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Survey of Biomedical Materials and Some Relevant Problems

By

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SURVEY OF BIOMEDICAL MATERIALS AND SOME RELEVANT PROBLEMS

Interest in implanted materials has grown immensely as a direct consequence of several remarkable developments in surgery and biomedical engineering. These include heart-lung machines, artificial kidneys, cardiac pace makers, arterial and heart valve prosthesis. Perhaps the most dramatic development is that of artificial implanted hearts and various types of cardiac booster pumps.

In the way of historical perspective it is well to recall that many of these developments have more or less tenuous roots extending to the beginning of this century and in some instances even earlier. Thus, the heart-lung machines are an outgrowth of the organ perfusion equipment developed by Frey and Gruber in 1885, Jacoby in 1890, as well as many others. However, the first clinical application occured about 1955; an achievment that was the result of extensive post World War II research by many workers. An excellent account is given by Gelletti and Brecker.(1) Similarly, the first artificial kidneys were investigated by Abel, Roundtree, and Turner in 1913 and the first clinically useful machine was introduced by Kolf about 1944. However, the present devices are also a consequence of the efforts of many investigators since the second World War.

If one asks why these developments were delayed, perhaps two main reasons can be stated, namely, the problems arising from blood clotting and the lack of suitable construction materials. As is well known, the

first problem has been solved by means of heparin and other anti-coagulants while the availability of physiologically relatively inert materials such as Teflon, silicones, Dacron, and metals like the 316 series stainless steels and Vitallium, have alleviated the second difficulty. Thus, Carrel's crude paraffin coated aluminum and glass tubes used as blood vessel replacements in 1912 have been successively replaced by polymethyl methacrylate hollow tubes by Hufnagel in 1947, Vinyon-N plastic fabric tubes by Voorhees in 1952, and finally the presently used knitted Dacron arterial prosthesis.

In what follows, two important problems associated with implanted materials will be briefly discussed, namely, the deterioration of the implant in the body and the effect of the implant surface on blood coagulation.

DETERIORATION OF MATERIALS

It is now recognized that the body provides a surprisingly hostile environment for both metals and plastics. The combined effect of the oxygen and chloride content of the blood is corrosive to stainless steel, as will be discussed subsequently. Implanted polymers are also attacked as indicated by tensile strength measurements in Table I. We note that polyurathane and Nylon are extensively degraded. Polyethylene, perhaps more surprisingly, is also attacked to a significant extent. Of course, tensile strength is a comparatively crude indicator of change. Some studies by Oppenheimer et. al.[2] provide more direct evidence that the host tissue can break down plastics. Thus, C^{14} labelled polyethylene gives rise to C^{14} in the urine in 26 weeks after

implantation. Similar results are obtained for polystyrene and polymethyl methacrylate. On the other hand Teflon, methyl silicone and Dacron appear to be more stable.

Very little is known concerning the mechanism by which implanted polymers are degraded. Evidently a number of possibilities must be considered. For example, hydrolysis of polyesters or polyurathane may be brought about by means of a direct chemical attack by hydrogen ions, hydroxyl ions or water molecules. The role of the hydrolytic enzymes in the deterioration of plastics is completely unknown.

The degradation of polymers such as polyethylene, which involves cleavage of a carbon to carbon bond by a free radical mechanism, could conceivably be initiated by tissue free radicals or oxygen. The oxidation-reduction enzymes would appear to be inaccessible to the polymer since they are largely confined to the mitachondria. Typical of some free radical mechanisms known to be involved under ordinary circumstances are those shown in Figure where the steps occuring in the initiation, chain transfer, and scission are indicated.

As is well known, the degradation may be random with the chain rupture occuring at random bonds along the chain resulting in large fragments. However, successive release of the monomer from the chain ends may also occur as indicated. In the latter case, the monomer may diffuse into the surrounding tissue and produce toxic reactions. On the other hand, the larger fragments produced in random rupture will not readily diffuse into the tissue. Thus, the mechanism of degradation may be quite important with reference to the toxity of the polymer.

When working with polymers, it should also be kept in mind that the commercial products may be complex mixtures containing such ingredients as plasticizers, catalysts, fillers, stabilizers and unpolymerized monomer. It is obviously necessary that these additives are nontoxic and noncarcinogenic. In this regard, it should be mentioned that one of the attractive features of the silicones is that no plasticizer is required.

PHYSIOLOGY OF CORROSION

As indicated earlier, the body presents a rather hostile environment to a number of metals, including the stainless steels. The combined presence of chloride ions and oxygen in physiological environments results in pitting of the latter metals. Though this tendency is least among the widely used 316 and 317 anstenitic steels, none the less, after several years of implantation pits may develop which will ultimately reduce the mechanical strength of the implant. In addition, the corrosion products may serve as a local irritant. The austenitic stainless steels are also subject to stress corrosion cracking in the presence of oxygen, chloride and applied or internal stresses. The Co-Cr-Mo alloy Vitallium is more resistant to corrosion in the presence of chloride than 317 steel and has been widely used despite the fact that it is difficult to machine. Unlike the stainless steels and Vitallium, titanium is resistant to pitting attack and stress corrosion cracking. Consequently, this metal and its alloys are under intensive study as orthopedic implants.

On considering the corrosion resistance of implanted metals it must be appreciated that a large number of interrelated physiochemical factors must be taken into account including the magnitude and presence of cyclic stresses, the wear occasioned by the rubbing of the metal against a hard surface, galvanic couples between dissimilar metals, the presence of active chemical species such as halogen ions, oxygen, hydrogen and hydroxyl ions as well as non-uniformities in their distribution, stray potentials arising from neuro-muscular action and other sources. It is not possible in this brief space to enter into a detailed discussion of all the factors and their complex interactions. For details, some excellent books (3,4) are available. However, in most instances a systematic study of the inter-relationship between the above factors in physiological environments has hardly begun.

As an interesting example of the complex mechanisms which may come into play we consider the case of a stainless steel nail embedded in bone, shown in figure 2a If the head of the nail on the outside of the bone is exposed to a greater oxygen pressure than the embedded portion then an oxygen concentration cell will result with an open circuit potential, E, given by

$$E = \frac{RT}{4F} \ln \frac{(O_2)_A}{(O_2)_B}$$

Where R is the gas constant, F is Faraday's constant, T is the absolute temperature, $(O_2)_A$ is the greater oxygen concentration, and $(O_2)_B$ the smaller concentration. In addition to such chemically induced potentials, stray potentials arise from muscular contraction as well as

from the stresses set up in the bone itself. It is now well established that compressive stresses in the bone result in negative polarization while regions under tension give rise to positive potential. The strain potential is shown in figure 2b together with the corrosion currents. In the case shown both the chemical and strain effects tend to enhance one another. At present it is difficult to evaluate the importance of such effects and here, too, a great deal of basic work is needed.

SURFACE POTENTIAL AND BLOOD COAGULATION

In applications where the material comes into contact with the blood it is often necessary to prevent clotting. It is well known that the surface of a material can exert an important influence on the rate of blood coagulation. Some data are shown in figure 3 taken from Ross et. al. (5). Here a probe made from the indicated materials was implanted into the superior vena cava of a dog. After a given interval of time, the probe was removed and the size of the clot evaluated on an arbitrary scale. We see that the surfaces of dextran, nylon, glass and polystyrene seems to promote clotting as compared to silastic, polyvinyl pyrrolidane (PVP) and chondriotin sulphate. The last item is interesting because related sulphonated polysaccharides (such as heparin) are powerful anti-coagulants. Indeed it has been found that the lining of the arterial wall contains the strongly ionized polysaccharides chonroitin sulphate and heparitin sulphate. Consequently, it has been proposed that the negatively charged arterial wall repels the simularly charged coagulation factors of the blood

such as fibrinogen, platlets, and possibly the Hageman factor which is thought to initiate clotting.

Experimental studies directed toward elucidating the surface effect have been carried out by a large number of investigators but with limited success. It has been found that there appears to be no relationship between the clot promoting action of the surface and the wettability of the surface (5). While it is known that the electrical charge on the surface may play a role, there appears to be no relationship between the sign and magnitude of the zeta potential of the surface in Ringers solution and the clotting time. The reason for this was subsequently clarified by Leininger et. al. (6), who found that zeta potential of all of the plastic surfaces studied on exposure to blood approached zero. This was attributed to the absorption of the blood proteins onto the surface. Thus, specific surface forces are also probably responsible for the observed effects. For example, specific centers on the surface may transform the inactive form of the Hageman factor into the activated state.

An interesting and important development is the discovery by Gott et. al. (7) that the heparin can be bound to various materials by pretreating the surface with benzalkonium chloride. Apparently, the positively charged benzalkonium ion is strongly absorbed into the surface and electrostatically binds the negatively charged heparin. These treated surfaces, unlike those mentioned earlier, apparently retain a negative zeta potential on exposure to blood. The reason for this difference remains obscure and provides an interesting area of research. An obvious

further development is that of introducing a positively charged group onto the side chain of a synthetic polymer. This group would then serve to bind heparin. Such polymers will probably play an important role in the future.

The effect of a negative zeta potential on the clotting time, in the instance of metals, was investigated by Sawyer, Brattain and Boddy (8). Tubes fabricated from various metals were inserted into the canine vena cava and aorta, and the patency of the tube determined in terms of the time required for complete thrombosis. The patency plotted against the position of the metal in the electromotive series is shown in figure 4. Clearly, metals which are high in the series, and hence which tend to readily ionize, have a greater patency than those lower in the series. The explanation offered is that the more positive metals, on ionizing, tend to build up an electrical double layer with the negative charge on the metal surface. The more noble metals, on the other hand, do not readily ionize and may absorb positive ions or acquire a positive surface charge.

(B) PROCESSED TISSUE

Still another area of biomedical research which may hold a great deal of promise is that of preserved animal tissue. Thiele (9) has carried out extensive work on reconstituted bovine aorta made by first removing the lipids and the mucopolysaccharides (MPS) from the aortic tissue. The resulting sol is then converted to a gel by infusing cadmium and other metal ions. The infusion is achieved by means of a porous clay tube into the collagen-elastin sol, to which 1% or 2% MPS has

been added, and filling the inside of the tube with cadmium nitrate solution. The metal ions diffuse through the wall of the tube and deposit the gel onto the outside wall. Subsequently, the metal ions may be replaced by hydrogen ions on dialyzing against dilute HCl. A reconstituted synthetic skin has also been made by similar techniques starting with pigskin. Of course with all such material of biological origin, the antigenetic response must be minor. Whether this will be the case with the reconstituted tissue remains to be seen.

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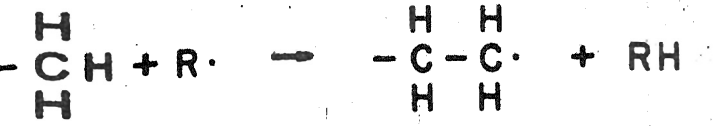
MATERIAL	TENSILE STRENGTH, psi	ELONGATION, %
POLYETHYLENE:		
CONTROL	2,700	780
17 MONTHS	1,930	
TEFLON:		
CONTROL	2,950	320
17 MONTHS	3,720	250
MYLAR:		
CONTROL	18,300	100
17 MONTHS	18,440	100
NYLON:		
CONTROL	9,300	550
17 MONTHS	5,200	140
SILASTIC:		
CONTROL	950	800
17 MONTHS	930	890

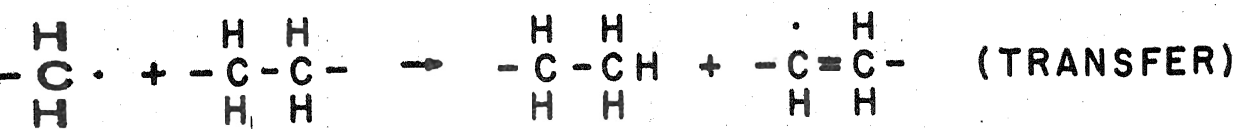
NGES IN PROPERTIES OF PLASTIC FILMS AFTER IMPLANTATION

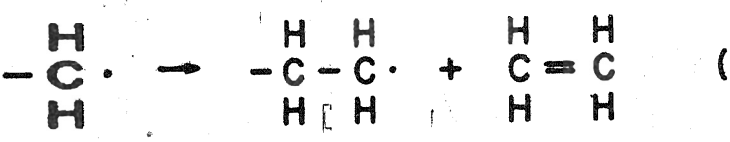
(FROM LEININGER, "CHANGES IN PROPERTIES OF PLASTICS DURING IMPLANTATION," *PLASTICS IN SURGICAL IMPLANTS*, ASTM SPECIAL TECHNICAL PUBLICATION NO. 386, 1964)

Table I

RADIAL DECOMPOSITION







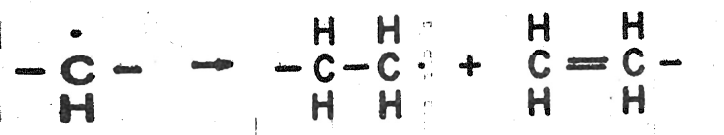
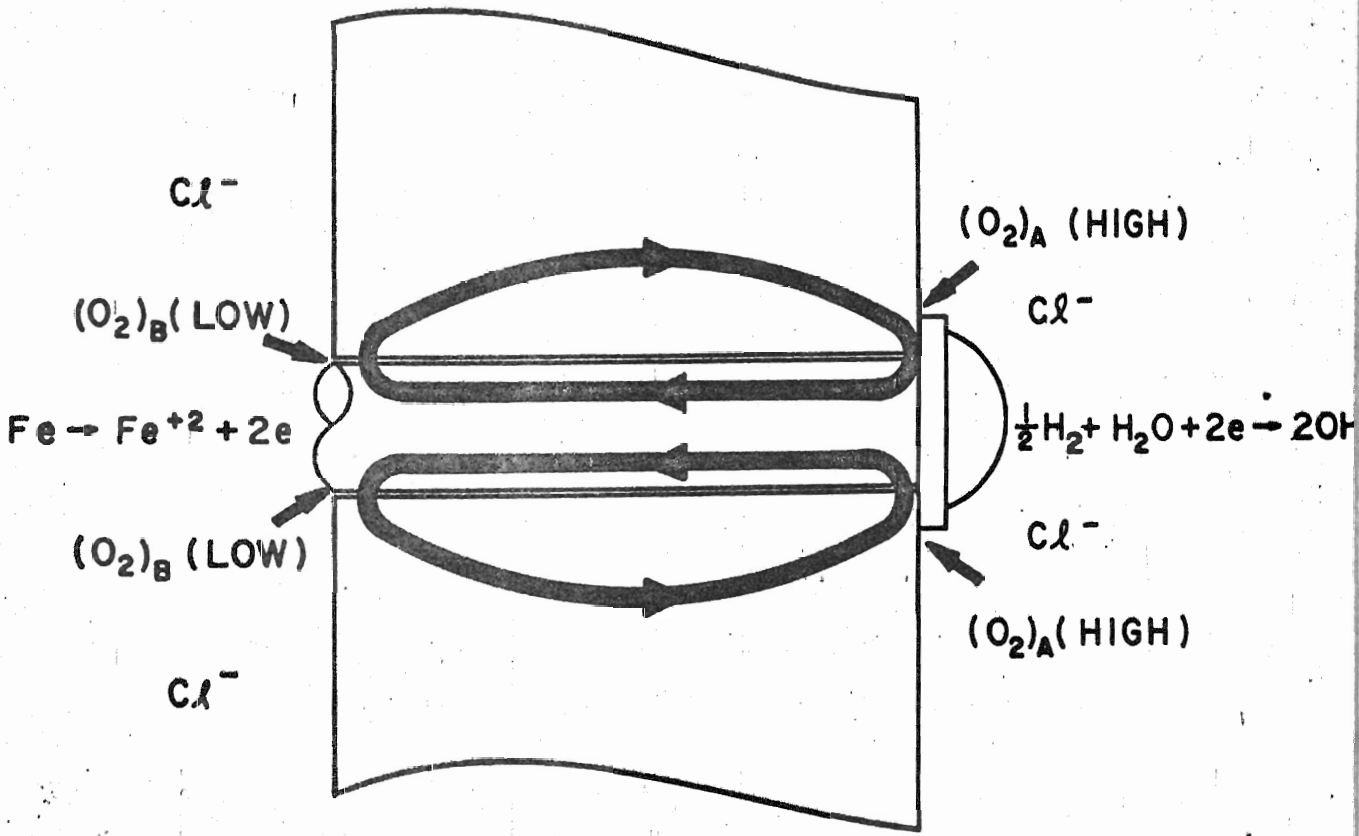
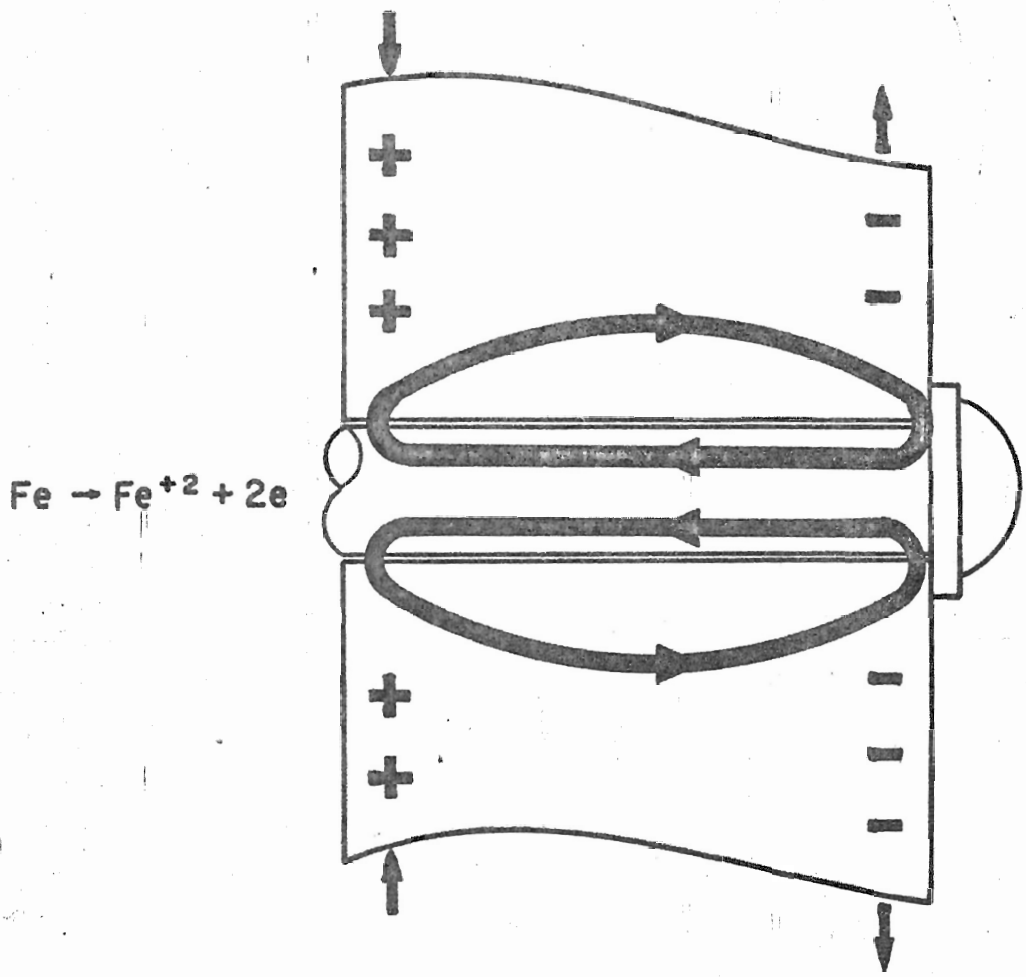


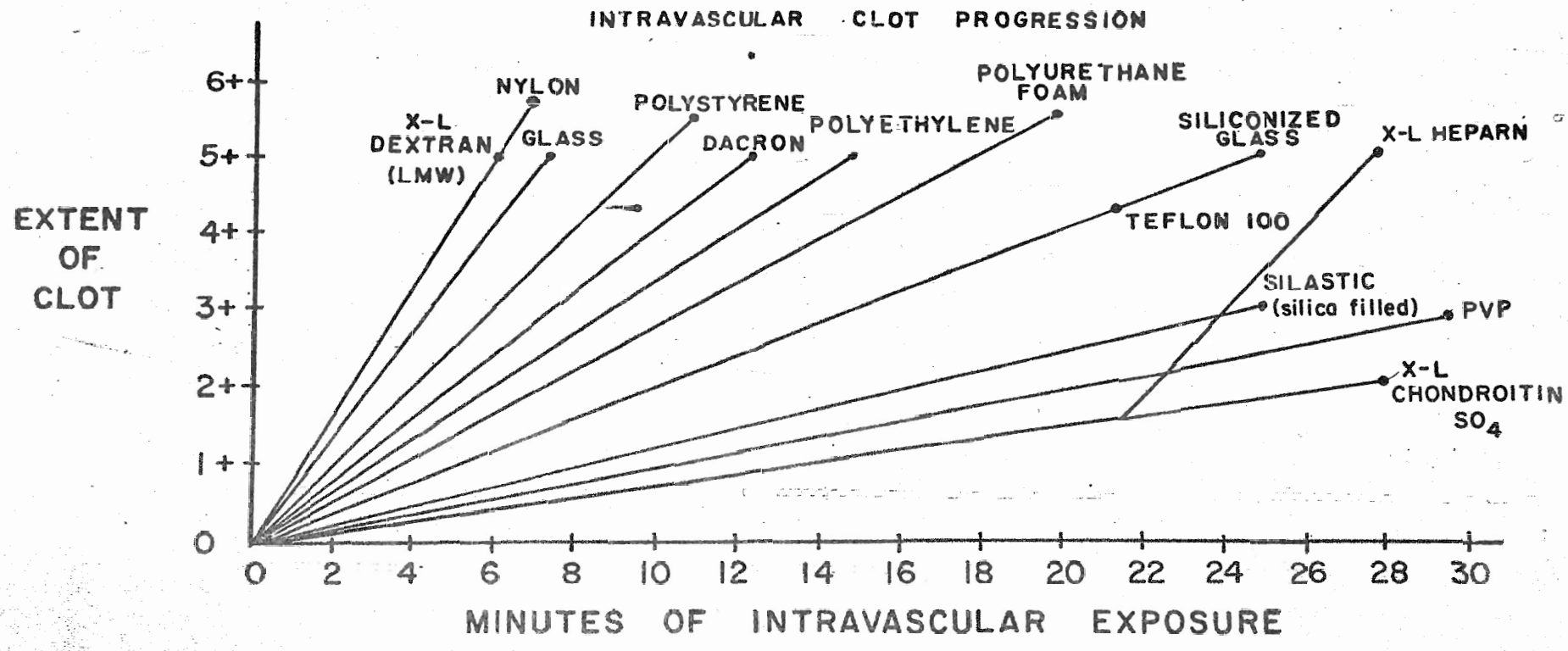
Fig. 1



OXYGEN CONCENTRATION CELL CORROSION



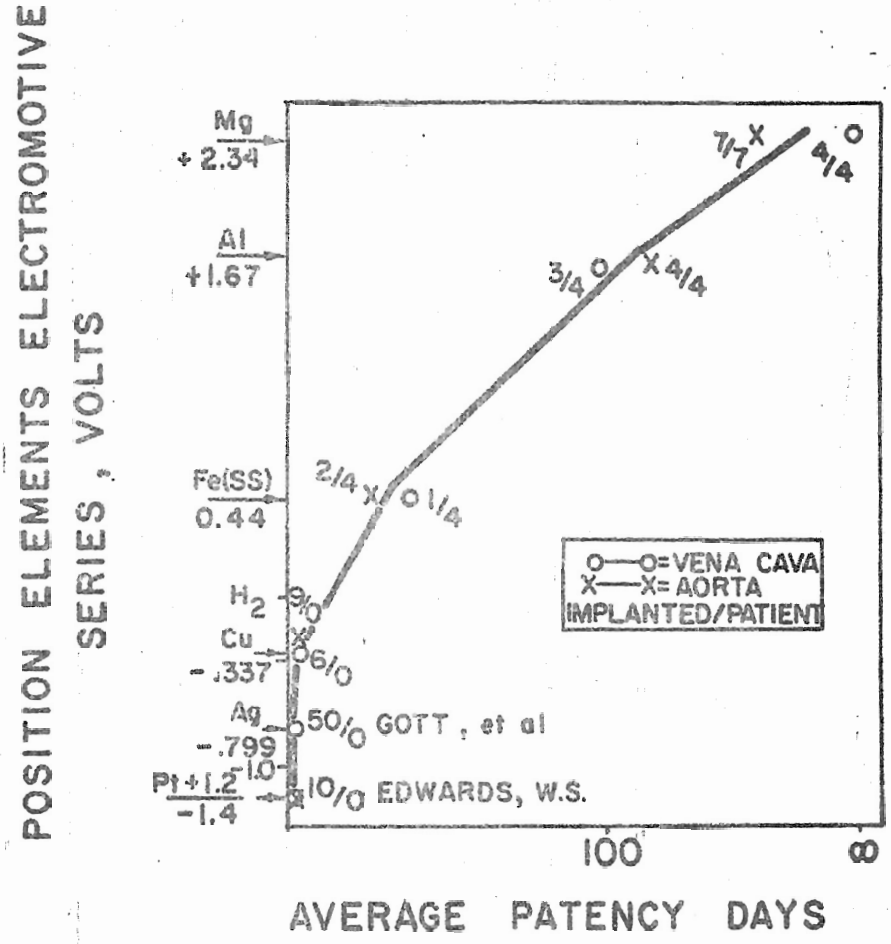
PIEZOELECTRIC INDUCED CORROSION IN BONE



RATE OF CLOT FORMATION ON INTRAVASCULAR PROBES MADE OF REPRESENTATIVE TEST SUBSTANCES

(FROM MERENDINO, *PROTHETIC VALVES FOR CARDIAC SURGERY*, CHARLES C. THOMAS, 1961)

Fig. 3



DURATION OF PATENCY OF VARIOUS METAL TUBES

(FROM SAWYER, et al, "ELECTROCHEMICAL CRITERIA IN THE CHOICE OF MATERIALS USED IN VASCULAR PROSTHESES," *BIOPHYSICAL MECHANISMS IN VASCULAR HOMEOSTASIS AND INTRAVASCULAR THROMBOSIS*, APPLETON-CENTURY-CROFTS, 1965)

Fig. 4