ELECTROCHEMICAL INTERACTIONS AT THE ENDOTHELIAL SURFACE

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INTRODUCTION

The Vascular Tree

The blood vessel wall–blood vascular interface exhibits a number of interfacial phenomena. Probably the most easily measured of these are linear streaming potentials produced by the flow of blood through the blood vessel (1, 2). Additional phenomena which are observed include transverse streaming potentials or "pressure equivalent electroosmosis" as it has been described previously (3) (Fig. 1). The first of these phenomena is obvious. The second results from pumping of positively charged ions and bulk water out through the "Swiss cheese" negatively charged blood vessel wall pores (4, 5). A pressure drop of 100 mmHg is maintained across at most a few microns of intima so that the pressure drop is of very significant proportions. Under normal conditions, the electric double layer of high field strength at the vascular interface and on the surface of the cells approaches 10^6-10^8 Volt cm^{-1}. These phenomena, plus the natural surface charge characteristics of the blood cells which cause them to repel each other (6) and the structural characteristics of the coagulation proteins which prevent their "recognition" of each other under normal conditions, all act to maintain colloid stability in the blood. The arterial tree is therefore maintained in a stable state and blood is maintained in the uncoagulated condition in the normal human by an effective, essentially passive low-energy-using system. The energy for support of the system is provided by the heart. However, colloid stability can be made relatively unstable by a number of different "recognition" phenomena including trauma (7), abnormal coagulation phenomena in blood, including the immune response at the vascular interface, and a wide series of toxic reactions in the vascular tree (8). On the venous side, the flows are nearly as great, but pressures are lower and nonpulsatile. Metabolic phenomena including oxygen utilization and ion transport are 5–10 times as great. The potential at the vascular interface is maintained at an homogeneous interface potential by the surface charge characteristics of the blood vessel wall, cells and the ionic composition of blood (9).

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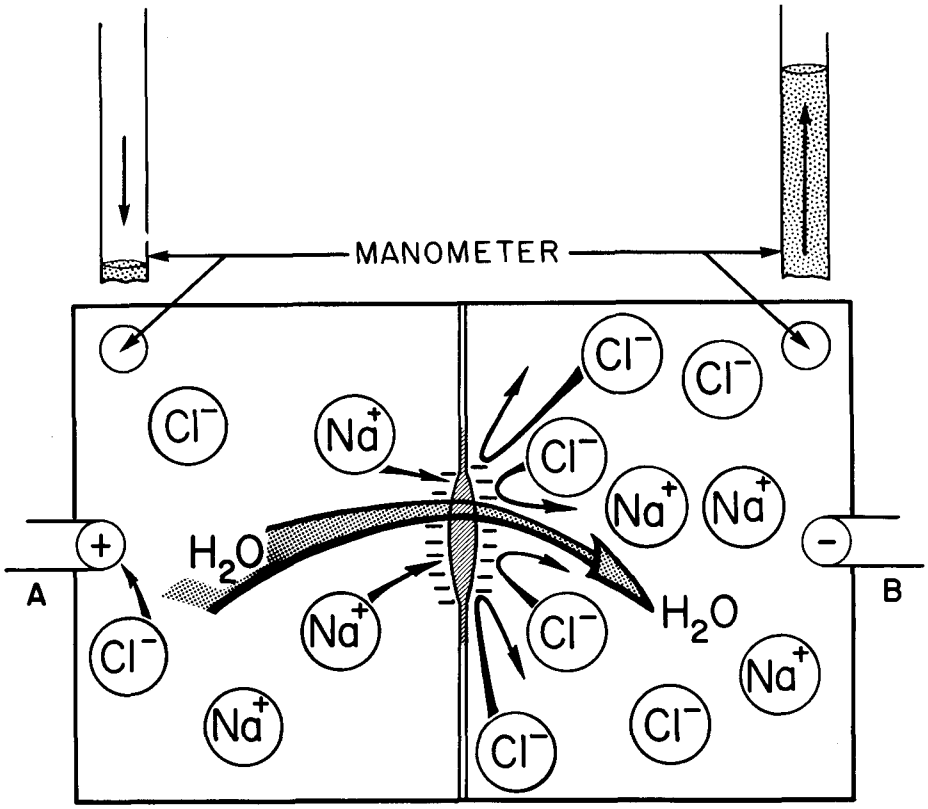


Fig. 1. Schematic of electroosmosis cell with electric current being passed across negatively charged blood vessel wall membrane. It is obvious that positively charged ions and bulk water will move more rapidly across the negatively charged pores so that sodium and chloride concentrate on the right-hand half of the cell. In order to prevent detonation of the cell, bulk water must move across to maintain dispersion of the ions in the right-hand half of the cell. The manometer measures the movement of the water. The direction in which the ions in water flow is an indication of pore charge. The rate at which they flow is an indication of the charge per unit area of pore. In normal blood vessel, the opposite phenomenon takes place, pressure is applied and ions and bulk water are pushed across the membrane by overt pressure, producing an "electric current." Thus the pressure equivalent electroosmotic characteristic is provided by blood pressure.

Interfacial Phenomena at the Vascular Interface (Classical Interfacial Phenomena at Solid–Liquid Interfaces)

What are some of the known electrochemical interactions at the vascular interface? As early as 1955, Teorell had described interfacial phenomena of the classic type which could be expected to occur at solid–liquid interfaces in biological systems. These were summarized very elegantly in a figure which he presented at a meeting in 1965 (10) on interfacial phenomena in vascular homeostasis.

As Teorell indicated, several types of interfacial phenomena have been shown to occur in the vascular tree (4).

The first of these are those types which occur in conducting materials as spontaneous corrosion potentials of metal surfaces in contact with blood (which is at least as corrosive as sea water).

The second type of reaction is absorption or surface charge phenomena which occur because of the interfacial charge arrangements on the surface charge of insulators.

The surface charge at the vascular interface appears dependent on diffusion of charged ionic species through the pores of the blood vessel wall. In contrast to this, the electric conductivity of proteins, collagen, and cellular components of the vascular tree may be considered to be of the order of that in semiconductors (11). The surfaces of the cells display specialized insulator characteristics in that they maintain on their surfaces charged species with appropriate dispersion to maintain one net negative charge per 1000 $Å^2$ (12). In effect, the cell walls maintain the surface of the "charged" pores so that diffusion through pores, while it is facilitated, is limited to certain ionic species and is rate limited with respect to various ions which will go through a unit area of the vascular tree per unit time (9). Therefore, the electric double layer characteristically must consist of two components: that produced by blood flowing through the blood vessel with the slowly flowing marginal layer looking at the endothelium, and that produced by high pressure pumping of both positive ions and bulk water out through negatively charged pores. Transverse streaming potentials or "pressure equivalent electroosmosis" therefore relates to both the structural characteristics of the wall and the surface charge on the cells of the pores.

The zeta potential, which is measured by any of the characteristic techniques, such as streaming potential, electroosmosis, precipitation potential, and electrophoretic mobility, shows only a fraction of the true interfacial potential, depending on the point of shear in the electric double layer. The point of shear is in the diffuse portion of the electric double layer. With increasing concentration of ions in the solution, the measured streaming potential is smaller, as is the calculated zeta potential. With maximum dilution of the electrolyte the calculated zeta potential approaches the interfacial potential. However, this is paradoxical because with decreasing ion concentrations, the biological characteristics of the tissues are more or less destroyed. Therefore, one must compromise between the need to obtain maximum dilution to get accurate measurements and the need to maintain physiologic concentrations to maintain viability of the tissues used in the experiment. The techniques for measuring streaming potential, electroosmosis, and electrophoresis and sedimentation potentials have been described in considerable detail in previous publications from this laboratory, particularly with reference to measuring characteristic electrokinetic phenomena in biological tissues (13).

THE BLOOD VESSEL WALL

Normal Cellular Anatomy

The normal wall of blood vessels consists of a series of layers. The most intimate of these is the endothelium in both arteries and veins, though each has a different gross and cellular structure. The evidence suggests that blood cells and proteins are kept by this thin layer of endothelium from actually "seeing" the underlying elastin and collagen supportive layers which provide strength for the wall (14). The intimal cells, including the endothelium, "help" to maintain the charge characteristics of the interface and the stability of pore charge while controlling ion and fluid escape and facilitated diffusion through the pores during pressure equivalent electroosmosis. The blood vessel wall is extremely porous, of the order of 10^3–10^4 pores cm^{-2} of wall. The inner layer appears anatomically intact in all mammalia. Physical integrity extends through to the outer part of the intima (Fig. 2) with no penetrating vessels and no anatomically discernible variations in space between

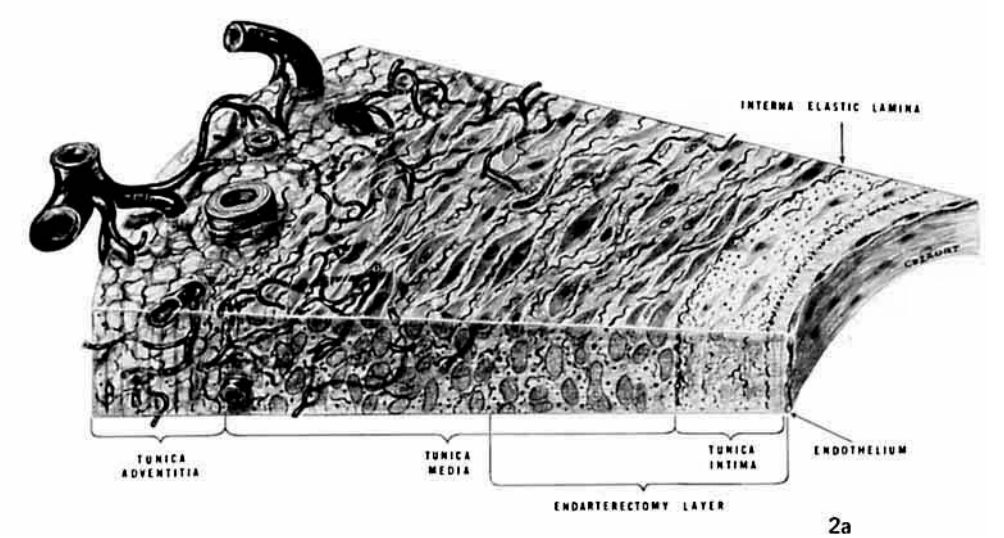
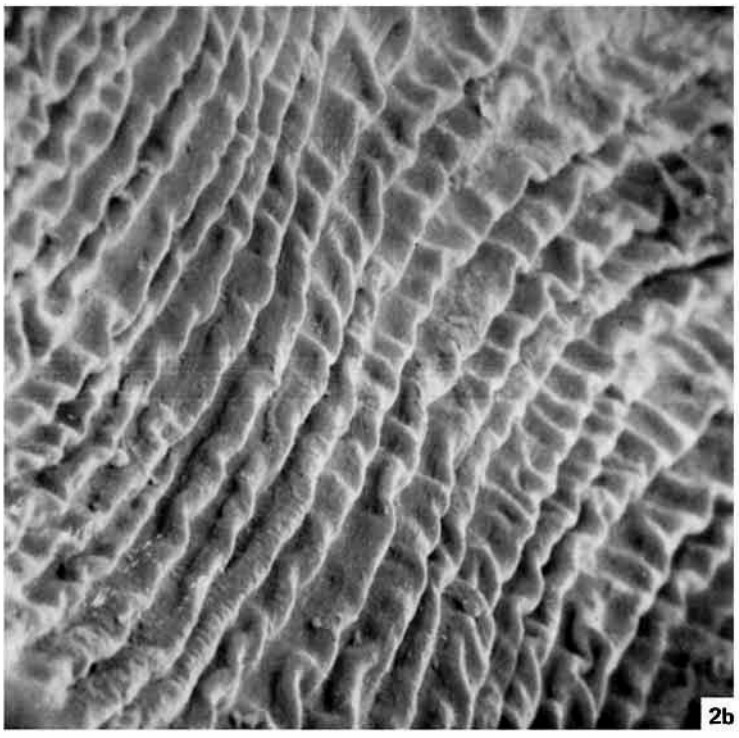
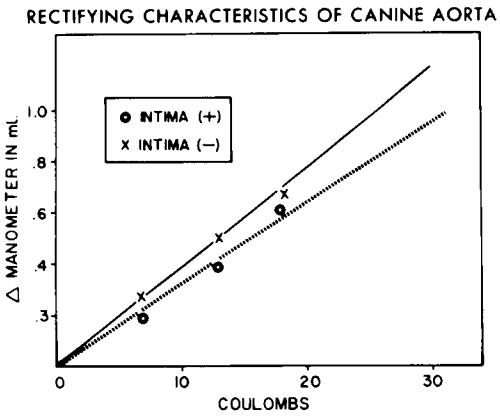


Fig. 2 (a). The normal blood vessel wall consists of a tunica intima, media, and adventitia. The outer layers of the wall are richly supplied with capillary bed, the most intimate layers, endothelium and tunica intima, are provided with oxygen from the blood stream, flowing within the vascular tree. The inner layers of blood vessel wall from the innermost capillary bed and the inner-third of the tunica media is an intact biological membrane. (b) The membrane's innermost surface, the endothelium. The rugated folded intact endothelial surfaces of the normal arterial wall are shown. The rugae provide both mixing effect and extra endothelial surface to provide for stretching of the wall under high pressure and contraction of the wall in diastole.





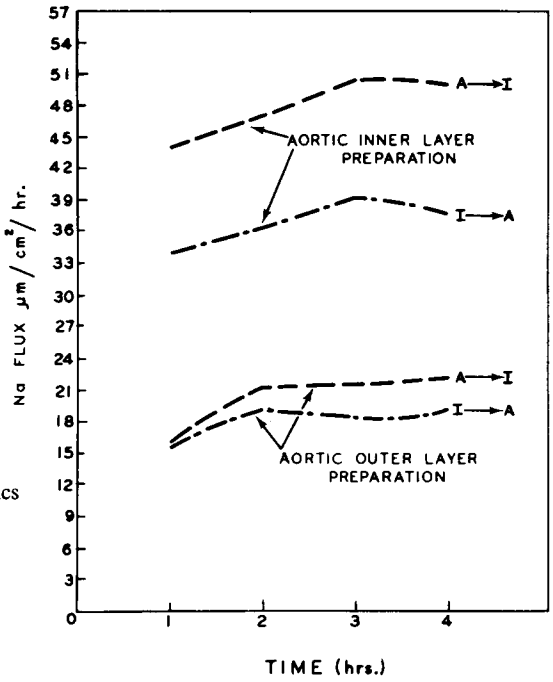


Fig. 3. Rectifying characteristics of canine aorta. The blood vessel wall displays rectifying characteristics with respect to a constant applied electric current. Active ion transport in general is related to the intact inner layers of the vascular tree where it is much greater than that found with the aortic outer layer preparation, the outer media, and adventitia. The data illustrated here are for sodium flux.

the cells. The layer displays classical ion flux for Na^+, Cl^-, Ca^{++}, and K^+ exchange diffusion and charge (2–5). These capacitance and conductance characteristics are assymetric with respect to the inner and outer layers of the wall (Fig. 3). The blood vessel wall is approximately 67% space and 33% solid (or cellular), much of the solid being collagen and eleastin and the remainder being largely muscle cells. The outer layers of the wall, three layers of muscle in the media, and the adventitia are richly supplied with blood vessels from the periphery. Between the inner-thrid and middle-third of the media is a rich capillary bed which provides oxygen and nutrition to the inner layer of intima and apparently absorbs the ions and bulk water which go through the inner layer pores under pressure.

Some of the best information concerning the essential physical–chemical structure of the vascular interface has been obtained from vascular prostehtic grafts. Those grafts which are nonporous tend to occlude and thrombose immediately unless a negative surface charge is properly "ordered" by nature of the chemical structure of the polymer from which the tube is cast. Porous tubes may be constructed of virtually anything including perforated toothpaste tubes which will alllow pressure diffusion through pores. Porosity per se will, in essence, prevent thrombosis under most conditions (15, 16).

Effects of Aging

Pores occlude with aging. This occlusion has very little effect on pressure-equivalent electroosmosis and streaming potential until a vast majority of pores per unit area are lost (17). This process has been shown in two ways: (1) by electroosmotic evaluation of progressively atherosclerotic arteries taken at autopsy from the human (Fig. 4), and (2) by decreasing the size of the lumen in the electroosmosis cell orifice until it is less than 1 mm^2 in area while maintaining constant current flow across the wall (Fig. 5).

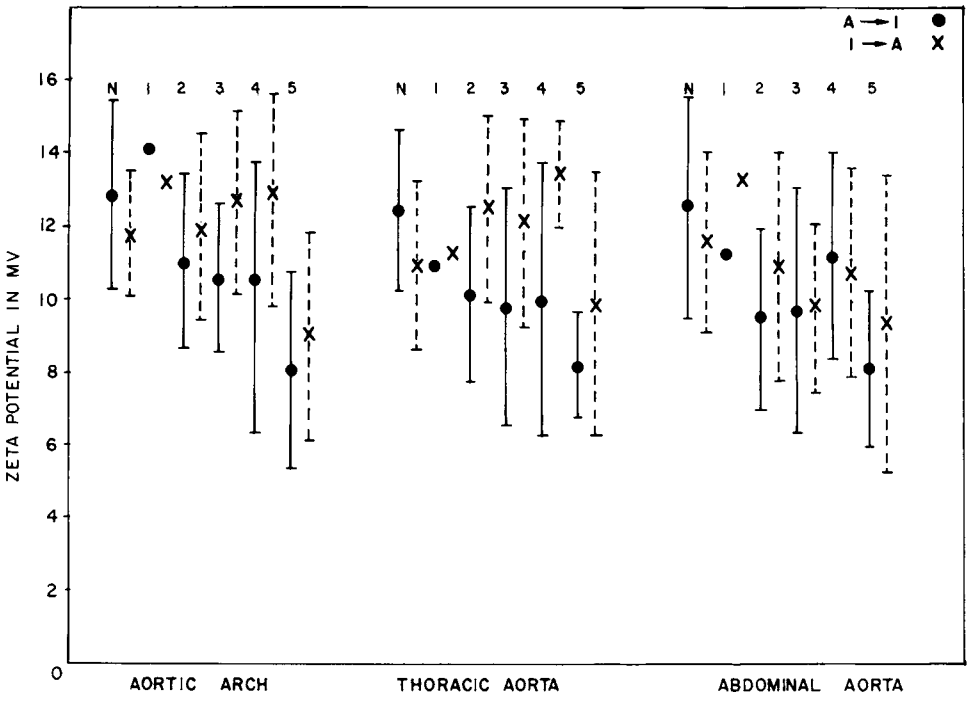


Fig. 4. There is essentially no change in electroosmotic characteristics of blood vessel wall until one gets to grade 5 virtually calcified pipe type of atherosclerosis at which time there is a drop in the electroosmotic potential across human blood vessel walls. These data are for aortic arch, descending thoracic aorta, and the abdominal aorta.

With a hundred fold decrease in area and a constant current flow no decrease in electroosmosis was found. Therefore the critical blood vessel wall area which would produce an essential breakdown in pore integrity and loss of effective electroosmosis was not reached. Moreover, the original experiments using atherosclerotic human blood vessel wall revealed that one must carry out electroosmosis on vessels with maximal atheroscelerosis levels before finding changes in electroosmotic characteristics of the wall, or in fact finding any change in linear streaming potentials.

Effect of Injury on the Blood–Intimal Interface in Blood Vessels

With mechanical injury, including meachnical crush (7), balloon rubbing of the inner intima, or electrical current, an immediate decrease in the negative interface potential of the wall is observed (Fig. 6) (18). The phenomenon is entirely local, occurring only at the point of injury. In some instances, the injury is sufficiently traumatic for the negatively charged interface to reverse polarity and become positive. This is normally attended with immediate thrombus deposition which can be seen grossly after several minutes (Fig. 7).

Scanning Electron Microscope Information

Scanning electron micrographs (18) reveal characteristic thrombus deposition on the wall at the points of injury in vivo in both arteries and veins (Fig. 8). The thrombi formed appear classical in type, depth, and size, under the scanning electron microscope.

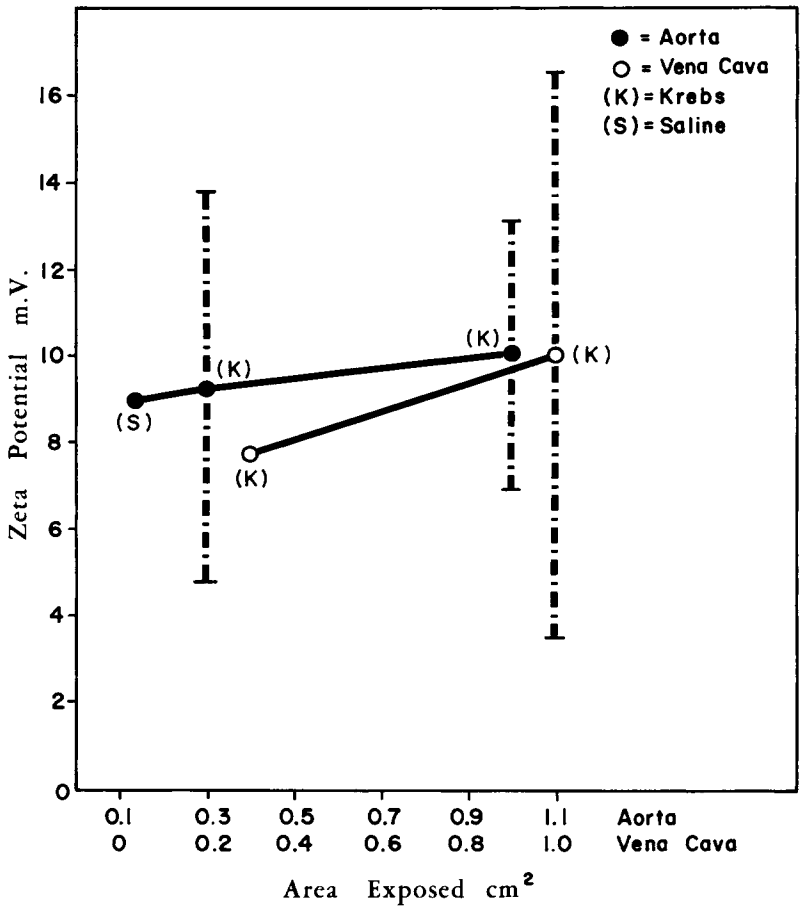


Fig. 5. The orifice diameter for the electroosmosis cell was decreased to 0.1 cm^2 without significantly changing the electroosmotic characteristics of normal canine blood vessel wall. This information reveals two facts: (1) that electroosmotic characteristics are area independent, and (2) that the aortic wall is capable of accepting very high current flows without destruction of the integrity of the vascular pores, at least for short periods of time.

The normal blood vessel wall has "rifling" in the form of rugae (19) which are immediately visible in the scanning electron microscope pictures of normal vessel (Fig. 4). Crush injury or rubbing with the Fogarty catheter balloon largely destroys these rugae, exposing underlying intima or media "collagen." An evaluation of the scanning electron microscope photographs immediately after injury reveals deposition of platelets, red cells, and white cells on the exposed underlying surfaces (Fig. 9). Sequential platelet deposition on collagen appears to catalyze release of ADP, to further platelet deposition and aggregation, and to begin thrombus formation. This involves all the blood cells, as shown by light and electron microscopy. Arrested thrombus deposition after injury is found following intravenous infusions of heparin or dextran (18). Multiple studies on rat mesenteric preparations, rat and rabbit major blood vessels, dog carotid and femorals, and normal and hemophiliac humans reveal that the usual response to injury may not take place in massively heparinized or coumadinized or hemophiliac dogs and rats (20), or in hemophiliac humans, or following large infusions of dextran in man.

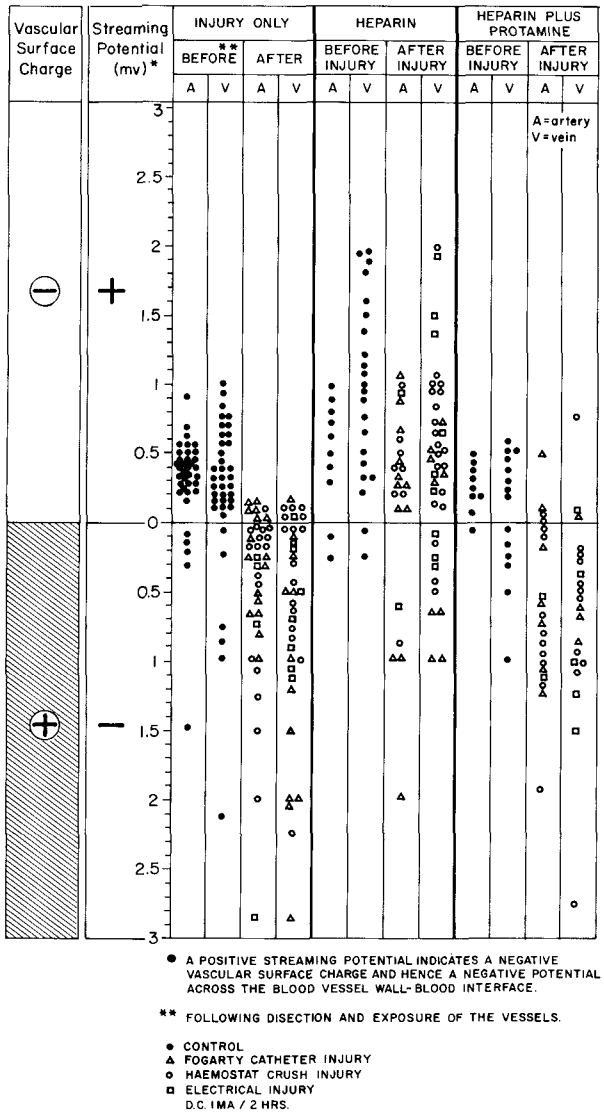


Fig. 6. Effect of injury and of drugs on in vivo streaming potential in canine blood vessels. Almost any form of injury causes a reversal of the normal negative interfacial charge of the vascular tree, as shown in streaming potentials.

As shown in columns 6 through 10, the presence of intravenous heparin during injury normally prevents reversal of interface potential following injury. This is apparently true because the highly negatively charged heparin prevents reversal produced by injury by blanketing the injured areas. If one introduces protamine into the vascular tree, the specific neutralizing agent for heparin, positive injury potentials are again discernible as shown in the last four columns. This is true for both arteries and veins. (●), control. (△), Fogarty catheter injury. (○), Hemostat crush injury. (□), Electrical injury, current, D.C. 1 mA for 2 hrs.

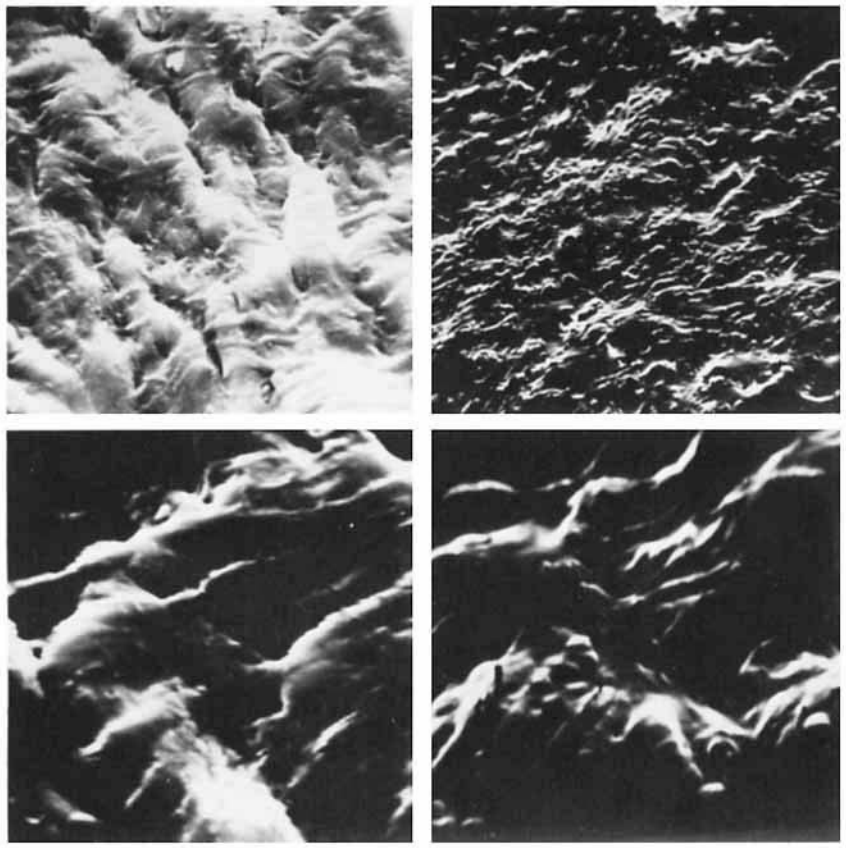


Fig. 7. Thrombosis on injured blood vessel wall surfaces. Thrombosis on artery left and vein right at 500 X (top) and 1000X (bottom) magnifications. The normal rugations of the vascular tree are partially disguised by the deposited fibrin filaments and the platelet aggregates seen.

Role of Blood Coagulation Factors

The available evidence indicates that the coagulation mechanism must be intact for spontaneous or electrical thrombosis to occur under both physiologic or experimental conditions described heretofore or in subsequent experiments. Thrombosis does not take place in the absence of the normal coagulation cascade or during various enzymatic defects which prevent recognition or electron transfer from enzymes following platelet-glucosyl transferase, collagen–galactose combinations which normally occur following "recognition" (21). If the injured area is sufficiently rapidly "negatively recharged" through massive heparin infusion or if the coagulation enzymes are "inhibited," recognition or "tunneling" as described by Weiss (22) and Shulman (8) cannot take place.

Effects of Anticoagulants on Thrombosis in Injured Vessels

Different types of injury and each of the major anticoagulants tested produce variations in the type of thrombus structure deposited on the injured points. Following crush injury, the coagulation response routinely yields a pure trench filling thrombus. Fogarty

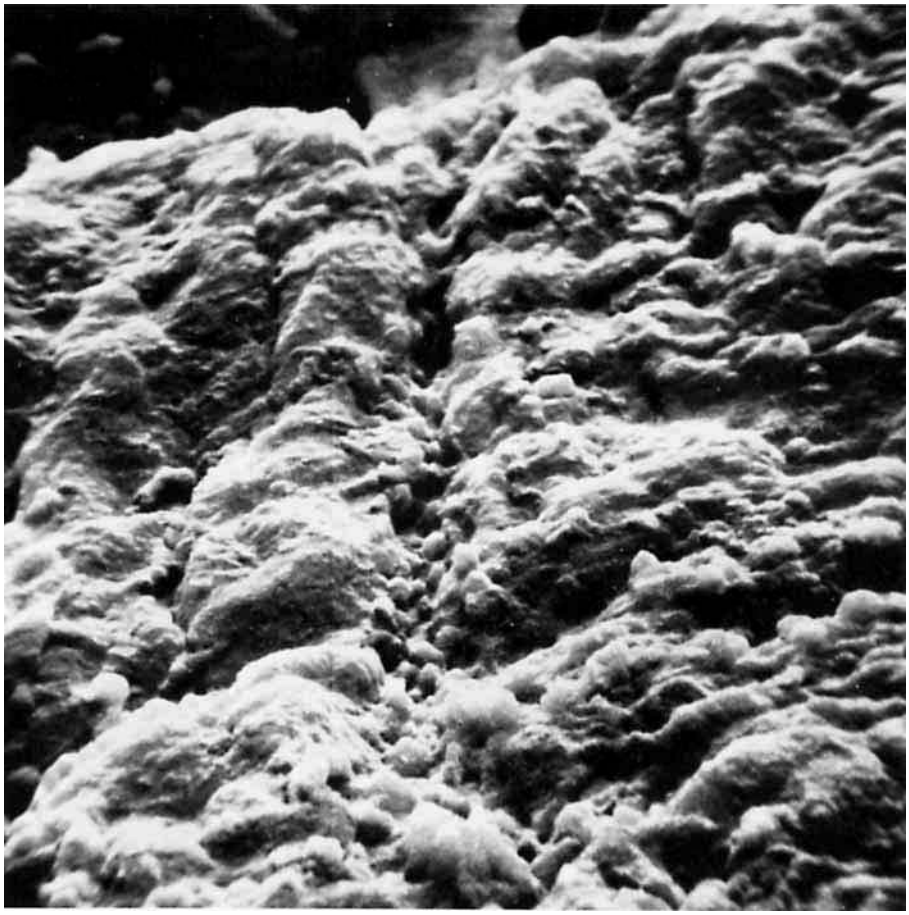


Fig. 8. Thrombus deposition, platelets, white cells, and heavy layer of fibrin on underlying rugae, produced by Fogarty balloon injury to femoral artery. The thrombus is clearly visible. The platelets are accelerating more thrombus formation. The characteristic injury of the surface area is clearly visible here at 1800X.

catheterization produces a diffuse covering of fine platelets and fibrin thrombus wherever there is visible intimal separation from underlying collagen (Fig. 9). Electrical injury produces a very amorphous looking "cobble stone" (Fig. 10) type of thrombus deposition on a wall structure of abnormal appearance. On electroosmosis and scanning electron microscopy this segment of wall is found to have lost normal metabolic and architectural characteristics.

Heparin yields a very significant change in thrombus formation and structure, making deposition fibrillar. If heparin is administered after injury, thrombus deposition tends to be arrested at the time of infusion. Thrombus formation then depends upon the passage of time between injury and infusion. Scanning electron microscopy indicates that dextran

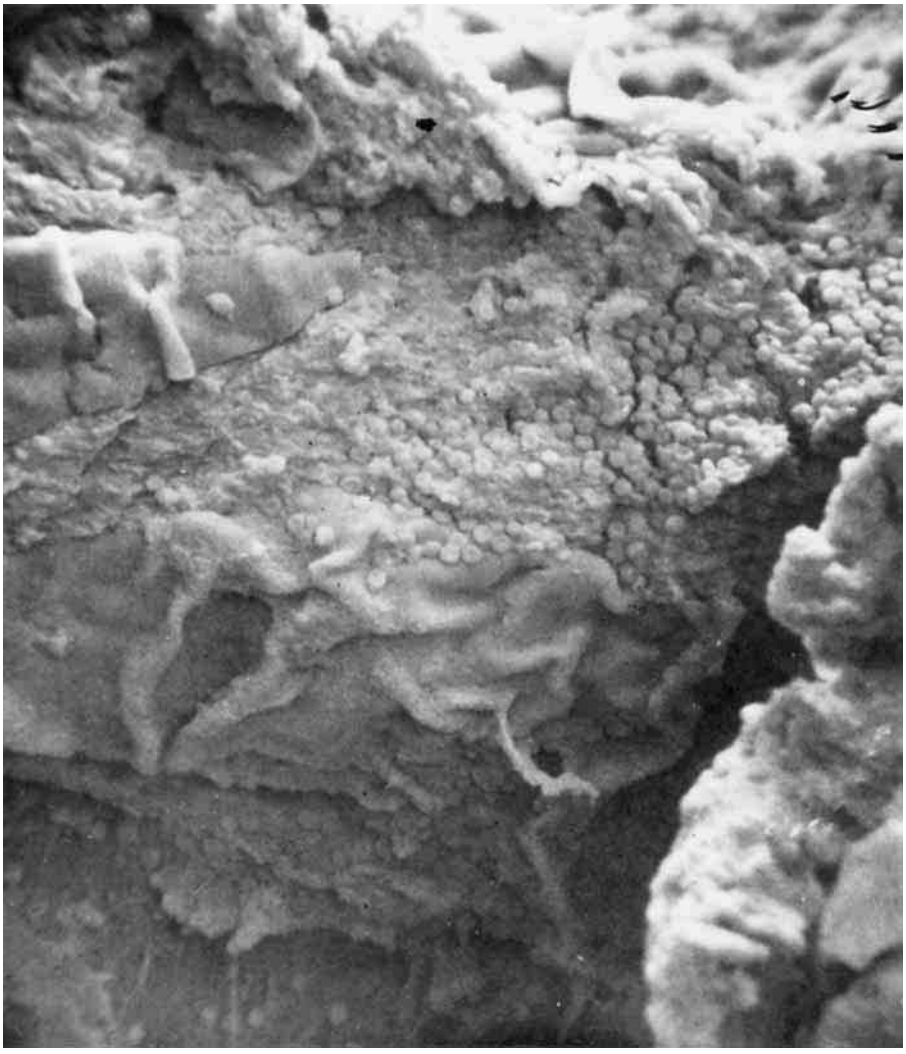


Fig. 9. Thrombus deposition with red cells, white cells, platelets, and fibrin are clearly visible on an evulsed layer of intima showing exposed underlying collagen with rapidly progressing thrombus deposition in a torn fold of blood vessel wall. (2000X).

in concentrations of 0.5 gm/Kg and greater blocks visible thrombus formation in all injured vessels in the dog (Fig. 11). Heparin, while modifying thrombus structure, also tends to return the vascular interface potential back to the normal range, from more positive to more negative, causing significant changes in electrokinetic phenomena. Dextran tends not to be effective in this regard. The result is a measure of the change in both interface potential and surface charge density, under the conditions of the experiment, both in vivo and in vitro, and in the human under clinical conditions. The "dextran effect" has recently been described at least in part in a series of papers on the displacement of cations from the diffuse electric double layer (23).

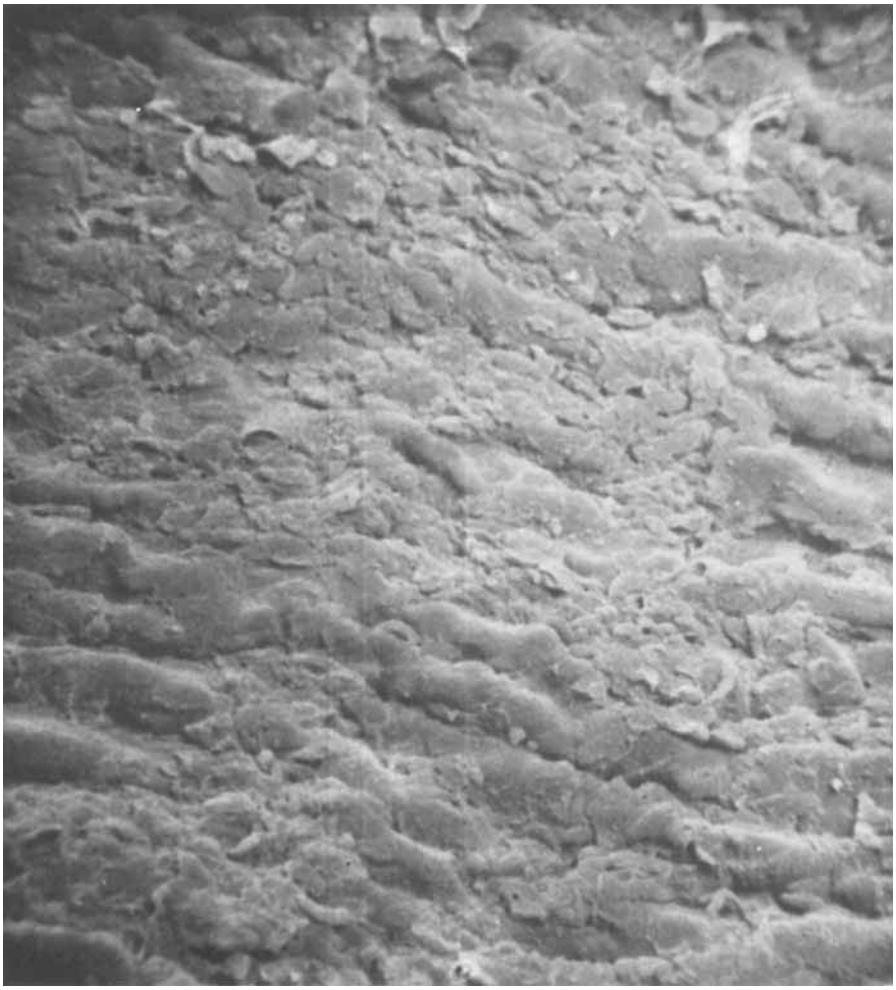


Fig. 10. "Cobble stone" thrombosis on arterial wall produced by electrical injury which tends to destroy the normal structural characteristics of the blood vessel wall pores. (500X).

ELECTROCHEMISTRY OF THROMBOSIS

Thrombosis and Faraday's Laws

Electrical thrombus deposition on the wall beneath the positive electrode was observed very early (7). The size of the thrombus seemed roughly proportional to current passed; but it was difficult to quantify the phenomenon in vivo.

Ultimately, this was done in vitro. A positive electrode placed in citrated blood forms a rather characteristic type of "clot," the weight of which is directly proportional to the quantity of electricity passed (Fig. 12). Electrical thrombus deposition on an electrode appears to obey Faraday's law. Under conditions of spontaneous thrombosis, this law is also followed in that thrombus deposition continues relatively inexorably until occlusion occurs, or until a change in conditions is produced and thrombus deposition ceases.

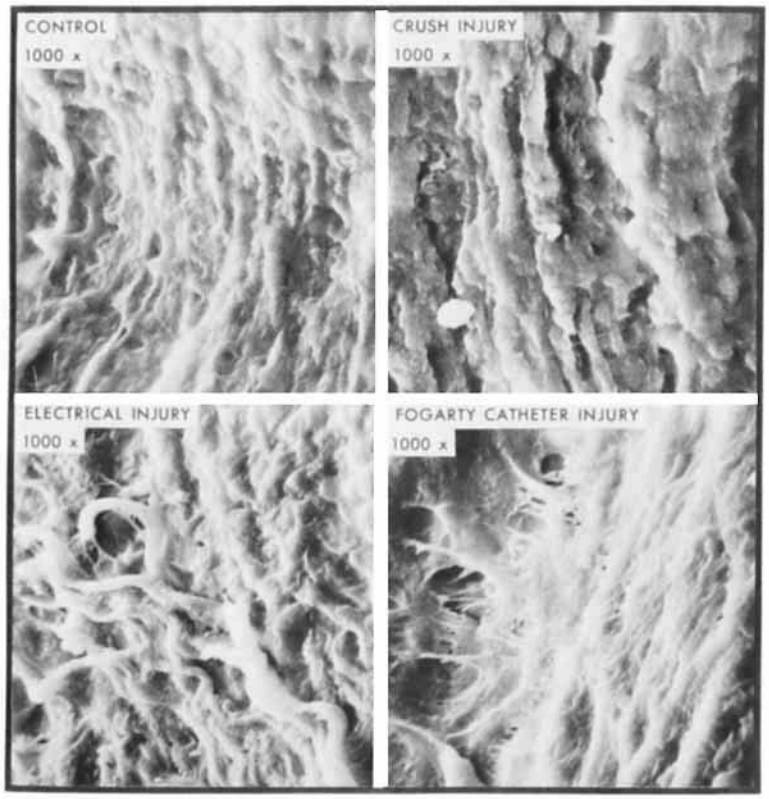


Fig. 11. 0.5 gm/kg low molecular dextran. Dextran tends to prevent thrombus deposition in all except the most filamentous variety following injury.

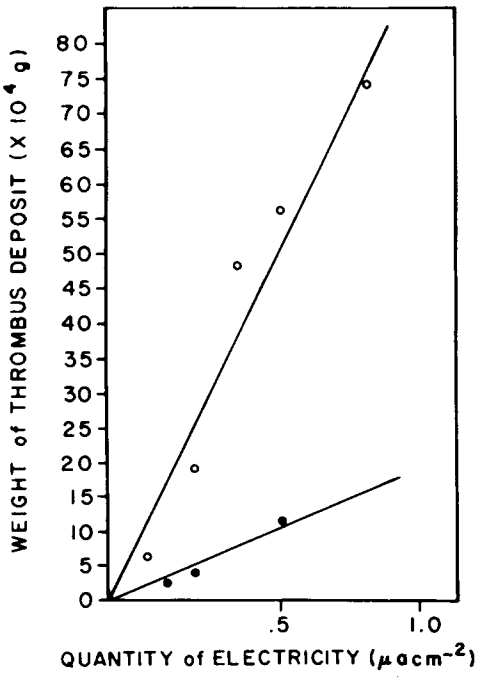


Fig. 12. The rate of thrombus deposited on a precipitating electrode from either heparinized, citrated, or raw blood is directly proportional to the coulombs of electricity passed.

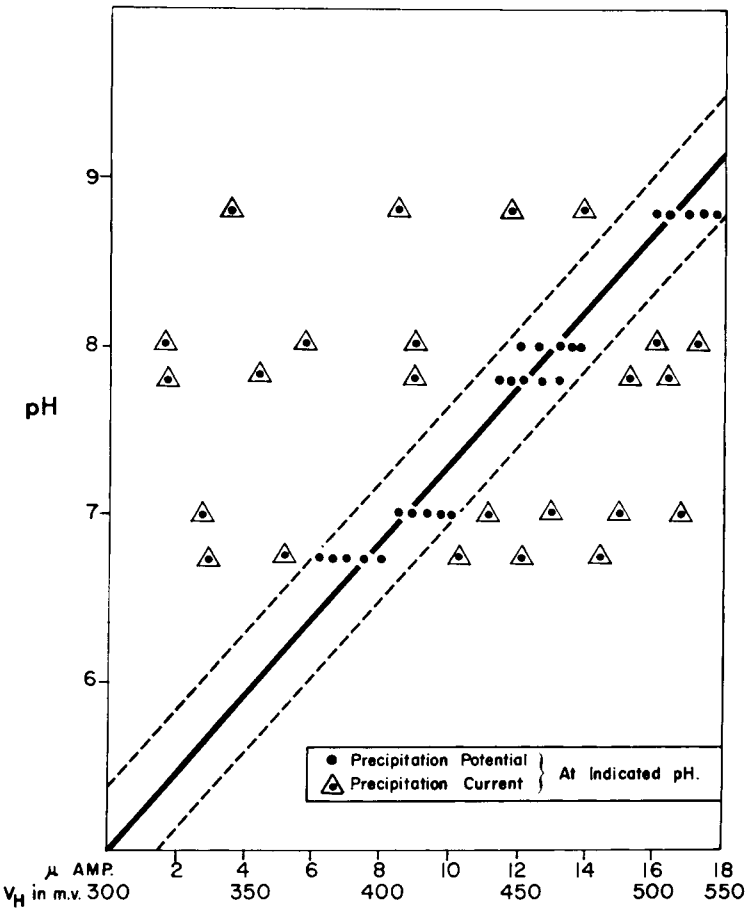


Fig. 13. Precipitation potentials for red cells, white cells, and platelets as shown here are directly related to the potential of a precipitating electrode and are not related to the currents necessary to produce the precipitation potential of the electrodes. Precipitation potentials for platelets are approximately the same as those for red cells when taken from normal humans. The precipitating electrode used was platinum.

Thrombosis – Potential or Current Dependent Phenomenon?

Early in the experiments, in fact for the first 10 years, it was not known whether thrombosis was potential or current dependent (24, 25). Though the early information suggested that thrombosis was "potential dependent," this suggestion could not be proved. The experiment suggested by Walter Brattain (26) made it possible to determine that cell deposition on a platinum or gold electrode, and ultimately thrombus deposition in vivo on both electrodes and natural blood vessel wall, was ultimately related to the potential difference at the interface with respect to the normal hydrogen electrode (27). Erythrocytes, leukocytes, and platelets deposit on the positive electrode at a potential of approximately +300 to 400 MV with respect to the normal hydrogen electrode at physiologic pH's (Fig. 13). pH changes produce a consistent change in precipitation potential of +95 MV per pH unit.

Thrombus formation on intravascular wires in vivo at set potentials fulfills the same

DEPENDENCE OF THROMBUS DEPOSITION AT METAL ELECTRODES ON POSITION OF METAL IN ELECTROMOTIVE SERIES

Metal	M/M^{n+} standard electrode potential (V, NHE)	Resting potential at metal–blood interface (V, NHE)	Occurrence (✓) or non-occurrence (×) of thrombus deposition
Mg	−2·375	−1·360	×
Al	−1·670	−0·750	×
Cd	−0·402	−0·050	×
Cu	+0·346	+0·025	✓
Ni	−0·230	+0·029	✓
Au	+1·420	+0·120	✓
Pt	+1·200	+0·125	✓

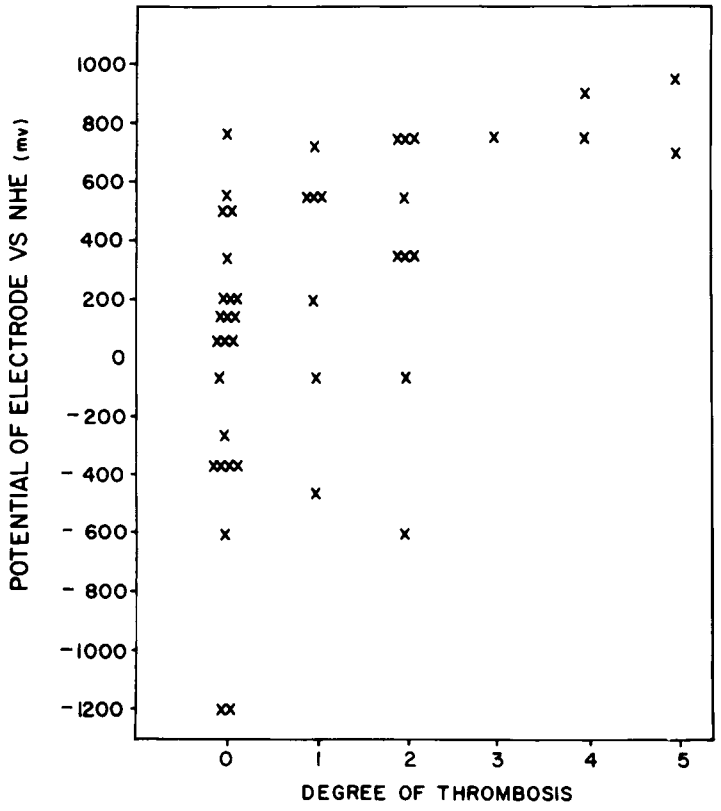


Fig. 14. (a) Thombus deposits at spontaneous potentials on metal electrodes more positive than +300 MV with respect to the normal hydrogen electrode used here. (b) The more positive the electrode potential of a platinum electrode at set potentials the greater the weight of the thrombus deposited on the electrode; semiquantitatively similar to the experiment carried out with an electrode in vitro (see Fig. 12). Both (a) and (b) were carried out in vivo with the electrodes placed into flowing blood in the arteries and veins of dogs.

obligation (28, 29). The weight of the thrombus deposited in large part depends on the period of exposure of the wire at appropriate potentials to the blood flowing by the thrombotic surface (Fig. 14).

Spontaneous Potentials of Metallic Prosthesis and Thrombogenesis

A more critical experiment was carried out, in which metal tubes were used to replace

both arteries and veins in the vascular tree (30). Those high in the electromotive series which develop a negative potential in contact with blood are very resistant to thrombosis.

The more noble metals at the lower end of the electromotive series, as would have been predicted by this experiment, deposited thrombosis very rapidly.

Copper, a highly thrombogenic surface, was made nonthrombogenic when maintained at cathodic potentials artifically by a suitable polarizing circuit (31). This indicates that negative potential is responsible for antithrombogenic behavior. The chemical characteristics of copper were not changed by the imposed potential difference. This was also shown to be true of heart valves. Another problem relates to the purity of the surface of the material. Heart valve surfaces composed of identical metals deposited thrombusion their surfaces in inverse proportion to their cleanliness. Ultraclean and electrochemically clean surfaces were very resistant to thrombosis. The same metals, poorly cleaned or uncleaned, or covered with fingerprints, dirt, and oxides on the surfaces, rapidly deposited thrombus because of the mixed potentials developed at the transitional points between clean and dirty junctions on the same surfaces (32, 33).

STUDIES ON THE MECHANISMS OF THROMBOSIS – ACTIVATION OF FACTORS INVOLVED IN THROMBOSIS

Electrochemical Activation of Isolated Coagulation Factors Potentiostatic Study

Purified prothrombin preparations can be converted to a thrombin-like product and fibrinogen to a reasonable facsimile of fibrin (34), on electrodes maintained at a potential more positive than +400 MV the normal hydrogen electrode (Fig. 15). Maintaining highly cathodic potentials in the range of −800 to −600 MV converted conventional fibrinogen into a very antithrombogenic anticoagulant form of fibrinogen.

Structural changes or possible polypeptide separation have not yet been identified. However, investigation of this phenomenon should prove most interesting.

Platelet Interactions at Metal Surfaces

Zivkovitch et al. (35) have recently completed a series of experiments which demonstrate that platelets exposed to several metals covering a wide range in the electromotive series display progressive release of adenine nucleotides as the more noble end of the series is reached. Cu, Ag, and Pt yield rather complete release of glucose 6+ phosphate (Fig. 16). The available evidence thus indicates that electrical or surface portential activated-thrombus formation operates through activation of platelet and ADP release, the classical route.

Biophysics and Biochemistry of Thrombosis Enzymology

Primary Hemostasis: A series of workers have recently summarized in increasing detail the biochemistry of the physiochemical phenomena described above.

Nossel (36) and his coworkers, Jamieson (21, 37), Massini and Colman (39), and Luscher (38), and coworkers have begun to describe the physical chemistry and biology of this phenomenon. Nossel was the first to carefully categorize the physical chemistry of platelet aggregation on natural collagen. This was done by showing that intact normal collagen is required to produce platelet aggregation in an aggregometer in vitro. With

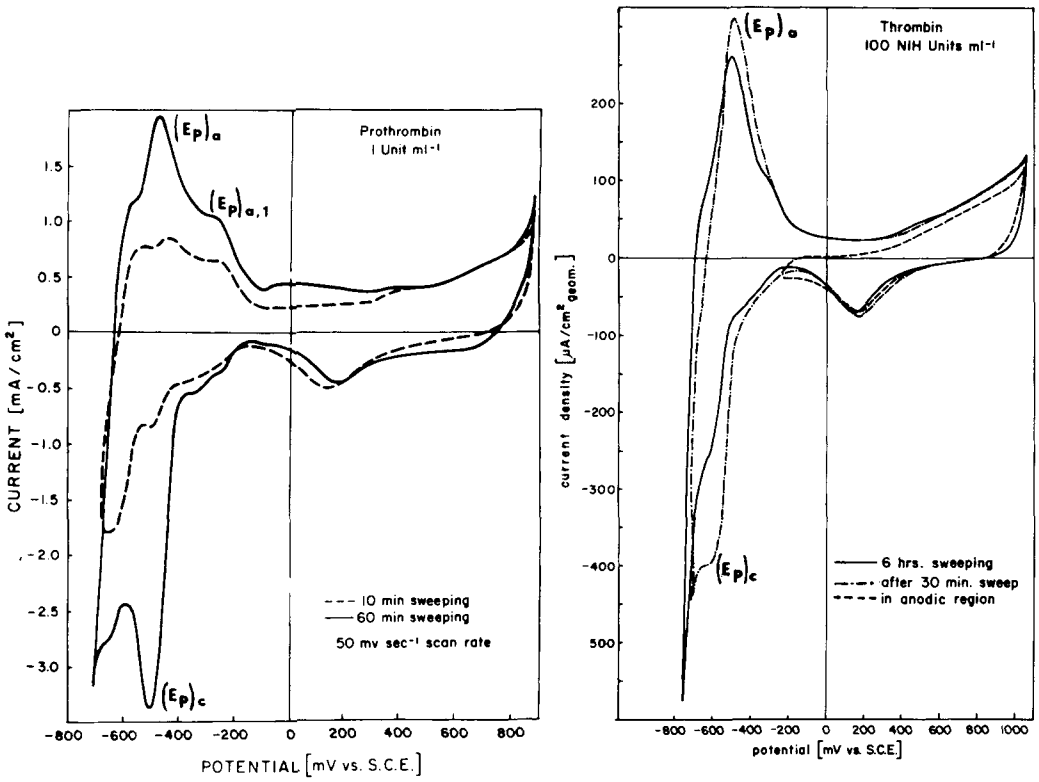


Fig. 15. Prothrombin may be converted to a form of thrombin by continuous cycling with an electrode sweep generator as shown in (a) and (b). Progressive recycling produces a greater and greater irreversible change with marked peaks from the converted prothrombin.

When placed in plasma, the material is found to accelerate thrombus formation as is the case with pure thrombin.

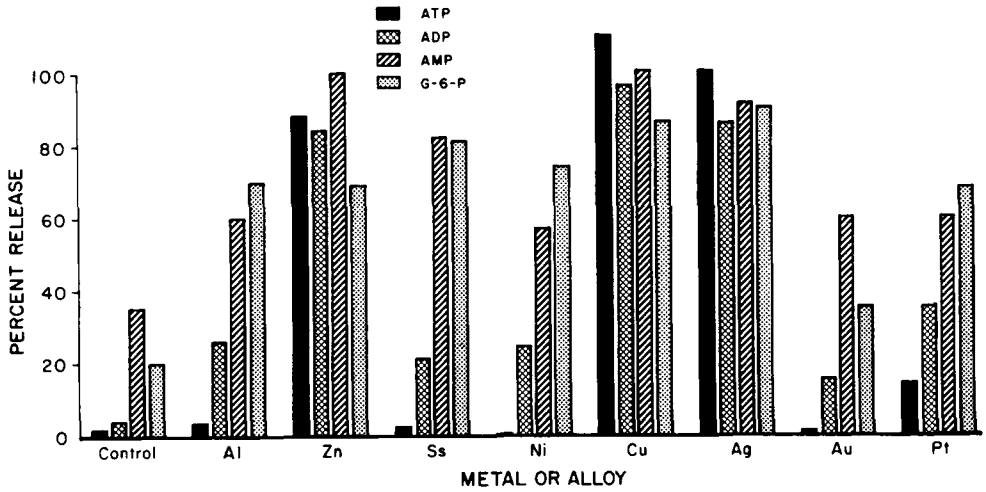


Fig. 16. Exposure of platelet-rich plasma and platelet buttons resuspended in Ringers solution to metals, including aluminum, zinc, stainless steel, nickel, copper, silver, gold, and platinum, reveals rather classical variation in the responses of the platelets. There is marked increase in ADP release produced by all of the noble metals with the exception of gold, which has a less destructive effect on exposed platelets. In all other instances, particularly with copper and silver, there is rather marked destruction of platelets with release of all contained energy, phosphate-containing materials, including ATP, ADP, AMP, and glucose VI phosphate. The response of platelets on exposure to gold may in some degree explain the unexpected antithrombogenic characteristics of gold used as a valve cage in valve experiments carried out by ourselves and Lester Sauvage.

progressive destruction of the collagen or neutralization or blocking of amino groups, it was possible to make collagen a progressively nonthrombogenic surface. Blocking of the carboxyl (COO^-) groups with potentiation of the epsilon amino groups on the other hand made collagen an even more potent thrombogenic surface.

Colman (39) has recently confirmed that both progressive destruction of collagen with colagenase and oxidation of the galactose ring on the collagen side chain progressively inhibit platelet interactions with collagen.

Luscher and his group have described the necessary reduction in surface charge density of the platelet by polyvalent cations as an obligatory component in aggregation. This requires a structural derangement firstly in the electric double layer at the vascular interface and secondly of the platelets on contact for the production of intravascular thrombosis.

Normally platelets and collagen look at each other through a highly charged double layer of 10^6-10^8 Volts cm^{-1}. Weiss (22) has described "tunneling" characteristics which induce recognition between the charge groups on platelets etc. and the injured blood vessel wall or endothelium. Jamieson (21) has categorized the biochemistry of this recognition pehnomenon between glucosyl transferase, on platelets and the galactose, and glucose side chain residues on the surface of exposed collagen. The speeding up of the kinetics of attachement is produced by UDPG in the platelet, releasing glucose to complete the bonding process by which the platelet attaches firmly to collagen, ultimately releasing ADP and causing platelet aggregation. The energy for these phenomena is yielded by the aerobic cycle through high energy phosphates in which cyclic AMP obviously participates (35). In this instance, the available evidence suggests that platelet membrane cyclic AMP acts to inhibit these phenomena, blocking dephosphorylation and potentiating phosphorylation, while released ADP acts to potentiate the thrombotic phenomenon. Saltzman (40) has recently categorized and summarized the antithrombogenic characteristics of cyclic AMP in platelets during interactions at the vascular interface.

Shulman (8) and Booyse (41) have recently summarized the series of interactions which can occur due to a number of platelet release reactions, including immune response and endothelial injury, at the vascular interface to potentiate mural thrombus deposition. Thus the known physical biochemistry mirrors the in vivo reality of the surface physical chemical phenomena (42, 43). It also provides information concerning the nature of the enzymatic processes involved. Thus within a very short period of time, approximately 18–24 months, there has been a catalytic increase in both the knowledge and understanding of the physical biochemistry cell–cell, cell–protein, and cell–collagen recognition and interactions at the vascular interface. It would now seem that we are in an era in which further understanding of the biochemical interactions at the vascular interface and of how these interactions can be modified to prevent abnormal thrombosis may be of great use in clinical medicine.

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