*ELECTROCHEMICAL PRECIPITATION OF BLOOD CELLS ON METAL ELECTRODES: AN AID IN THE SELECTION OF VASCULAR PROSTHESES?**

BY P. N. SAWYER, KWANG-TZEN WU, S. A. WESOLOWSKI, W. H. BRATTAIN, AND P. J. BODDY

DEPARTMENT OF SURGERY AND SURGICAL RESEARCH, THE STATE UNIVERSITY OF NEW YORK, DOWNSTATE MEDICAL CENTER, AND BELL TELEPHONE LABORATORIES, INC., MURRAY HILL, NEW JERSEY

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The stability of blood within the vascular system and its comparative instability with respect to clotting when in contact with many, but not all, foreign surfaces indicates that the arrangement of charges and/or chemical groups on the solid surface is a critical factor.

A variety of experiments have contributed to characterization of the blood-intimal interface and to an understanding of some of the simpler electrochemical concepts which may be of importance in the highly complex process of clotting. Among these are (1) measurement *in vivo* of vascular transmural potential differences;[1] (2) demonstration of the tendency to form a clot on the vessel wall beneath the positively polarized member of an electrode pair applied *in vivo;*[2, 3] (3) observation of clot formation both *in vivo* and *in vitro* on a positively polarized electrode of an electrode pair inserted in blood;[2, 3] (4) observation of spontaneous clot formation on platinum *in vitro* or on solid-walled plastic tubes inserted as prostheses *in vivo;*[2, 4] (5) measurement of transmural flux, mural adsorption, concentration, and the turnover rates of Na^{24}, K^{42}, Ca^{45}, and Cl^{36} by blood vessel walls;[5–7] (6) demonstration of the negative charge on the pores of blood vessel wall by electroosmosis;[6–8] and (7) demonstration *in vivo* of longitudinal streaming potential produced by pulsatile blood flow.[9] Several aspects of these experiments have suggested the importance of physicochemical surface phenomena in the initial stages of the clotting process.

This concept led us to study the interaction between the cellular components of blood and polarized metal electrodes, in an effort to distinguish between processes of an electrostatic and a more specifically chemical nature. These experiments[10] indicated that human erythrocytes and leukocytes in suspension in Krebs' solution at physiological pH values were deposited on both platinum or gold electrodes at electrode potentials (V_H) more positive than approximately +0.33 volt with respect to the normal hydrogen electrode. If the potential was made less positive than this value, the cells were redispersed. Similarly, platelets in plasma containing acid citrate dextrose (ACD) deposited at about +0.40 volt.

Although no detailed explanation of this phenomenon has yet been provided, it is nevertheless clear that the role of electrochemical interactions, possibly including charge transfer between the electrode and appropriate chemical groups on the surface of the cellular species, merits further consideration as an initiator of thrombus formation. The experiments described above suggest that deposition of blood components on prosthetic devices may be avoided by using metals which, because of the nature of their interaction with the plasma, do not spontaneously acquire excessively positive potentials. This requirement is met by those metals near the active end of the electromotive force series of the elements, by virtue of their tendency to lose positive ions to the solution and hence acquire a negative charge due to excess electrons. These correspond to the "low work function metals" which we had previously predicted to be suitable prosthetic materials.[10] The final test of this proposition must rely on experiments carried out *in vivo*. The available literature[4, 12–16] indicates that solid-walled metal tubes previously inserted into the vascular tree were nearer the noble end of the electromotive force series. They were found to occlude rapidly. Therefore, insertion of solid-walled tubes of metals from the active end of the series into the aorta constituted a critical experiment.

For this reason we have inserted such tubes into defects created by excision of a segment of the thoracic aorta of mongrel dogs. The length of time that they remained patent (i.e., no occlusion due to thrombus formation) was found to be correlated with the position of the metal in the electromotive force series. Active metals such as magnesium and aluminum remained patent for longer periods than the more noble metals, stainless steel, and copper. Magnesium tubes have been found, in fact, to remain patent for periods currently as long as one year.

Materials and Methods.—The electrode potential at which canine erythrocytes would deposit on a metal electrode was determined to check that this factor was of the same degree of importance, and occurred in the same range, as for human erythrocytes.

A drop of canine blood was drawn into a syringe immediately before dilution in Krebs' saline serum substitute, and the potential at which precipitation on a platinum electrode occurred was determined as previously described.[10] The value was found to be close to that for human erythrocytes, $V_H \approx +0.25$ volts at a pH value of 7.4. The measured potentials at various pH values are shown in Figure 1. Experiments on canine leukocytes and platelets have not been carried out, but it is expected that they would precipitate in the same general range of electrode potential.

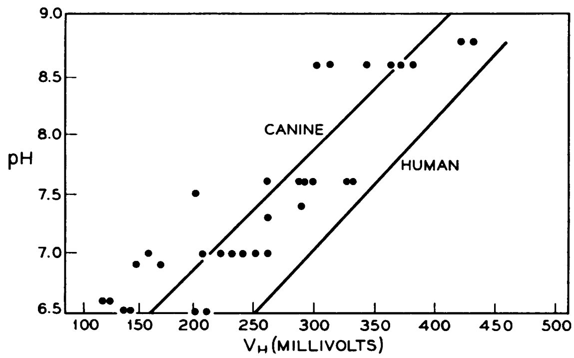

FIG. 1.—Comparison of the precipitation potentials for human and canine erythrocytes.

Twenty-four solid-walled tubes (length 5–8 cm, i.d. 1 cm, wall thickness 0.1 cm) with grooved ends for holding ligatures (Fig. 2) were successfully inserted into a defect created in the descending thoracic aorta of healthy mongrel dogs. They were ligatured and sutured in place as illustrated in Figure 3.

The magnesium tubes were made from an alloy (AZ 31), containing in addition to magnesium, 3% aluminum and 1% zinc. The aluminum tubes were essentially pure, containing trace amounts of rare earths. The stainless steel tubes (number 304) contained 0.08% C, 2% Mg, 0.045% P, 0.30% S, 1% Si, 18–20% Cr, 8–12% Ni, remainder Fe. The copper tubes contained trace amounts of zinc and lead.

All tubes were cleaned with dilute nitric acid and washed in physiological saline prior to insertion.

In addition, 10 platinum tubes (length 2.5 cm, i.d. 0.6 cm) were previously inserted into the aorta of dogs in 1962 in a joint project planned with Dr. W. Sterling Edwards.[17]

Results.—As can be seen from Table 1, all magnesium (AZ 31) tubes successfully implanted and not subsequently removed have remained patent for periods ranging from 253 to 377 days, with a mean of 293 days. The undisturbed aluminum tubes have remained patent for periods of from 115 to 355 days, with a mean of 241 days.

TABLE 1

DURATION OF PATENCY OF METAL TUBES IMPLANTED IN CANINE DESCENDING THORACIC AORTA

Metal*	Total number	Thrombosed (days implanted) Number	Mean	Range	Patent (days implanted)† Number	Mean	Range
Magnesium	7	0	—	—	4	293	253–377
					Three removed for examination while still patent at 7, 166, and 220 days.		
Aluminum	4	0	—	—	3	241	115–355
					One removed due to aortic rupture while still patent at 6 days.		
Stainless steel‡	4	3	28	14–45	1	250	—
Copper	9	5	2	1–3	4	5	2–7
Platinum§	10	10	1	0.5–2	0	0	—

* The metals are arranged in the order of the electromotive force series.
† December 1, 1964.
‡ Assumed as iron.
§ Implanted by Dr. W. Sterling Edwards.

Aortograms similar to those seen in Figure 4 have been taken to indicate the status of the tubes during the experiment.

In contrast, all but one stainless steel tube had occluded by 45 days, the mean being 28 days. A single stainless steel tube from the original group of four has now remained patent for 250 days.

Copper tubes remained patent on average of 2 days, ranging from 1 to 7 days. Some copper tubes were removed for examination prior to occlusion, after it was realized that they would most probably occlude soon after insertion. Platinum tubes remained patent up to about 2 days, the mean being approximately 1 day.

Histology: Following insertion, a thin layer of material deposited rapidly on the surfaces of magnesium and aluminum tubes exposed to blood. Histologic evalua-

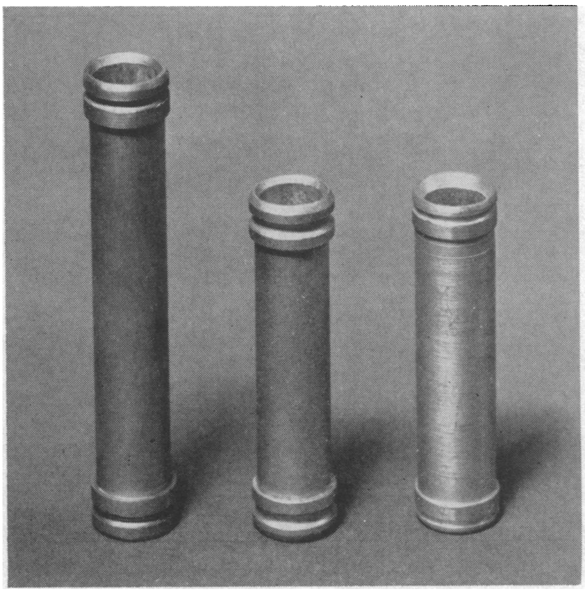

FIG. 2.—Typical magnesium and aluminum tubes used in these experiments. The stainless steel and copper tubes were of similar structure.

FIG. 3.—A photograph of the tube in the descending thoracic aorta of the first dog in which a solid-walled magnesium tube was inserted successfully. The tube was held in place by umbilical tapes tied tightly over the grooved ends. The resected aortic edges cephalad and caudad were then further approximated by retention sutures to hold the tube in place.

tion indicated this material to be composed of protein, almost certainly fibrin with a few trapped leukocytes and erythrocytes in the interstices.

The occluded stainless steel and copper tubes generally contained a well-organized thrombus. A soft, less organized clot was frequently found attached to and trailing downstream from the thrombus.

Discussion.—We had previously predicted that metals of "low work function" (i.e., having a relatively small tendency to accept electrons) would be least likely to promote deposition of blood components and hence by extension least likely to promote thrombus formation.[10, 11] This prediction arose very simply from the fact that an increase in the positive polarization of a metal electrode (i.e., an increase in the probability of electron transfer from an external species to the electrode) was observed to cause deposition. Any factor decreasing the probability of electron transfer in this direction is assumed to decrease the deposition of blood components. Among such factors are more negative polarization of the electrode and, in the language of surface physics, decrease in the work function. The concept of

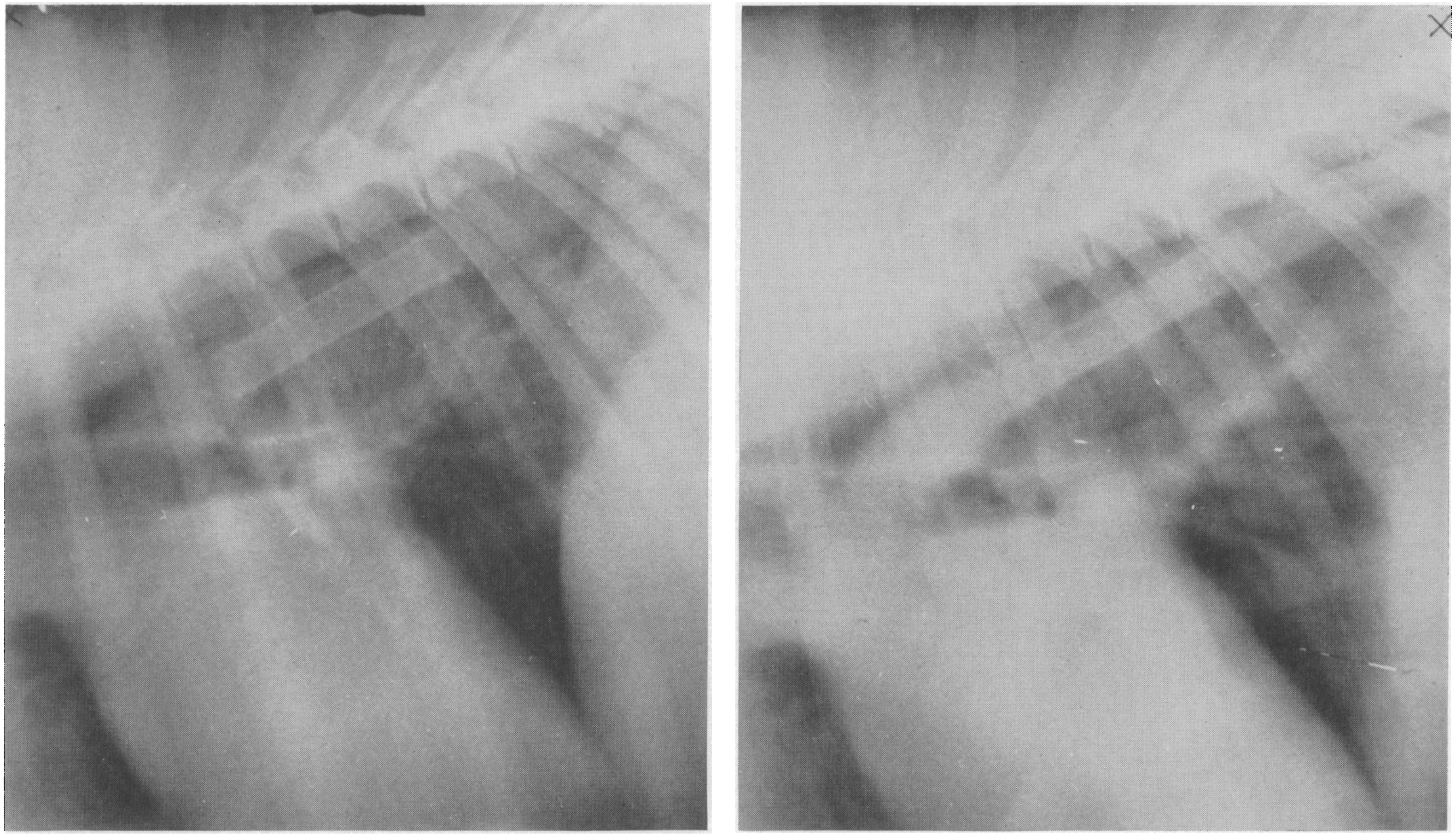

FIG. 4.—(*Left*) Thoracic roentgenogram of a 5.0-cm-long magnesium tube in the descending thoracic aorta. (*Right*) Aortogram using 75% Hypaque showing intraluminal patency of the tube seven months after implantation.

work function is most usually applied in the case of metal surfaces in high vacuum. When the metal is immersed in an electrolyte, interaction with both solvent and solute species may modify the picture somewhat and one cannot expect a quantitative correlation between work function measured in vacuum and electrolytic behavior. In this case it seems more reasonable to consider the efficacy of low work function ("active") metals as being due to their corrosion behavior in plasma and other electrolyte solutions at physiological pH values. Such metals tend to lose positive ions to the solution and consequently build up an electrical double layer at the interface with the negative charge on the metal and the positive charge in the solution. Hence the metal spontaneously tends to become negatively polarized with respect to the solution which, as we have shown, is the region where deposition does not occur.

At the other extreme the noble metals (e.g., platinum, gold, etc.) show a negligible tendency to corrode in these solutions. Their electrode potentials are very variable due to the low rates of potential determining electrochemical processes and may frequently become positive, i.e., within the range of deposition of blood components. Metals of intermediate character would show behavior between these extremes.

There is a possibility that the result with copper is due to a toxic effect, since copper is a known cytotoxic agent. This possibility is in some degree negated by the result with aluminum tubes, since Al^{+++} has been shown to be even more cytotoxic than Cu^{++}. In any event, the result with the more noble metal, platinum, could not be explained on the basis of toxicity.

The success of magnesium and similar metals in preventing thrombus deposition is seen to be due to an inherent tendency toward dissolution in the aqueous environment with a consequent build-up of negative charge on the electrode This should not be taken to imply that such materials are necessarily unsuited for long-term use *in vivo*. The actual rates of corrosion may be very slow for suitably chosen metals or alloys due to passivation of the metal or inherently slow kinetics of the dissolution process. The useful lifetime *in vivo* of magnesium and aluminum still remains to be determined. Nine of these tubes have now remained patent for periods exceeding 200 days and seven for periods in excess of 330 days as indicated by physical examination and aortograms.

These findings suggest that further insight into the nature of the blood-intimal interface should aid in the selection and construction of vascular prostheses capable of performing similarly to the normal vessel wall. They further would seem to support the validity of the hypothesis[1, 2] relating electrical and electrochemical phenomena at the blood-intimal interface to intravascular thrombosis.

Summary.—Examination of the behavior of aqueous suspensions of erythrocytes, leukocytes, and platelets at polarized metal electrodes has shown that deposition occurs if the electrode potential becomes more positive than a critical value. This suggested that metals near the top of the electromotive force series of the elements would be effective materials for vascular prostheses due to their tendency to establish an interfacial double layer with the negative charge on the electrode. Accordingly, we have compared tubes made from various metals inserted in the canine aorta with respect to the length of time they remained patent. The results show a definite correlation between the duration of patency and the position of the

metal in the electromotive force series. In particular, magnesium tubes continue to be patent one year after insertion.

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