open-circuit potential reading always preceded the start of the measurement sequence proper.

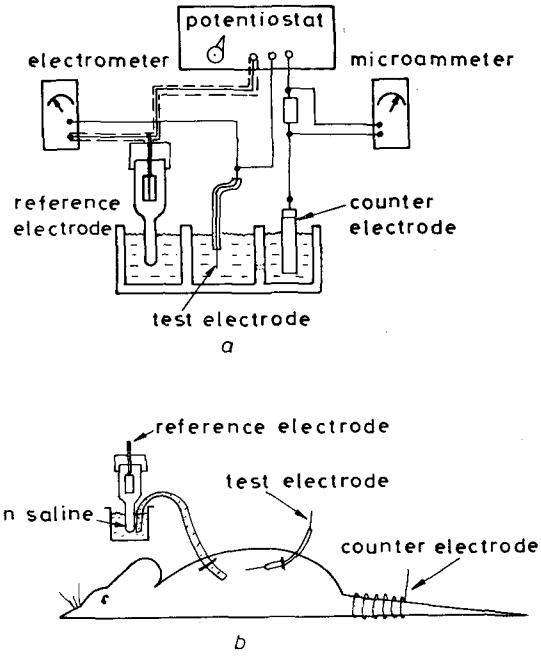

Fig. 1 Experimental arrangements (a) in vitro *measurements in culture medium with serum (b)* in vivo *measurements in rat muscle. The meter connections for the latter were as for (a). The test electrode was 10 mm² in area (geometrically) and the counter electrode was graphite in (a) and stainless steel in (b)*

The test electrodes themselves were cut from pure drawn wire (99·9+%), wiped with acetone and insulated with lacquer leaving 10 mm² exposed in all cases (cut tips covered). They were then rinsed briefly in distilled deionised water. No other surface preparation was attempted in this first study since the actual use of these materials for osteogenesis also generally involves no special surface treatment. Each electrode was only used once and always operated cathodically with respect to the open-circuit resting potential. Each measurement sequence was performed with a new electrode and the means of duplicate runs reported.

3 Results

3.1 *Electrical characteristics of metal cathodes*

The results of d.c. steady-state potentiostatic measurements in culture medium for the pure metals are shown in semilogarithmic form in Fig. 2*a* and

for the alloys in Fig. 2*b*. On the basis of these characteristic curves the metals may be grouped into three types. Group I (Pt, Pt-Ir, Pd, Ag-AgCl) were by far the best conductors over the low and medium potential range. Group II (Au, Ag, SS316L, Elgiloy) had resistances about an order of magnitude higher than the Pt group, with the alloys showing slightly higher resistances and more complex behaviour. Ti, Ta and Vitallium (Co-Cr F-90) form Group III with the highest resistances (lowest currents) of all. Ti and Ta are traditional 'valve metals' with highly resistive oxide coatings.

cathode materials in Group I displayed *in vivo* interfacial conductivities $\frac{1}{8}$ to $\frac{1}{4}$ of the *in vitro* values, while those of Group II were about $\frac{1}{3}$. Those of Group III *in vivo* were about the same as *in vitro*. Exceptions were titanium, whose d.c. conductivity was 1 to 2 orders of magnitude higher *in vivo* at low potentials, and silver, whose conductivity over most of the useful range was identical *in vivo* and *in vitro*. The differences may be related to the variety of complex proteins *in vivo*, the availability of oxygen, the physical constraints of the tissue and the anaesthetic state of the animal.*

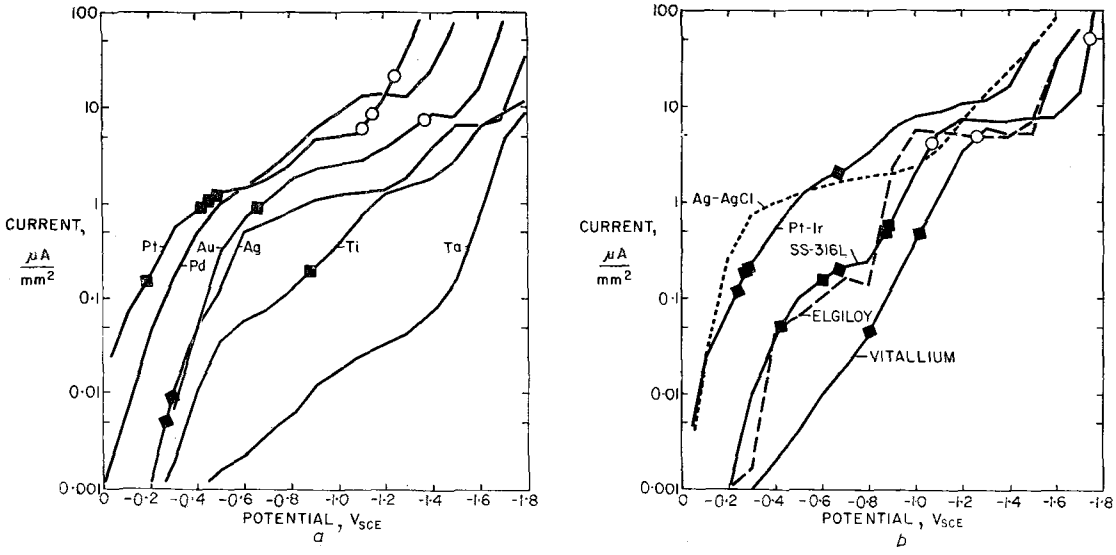

Fig. 2 Cathodic polarisation curves: (a) Pure metal electrodes in vitro *(b) Alloy electrodes* in vitro. *Currents were measured at 100 mV per 5 min intervals while the potential was maintained with respect to the calomel reference. Each curve is the mean of two identical experiments with new electrodes. The dark squares mark conditions and metals for which osteogenesis has been reported to occur and the open circles conditions at which necrosis has been observed (Spadaro, 1977)*

Thus the efficiency of coupling d.c. supply currents into biological fluid varies over several orders of magnitude and depends on the metal. The behaviour of all metal cathodes tested was similar, however, for potentials more negative than 1 V (with respect to calomel). There is a flatter slope coinciding with the formation of minute gas bubbles on the surface and then a large increase in current as gas evolution and hydrolysis proper occur. Similar *in vitro* measurements were performed galvanostatically (i.e. by measuring potentials for a series of constant currents) and essentially gave the same polarisation curves as in Fig. 2. This is noteworthy, since most implanted electrodes, as a matter of convenience, are operated at constant current.

The results of current-potential measurements in rat muscle *in vivo* are shown in Figs. 3*a* and *b*. The general form and distribution of the curves are similar to those made in culture medium. The

For the most part, however, the differences between metals was considerably larger than between environments, indicating that the culture medium with serum is a reasonable first approximation to the muscle implant. Similar comparisons with electrodes in bone marrow, cortical bone and fibrous tissue have yet to be made.

3.2 *Current ranges and osteogenesis*

It is interesting to correlate the polarisation curves with the current densities found in published reports of electrode induced osteogenesis (Spadaro, 1977). These values appear in Figs. 2 and 3 (at the appropriate current density and metal) as dark squares if success has been reported and open circles if

* *A current reduction of* $\frac{1}{2}$ *from* in vitro *to* in vivo *would correspond, if the current were held constant, with a potential increase of about 100 mV (see Figs. 2 and 3)*

necrosis instead of bone growth was elicited. On this basis, a rather sharp upper limit for successful osteogenesis seems to occur between 3 and 5 $\mu A/mm^2$. A lower limit, if one exists, is not yet evident, since data below 0·04 $\mu A/mm^2$ are generally unavailable. The data concerning destructive tissue reactions are not numerous, but sufficient to indicate that the region above 5 $\mu A/mm^2$ and cathode potentials exceeding 1 V (with respect to calomel reference) is probably to be avoided with any of these electrode metals. They also point to the need for better control of current density and electrode potential in animal and human implants.

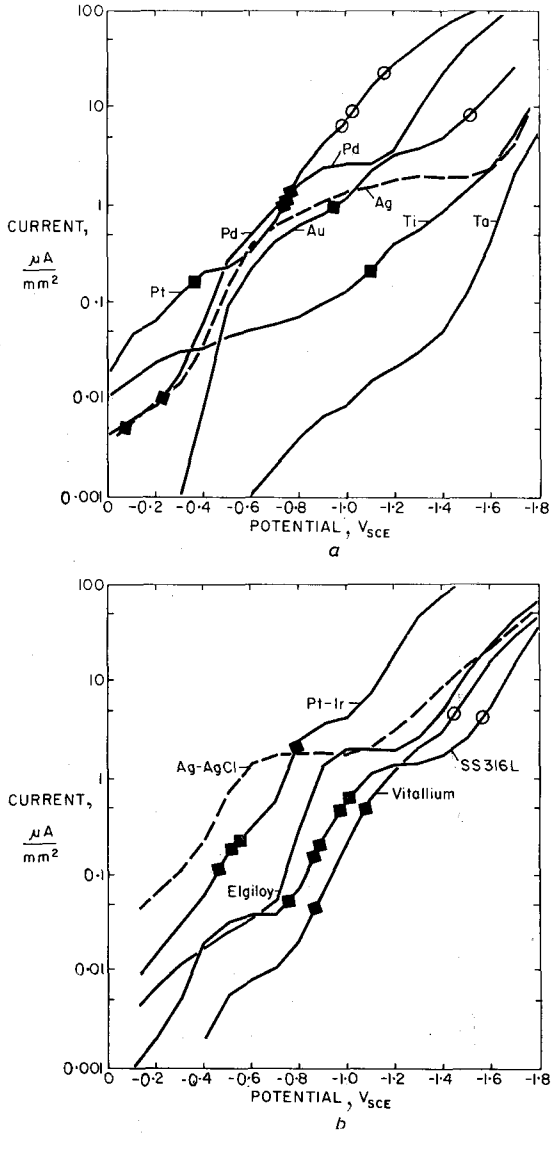

Fig. 3 Cathodic polarisation curves taken in living rat muscle for (a) Pure metals, as Fig. 2 (b) Alloys, as Fig. 2

3.3 *Dependence on oxygen*

A series of d.c. supply current-potential measurements were made *in vitro* under dry nitrogen purge so that most of the molecular oxygen was removed from the test chamber and the incubator in which it was located. After equilibration, the characteristic curves were obtained as previously noted. The results for Pt, Ag, stainless-steel 316L and Vitallium F-90, are shown in Fig. 4. Under nitrogen, the current was reduced by about 30-fold for all metals tested, except for Vitallium, which suffered only a 3- or 4-fold reduction. This reduction in current generally vanished at higher potentials at which electrode reactions involving hydrogen evolution begin to predominate.

A comparison of currents in air and under nitrogen purge for several metals, held at −0·6 V (with respect to calomel), is shown in Fig. 5; the large differences in coupling efficiency for d.c. supply current and the marked reduction of current in an oxygen-poor atmosphere are clear. Upon readmitting air to the system, the current always returned to the previously expected levels. This return for the gold electrode is shown in Fig. 6. This set of experiments implies that cathode electrodes, in current ranges typically used for osteogenesis, depend largely on molecular oxygen for the transduction of current into the biological system. The electrode materials which perform this reaction best would therefore be the most 'efficient' transducers requiring less potential for a given current to be introduced.

4 Discussion

In addition to operational utility in choosing an electrode system for d.c. osteogenesis, the data reported above emphasise the importance of oxygen reactions at the electrode interface. The cathodic reduction of molecular oxygen to water, which occurs over most of the useful potential range, involves a complex series of one electron reactions and results in the production of free radicals and active intermediates such as O_2^- (superoxide radical), H_2O_2, $OH\cdot$, and OH^- (HOARE, 1968; FRIDOVICH, 1978). H_2O_2, for example, can accumulate in concentrations of 10^{-6} M to 10^{-5} M near platinum electrodes because of its relative stability.

The data in Fig. 3 indicate that oxygen reduction reactions occur at an electrode implanted in body tissues as well as *in vitro*, although somewhat modified by the presence of additional organic constituents. We suggest that the reaction intermediates would be in continual supply and are likely to be biologically active. They could, in fact, be responsible for the elaboration of bone at implanted d.c. cathodes. On the other hand, an entirely different mechanism may be involved, in which case the electrode products could either aid the process, inhibit it or play no role. The possibility of unrelated

side effects must also be considered.

How could such electrode products mediate the cellular events which result in bone? Three general schemes can be postulated. First, direct interaction is possible, in which the agent binds to or changes a component of the target cell (osteoblast, chondroblast, fibroblast etc.), causing metaplasia or increased activity. Secondly, the agent can act indirectly by first combining with another element in the extracellular fluid, which in turn can act on the target cells. Thirdly, the electrode products can act enzymatically, i.e. by tying up the enzymes that normally scavenge them and/or by upsetting the redox enzyme balance. Important in this respect are the enzymes catalase and superoxide dismutase (FRIDOVICH, 1968).

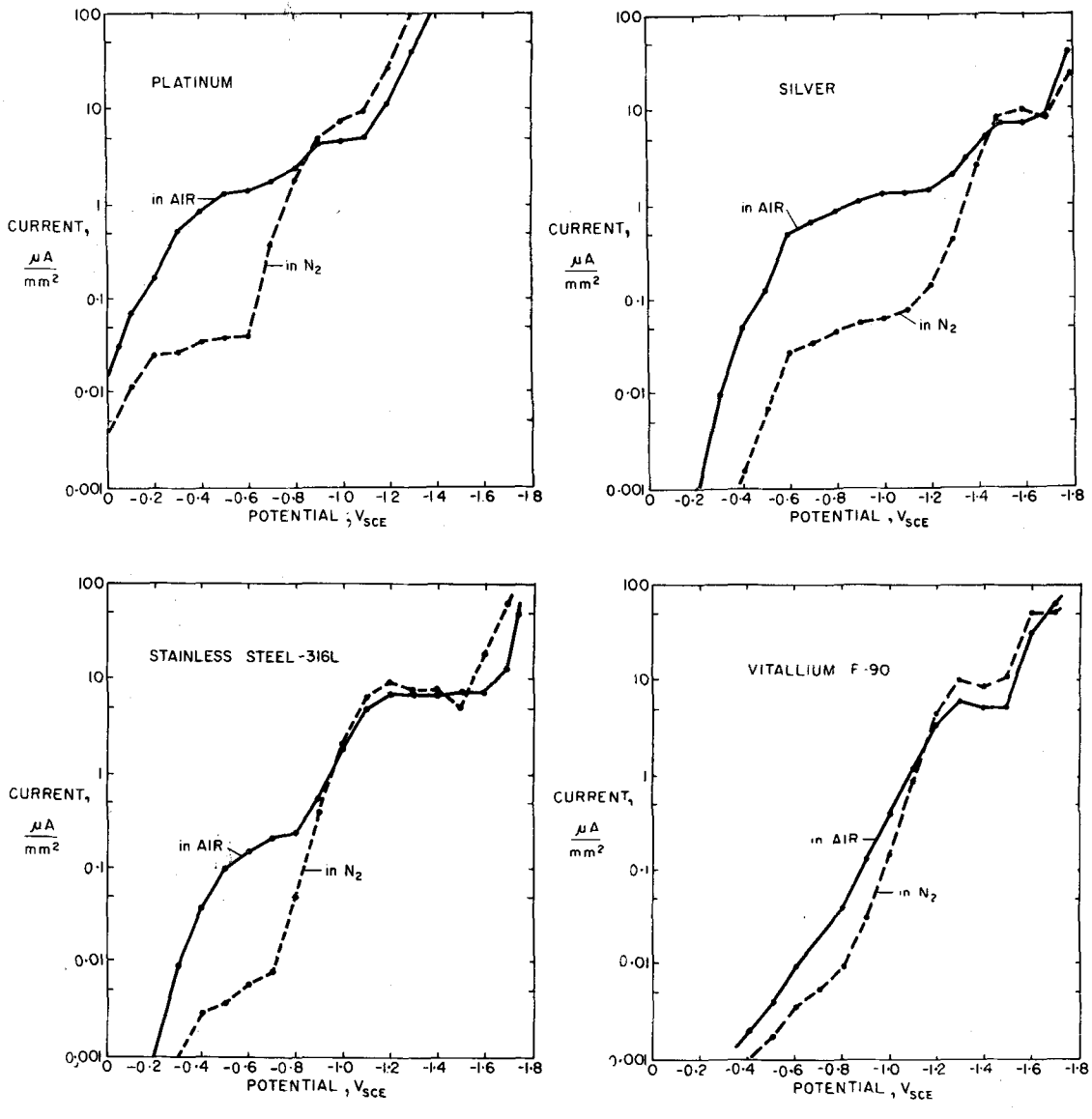

Fig. 4 Cathodic polarisation curves in vitro *for four metals that have been used in electrical osteogenesis, taken in air and under nitrogen purge. The nitrogen was not filtered and residual oxygen may have been present. Significantly lower current was found at potentials below that at which hydrogen reduction begins. Vitallium (Co-Cr F-90) had only a modest reduction, indicating that it is a poor oxygen reducing electrode under these conditions*

BRIGHTON *et al.* (1975) measured the consumption of molecular oxygen at stainless-steel electrodes and found $2{\cdot}5\times10^{-12}$ moles of oxygen consumed per microampere per second. They have suggested that this loss of oxygen near the electrode is responsible for electrically-induced osteogenesis. However, the normal concentration of free oxygen in blood (and fluids in equilibrium with it) is about $0{\cdot}14\times10^{-6}$ moles/ml, the removal of oxygen *per se* by an electrode involves only a small fraction of that available, especially in the face of a continuous supply from the circulation and the bound oxygen

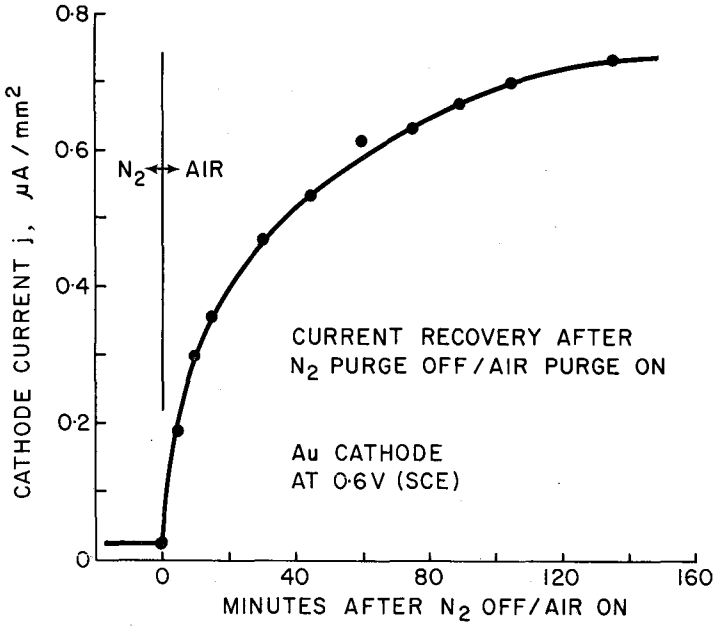

Fig. 5 Relative current densities for several implantable cathodes in vitro *compared. Values in air and under nitrogen purge shown for the same electrode potential (−0·6 V) against the saturated calomel reference. The efficiency of the noble metals and Ag-AgCl was also shared by platinum-iridium (10%) and palladium (not shown)*

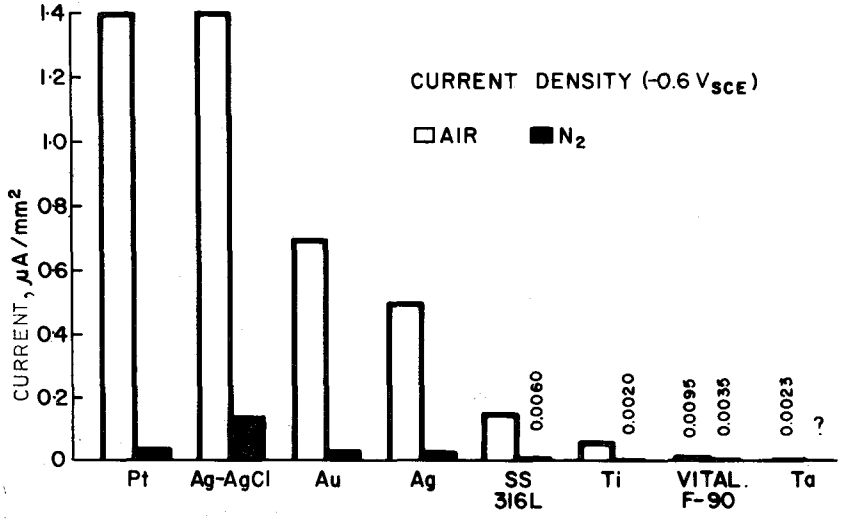

Fig. 6 Return of current to ambient levels after nitrogen purge was turned off and air introduced (Au electrode held at $-0{\cdot}6\ V_{sce}$) This behaviour was similar to that for the other metals in Fig. 5

pool. Thus, the reaction intermediates themselves, formed in above-normal intercellular concentrations, would seem to be a more likely candidate for osteogenic agents than the removal of a small fraction of abundant oxygen.

From such an hypothesis one might predict that different metal cathodes may differ in their osteogenic response according to the efficiency with which they produce oxygen reduction intermediates. One might also expect some osteogenic activity from the electrodes themselves (without current) due to spontaneous catalytic oxygen reduction, especially with noble metals. Oxygen reduction intermediates may also be involved in the responses of nucleated erythrocytes to low current electrodes *in vitro* (BECKER and MURRAY, 1967) as well as in the regenerative growth responses to electrodes observed in amphibia (SMITH, 1974; ROSE, 1978) and rodents (BECKER and SPADARO, 1972).

Experiments with different materials may help decide the relative importance of electrode reactions and bulk electric fields (and currents) in the proliferation of bone around implanted electrodes.

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