

BIOELECTRIC PHENOMENA, THROMBOSIS AND PLASTICS: A REVIEW OF CURRENT KNOWLEDGE

VELIMIR MIRKOVITCH, M.D.*
Department of Artificial Organs

THE rapid development of new plastic polymers and their immediate, sometimes regretfully early, application in cardiovascular surgery have brought up once more the problem of compatibility between blood and foreign surfaces. The manufacturers of plastics with their technologic facilities have almost succeeded in producing materials that would satisfy the classic standards of strength, elasticity, chemical inertness, biologic acceptability, water repellency, and smoothness. Experimental testing on animals and clinical application of these materials have given some fair and many disappointing results. If a truly imaginative application of plastics in cardiovascular surgery is to come, then a thorough study of the basic characteristics of blood vessels, blood, and hemodynamics should give us some understanding about the process that occurs when blood comes in contact with a plastic. This paper represents an effort to review and to coordinate some well-known data from the literature.

Thrombosis and Morphologic Changes of the Intima

For many years the smoothness and nonwettability of intima were considered to be responsible for the minimal friction of the circulating blood and, consequently, to be the defense against intravascular clotting. Later investigations of Samuels and Webster,¹ have produced evidence of an active reaction of the intima to physical and chemical damage, and the close relationship of this reaction to the thrombotic process. It has been found that at the beginning of the injury or when injury is not great, the cells of the intima do not change morphologically, but that fibrin and platelets temporarily adhere firstly to the intercellular lines and later cover the cells with a thin film. When the damage progresses or when it is great initially, the intercellular lines enlarge, the cells become vacuolated and separated, and fibrin is increasingly deposited over the area of cellular desquamation. While these morphologic changes described by Samuels and Webster¹ can be the results of the direct injury to the cells of the intima, O'Neill² has explained them as the consequences of impaired nutrition through the vasa vasorum.

The intercellular lines of the intima, their existence, nature, and function were the object of many investigations. Recent application of electron microscopy by Florey, Poole, and Meek³ revealed that there is no definite anatomic structure corresponding to the previously suggested intercellular cement of the normal intima, and that the overlapping of cell edges or cell junctions can give under the

This study was supported by United States Public Health Service Research Grant number HE-04448 from the National Heart Institute with Dr. W. J. Kolff as principal investigator.

**Fellow in the Department of Artificial Organs, the Division of Research.*

ordinary microscope the impression of an amorphous substance. Chambers and Zweifach⁴ have observed that the area in between cells, at that time still called "intercellular cement," undergoes changes with decrease in blood flow or damage to perivascular tissue. Ohta and associates⁵ have found that after injury, heparin-like metachromatic granules appear in the enlarged intercellular spaces, but that the further advance of injury inhibits the production of granules. They, as well as the other authors, have observed in experimental animals that histamine, dextran, peptone shock, and heparinization produce more of the metachromatic substance.^{1, 6} The perivascular localization of the mast cells and the diffusion of granules from them into the intima is the explanation suggested by McGovern⁶ and Riley,⁷ but the fact that mast cells are not found around all vessels has led to the conclusion that the cells of the intima themselves might be able to secrete heparin-like substances under various conditions of stress.⁵

Thrombosis and Electric Phenomena on the Intima

Sawyer and Pate⁸ were among the first investigators to explore the electric phenomena that appear on normal and injured blood vessels. In their many *in vivo* experiments that have been repeated under various conditions the existence of the potential difference between the normal undamaged intima and the adventitia has been established; the intima is electronegative up to 5 mv. This potential difference and the electronegativity of the intima can increase for a short time at the beginning of injury.⁹ Later, when injury—piercing, transection, or crushing—advances in intensity and duration, the potential difference decreases, disappears, or reverses and the intima becomes electropositive up to 10 mv.⁸ Fresh blood vessels kept *in vitro* retain their normal potential differences for about one hour after extirpation; then the electronegativity of intima decreases, disappears, and after five hours it repeatedly shows electropositivity.¹⁰ Not only do the potential changes of the injured vessel correspond to the degree and the duration of injury, but the appearance and extension of the subsequent thrombosis in them are also closely related to the amount and the duration of the injury current.⁹ Follow-up studies of fresh homografts of the abdominal aorta in dogs showed, too, that an increased electropositivity of the intima of the graft is always present together with thrombosis and infection.⁸

While the decrease and the reversal of the differences in normal electric potential of blood vessel wall have been found to be closely related to injury and thrombosis, it was noticed, too, that injury to perivascular tissues influenced the normal potential differences of blood vessels in a similar fashion, even when the blood vessel itself was spared.⁸ Once more, the extent of thrombosis was directly related to the severity of the perivascular injury, the duration of the injury, and the diameter and wall thickness of the vessel.¹¹ Attempts to create around blood vessels an electric field of a magnitude similar to that of the previously determined currents of injury, have resulted in values of "thrombotic" current close to the current of

injury, 20 μ a.¹² In other experiments in which enzymatic action of thromboplastin of injured tissue was prevented by shielding the intact blood vessel with a dialyzing membrane, electric or ionic factors or both were demonstrated in the pathogenesis of thrombosis resulting from perivascular injury.¹³ The reproducible occurrence of thrombosis in that part of a blood vessel that is electrically made positive has established electric thrombosis as one of the most reliable methods for the standardized experimental production of intravascular clotting.^{14, 15} Moreover, the ability of a positive electrode to induce occlusion of small blood vessels by thrombi has been successfully used as a hemostatic tool in a limited number of surgical patients with the postoperative complications caused by defects of the blood-clotting mechanisms.¹⁶

At the same time when the described injury currents of the vascular wall or perivascular tissues were related to intravascular clotting of blood, it was demonstrated, too, that in an injured vessel the thrombosis could be totally or partially prevented, if the vessel was negatively charged with the passage of the electric current of low voltage and amperage of the same order of magnitude as the injury current.^{17, 18} On the other hand when a vessel is shielded from the injured perivascular tissues with an insulator, the appearance of mural thrombi is not so frequent, and only low injury potential differences were measured between the intima and the surrounding points of injury.¹⁹ Schwartz and Richardson²⁰ have negatively charged intravascular stainless steel tubes, and kept them free of thrombi for from 1 to 12 hours during the passage of current. It is not easy to explain why in their experiments the application of negative charges produced a prolonged (up to 72 hours) antithrombotic effect after the current had been discontinued. The application of currents of higher voltage by other investigators did not prevent the occurrence of thrombi in damaged blood vessels, and on the basis of the histologic changes probably damaged the vascular wall.²¹ With the advance and improvement of experimental technics, the previously found magnitudes of potential differences on normal and injured vessels will stand corrections, but the highly reproducible finding of the electronegativity of the normal intima, and reversal of polarity after injury must be considered as basically correct.

Recent and still incomplete experimental data about the origin of electric phenomena on blood vessels indicate that the metabolic processes in the intima or in the wall may be directly responsible for the electronegativity of intima, the existence of potential differences, and for their changes following trauma.¹¹ The existence of an active flux of sodium and chloride ions across the blood vessel wall was demonstrated with radioactive sodium and chlorine. In the aorta the flux has the direction from the intima toward the adventitia, with a net efflux of sodium ions, and a small excess of negative ions, usually chloride, on the side of the intima. The flux of ions across the wall of the vena cava has still unexplained direction—from the adventitia toward the intima—but it consists of a net influx of chloride ions, which creates a similar excess of electronegativity on the intima. The flux

across the vena cava five to six times higher than across the aorta is explained on the basis of the thickness of the aortic wall. A flux of potassium ions could not be detected in these experiments, and the measurements have not yet been performed on injured, thrombosed, or atherosclerotic vessels. An increase in temperature results in an immediate increase of the flux, and the increase per degree centigrade is surprisingly close to the increase of the metabolic rate in general. As long as the temperatures are kept within the physiologic range the direction of fluxes does not change.²² Anoxia increases the net flux at the very beginning, but it is immediately followed with a reduction, disappearance or reverse direction of fluxes with the net influx of positive ions across the wall of the aorta.^{23, 24} All these experimental data are encouraging the assumption that the active metabolic process in the intima or blood vessel wall are maintaining a certain normal, thrombosis-preventing potential difference with the intima electronegative.

It is interesting to analyze some experimental data that might be important to the explanation of the anticoagulant effect of heparin in the light of bioelectric phenomena. As mentioned before, at the beginning of injury there is a coinciding increase of heparin-like substance in the intercellular cement,⁵ and a sharp temporary increase of the electronegativity of the intima.⁹ Heparin is a mucopolysaccharide with a higher static electronegative charge than that of any other organic compound in the animal body.²⁵ When it is injected it increases the electronegativity of intima in respect to adventitia,¹⁸ and when it is given before the extirpation of vessels it protects the ionic fluxes against the effect of anoxia.¹¹ With these facts in mind it is understandable why the effects of heparin are limited if it is not applied at the very onset of thrombosis or if the other thrombus-promoting conditions, injury, stasis, anoxia, are persisting.^{21, 26} Heparin is capable of preventing the experimental "electric" thrombosis in positively charged blood vessels, even when the administration of Dicumarol* and low levels of prothrombin do not have a significant anticoagulant effect.^{15, 18}

Bioelectric Properties of Blood and Blood Flow

The existence of the negative electrostatic charges on the surface of red blood cells is a well-established fact:²⁷ under normal physiologic conditions it is a constant for a species; it ranges in different species from -7.0 to -21.1 mv.;²⁸ and its volume is progressively decreased with the age of subjects.²⁹ The origin of the negative charge is not yet clear. For the white blood cells, it has been found that in an electric field of low strength they move toward the anode, even faster than do the red blood cells.^{27, 30} This may be one explanation for the migration of polymorphonuclears toward the electropositive foci of injury, anoxia, or inflammation.^{27, 31} The surface of platelets contains negative electrostatic charges of the same strength as that of the white blood cells, causing the platelets to move with the same speed toward the positive pole during the electrophoresis.²⁷ The

*Bishydroxycoumarin, Wisconsin Alumni Research Foundation.

presence and importance of platelets for the triggering of the normal clotting of blood (platelets being one of the richest sources of thromboplastin) is challenged by the evidence that the clotting of plasma from which the platelets have been removed as well as possible can be started and accomplished *in vitro*, where the surface properties of different containers have a definite influence upon the length of the clotting time.^{32, 33} Even though the platelets may not initiate the fibrin formation, they play an essential role in the later retraction of the clot.³⁴ The passage of the electric current through the solution of fibrinogen, results in accumulation of fibrin on the positive electrode.¹⁶

The static negative electric charge on molecules of blood proteins is the basis of the everyday application of electrophoresis in clinical laboratories. The negative charges per unit of surface of protein molecules vary for different plasma proteins. Certain animal species with higher concentrations of globulins and fibrinogen, molecules with lower mobility, also have higher negative electrostatic charges on the red blood cells.²⁷ If one considers blood as a suspension of electronegatively charged cellular elements in the colloidal solution of hydrophylic electronegatively charged proteins, then it seems appropriate to expect that the local or general changes in pH, electrolytes, and concentration of various protein fractions will affect the stability of the suspension by altering the magnitude of charges and, consequently, will increase the tendency of particles to adhere together (faster sedimentation rate and rouleaux formation) or to the surface of the intima.

In spite of the firmly established gross relationship between the hemodynamics and the occurrence of a thrombus, there is a complete absence of data about the electric differences and ion fluxes in the blood vessel wall during hemodynamic changes. The intima reacts to the acute and excessive decrease in blood flow rate with an increased production of the intercellular material,⁴ and there is a temporary maintenance or increase of the electronegativity of its surface,⁹ but these phenomena are not intercorrelated yet, nor has the real importance of the acute flow reduction been determined. The striking importance of turbulence for the triggering and promoting of an acute thrombotic occlusion was described after the early experimental implantation of vascular prostheses with a "positive or negative" disproportion in diameters between the prostheses and host vessels,^{35, 36} but the possible existence of bioelectric phenomena at these localizations was not investigated. Certain anatomic structures in the arterial vascular tree, with the constant production of eddy currents at these parts, were described as the points of predilection for the occurrence of thrombosis,^{37, 38} but the ion fluxes of these segments also have not been measured.

Plastics

During the last hundred years an abundant volume of work has been done to create material with surface properties similar to those of the intima of blood vessels. The smoothness of the intima was the property of the intravascular lining

first to impress investigators; it was considered to be the most important quality for the prevention of thrombosis under physiologic conditions.³⁹ A rough surface had a destructive effect upon platelets, and consequently blood clotting time in rough-surfaced test tubes was shortened.⁴⁰ The original significance of this fact suffered greatly, since only a slight prolongation of clotting times occurred in test tubes with certain highly polished surfaces such as glass, methylmethacrylate, polyethylene, stainless steel.⁴¹ Moreover, early postoperative thrombosis appeared in smoothly lined experimental vascular prostheses of polyurethane, nylon, polyvinyl, polyethylene, and methylmethacrylate.^{42, 43} Technically it is not possible to obtain the same degree of smoothness on all surfaces.

Nonwettability was the other attribute of the intima which was considered to be of essential importance for the prevention of intravascular blood clotting, along with a possibly erroneous assumption that a water-repellent surface would necessarily be blood-repellent.^{39, 43-45} However, the length of times of clotting, in test tubes of various materials, could not be directly related to a coefficient of wettability as measured by the size of contact angles between the water and surfaces of these materials.^{46, 47} Furthermore, experimental vascular prostheses made of water-repellent materials were occluded by thrombi after their implantation into the animal body.⁴³

The advance of knowledge about the static electronegative charges on blood cells and proteins has led to the hypothesis that some materials (glass or stainless steel) contain ionic "active" surfaces. These surfaces activate or adsorb and concentrate a substance from plasma in the sufficient amount for the initial steps of blood clotting or thrombosis to take place; whereas electric nonconductivity of methylmethacrylate and paraffin should prolong the blood clotting time.^{33, 48-50} The thrombosis that occurs in vascular prostheses made of nonconductive plastics has challenged the value of this hypothesis.^{42, 43}

When no thrombi developed in the vascular prostheses made of woven or knitted plastic filaments of nylon, orlon, dacron, teflon, and other materials, despite the fact that neither the polymers nor the prostheses satisfied any of the previously mentioned standards, it was discovered that the internal surface of a graft should have a certain roughness or porosity, to offer a suitable basis for fixation of a fibrin layer.^{43, 51-54} Other possible mechanisms for the protective function of the porosity are not yet clearly explained. One would not have predicted this result; the prostheses accumulate locally a great number of platelets;⁵⁵ porosity and fibrin are conducive for the thrombus-promoting injury currents from the perivascular tissues after surgical implantation; and, although the differences of electric potentials between this layer and the surrounding tissues are not reported, it should not be expected that the fibrin film itself could be electronegative immediately after its formation. It is likely that the real and sole reason for the good results of these prostheses, besides, perhaps, a still unexplained role of the fibrin layer, lies in the favorable hemodynamic conditions, because the results are only good as

long as the diameters are larger than 4 mm., and prostheses are implanted in a straight, fixed position. A decrease in diameter below 4 mm., an increase in length, and a sharp angulation are followed by failures. A similar explanation could be given for the satisfactory results with freeze-dried homografts. Immediately after the operation they are electroneutral, and a normal electronegativity appears about 20 days postoperatively if infection and thrombosis do not occur.⁸ Results with homografts do not surpass those with plastic porous prostheses. Their usefulness lies in the supporting role of collagen, a polymer of animal origin.

The significance of hemodynamic conditions is even more evident in the case of the intracardiac implantation of plastic materials.⁵⁶ When the strips of plastics, 2 cm. long and 1 cm. wide, were sutured to the internal surface of the right atria of dogs, thrombi covered them regardless of the nature of material and smoothness of the surface. After implantation the thrombus was largest during the first week, later decreasing in size, and after 20 days it was organized and formed a smooth, thin, transparent membrane. To avoid direct contact with the suture lines, plastic materials were mounted only in the middle portion of a 4 cm. long and 1 cm. wide stainless steel frame, and a different result was observed. Thrombi at the suture lines were small and organized, and they could not extend over the plastic. When the plastic had smooth surfaces they stayed free of thrombi, and when their surfaces were rough an envelope of thrombus was deposited directly from the blood stream. From these data it was concluded that the points of turbulence with stagnating blood flow near the suture lines were the sources of thrombi, and that inside the heart (if not in the aorta) smooth surfaces not containing the foci of microturbulence will remain free of thrombi if exposed to the high-velocity blood flow. The clinical performance of the present ball valve as the successful valvular prosthesis with low resistance to the blood flow and high-velocity flow over almost all parts, has confirmed the above-mentioned conclusions.^{57, 58}

Gott and associates^{59, 60} performed experiments with plastics coated with a solution of colloidal graphite. They assumed that this substance might prevent the occurrence of thrombosis in intravascular tubular implants, by making their surfaces smooth, by dissipating any possible positive charges that would appear on the surface, and/or by a small negative charge on the graphite surface. Short and smooth plastic rings covered with colloidal graphite and implanted into the inferior vena cava of dogs stay free of thrombus for up to four hours. Our eight-day trials with longer, narrower, implanted tubes coated with the same solution of colloidal graphite did not result in protective action of graphite, nor did the insertion of the graphite cloth into the right hearts of animals produce less thrombosis than did knitted teflon.⁶¹ These contradictory data indicate that the action occurring at the interface between graphite and blood deserves further attention.

Blood—Plastic Interface and Compatibility

The determination of the clotting time of blood or plasma in tubes and/or

intravascular or intracardiac implantation of plastics have been the main if not the only technics for the determination of compatibility of blood with "foreign surfaces." The inadequacies of these two methods for the investigation of phenomena at the blood—plastic interface may be the cause of the contradictory evidence of the past.

The length of time of the *in vitro* blood clotting is a function of: the existing blood-clotting system in the animal; its damage during sampling; surface properties of the material of the container. Trauma of still crude technics of blood sampling initiates the blood-clotting process before the sample reaches the container. When the sample reaches the test tube, only a thin film of blood is in close contact with the test tube walls, and the surface properties of the material cannot influence the clotting process that is advancing in the other parts of the specimen under rather favorable conditions of anoxia and standstill. Moreover, it is difficult to distinguish whether or not, or to what extent the surface of the container influences the progress of blood clotting. It is hard to believe that improvements in the present technics of the clotting time test, such as less traumatic sampling, smaller and thinner containers, maintenance of adequate environmental temperature and humidity, adequate agitation and oxygenation of samples, could give us a much better understanding of the surface properties of materials.

The intravascular or intracardiac implantation of plastics offers some advantages over the blood-clotting test. In these experiments the material is usually placed in the position of its future application, and blood is flowing over it with more or less unimpaired hemodynamics. Beside this improvement the technic has many handicaps. The most important drawback of *in vivo* procedures is that they give only good or bad end results (plastics are not or are covered with thrombus), but they teach us nothing about the phenomena that occur at the blood—plastic interface and influence the final outcome.

The limitations of the above-mentioned methods have led to the study of surface properties of various materials through a determination of their zeta potentials. The streaming potential that can be measured as a fluid passes over the surface of a material, can be related to the magnitude of zeta or electrokinetic potential by the equation of Helmholtz:⁶²

$$S = \frac{Z R D P^*}{4 \pi \eta} .$$

Early work with this sensitive method was performed with capillaries of various materials, and dilute saline, potassium chloride, or plasma as fluids, it being assumed that higher concentration of electrolytes or presence of colloids would result in

**S* = streaming potential, millivolts; *Z* = zeta potential, millivolts; *R* = resistivity of fluid, esu; *D* = dielectric constant of fluid; *P* = pressure drop across capillary, dyne cm⁻²; *η* = viscosity of fluid, poise.

low and practically insignificant values of zeta potential.^{47, 63} Subsequent modifications of the apparatus and technic permitted the use of undiluted fluids and whole blood.⁶⁴ It has been found that materials such as glass, quartz, polyethylene, polystyrene, sulfonated polystyrene, or glass coated with colloidal graphite, as tested with saline or Ringer lactate have well-defined, reproducible, individually different values of zeta potential. The values ranged from -15 to -31.5 mv., and the highest electronegative zeta potential was recorded with sulfonated polystyrene. When the same materials were tested with fresh or heparinized blood, plasma, or serum the magnitude of zeta potential dropped close to zero in the fraction of a second, and significant difference between various materials disappeared. It seems that the zeta potential is almost immediately abolished by the deposition of a layer when a protein-containing fluid is passed through the capillary. As a working hypothesis we assume that this coat is either fibrin or globulin; thus it is unlikely that the zeta potential itself has the ability to prevent the occurrence of thrombosis on plastics. However, a profile of the zeta potential in relation to time, when plastics are perfused with diluted solutions of plasma proteins, may teach us something about the very first phenomena that occur when blood comes in contact with plastics.

Conclusion

The existence of bioelectric phenomena in the walls of blood vessels has been repeatedly demonstrated, through the potential difference between the normal intima and adventitia; the intima is electronegative. Experimental data suggest that the metabolism of the blood vessel wall or intima may be responsible for maintaining the potential difference. Moreover, a decrease, disappearance, or reversal of potential difference is related to the occurrence of thrombosis in blood vessels. There is no known relation to the morphologic changes in the intima during the thrombotic process. Exposure of an injured blood vessel to the negative pole of a low-voltage battery has prevented thrombosis. It is likely that future improvements of apparatus and experimental technics will yield different and more exact values for voltages of "normal" and "thrombotic" potential differences, but it is equally likely that the principle of a direct correlation between the electropositivity and thrombosis will stand the test of time.

Present-day plastic materials do not match the surface properties of the normal intima, when the surface of the plastics are not exposed to ideal hemodynamic conditions of undisturbed high-velocity flow. Current technics for the study of the blood—plastic interface, *in vitro* clotting time and *in vivo* implantation, are inadequate to reveal the phenomena that occur at the interface. It is our hope that the determination of the profile of zeta potential in relation to time, determined with various prosthetic materials when brought in contact with blood fractions, will enable us to learn about the changes that appear at the blood—plastic interface at the very inception of thrombosis.

References

1. Samuels, P. B., and Webster, D. R.: Role of venous endothelium in inception of thrombosis. *Ann. Surg.* 136: 422-438, 1952.
2. O'Neill, J. F.: Effects on venous endothelium of alterations in blood flow through vessels in vein walls, and possible relation to thrombosis. *Ann. Surg.* 126: 270-288, 1947.
3. Florey, H. W.; Poole, J. C. F., and Meek, G. A.: Endothelial cells and "cement" lines. *J. Path. & Bact.* 77: 625-636, 1959.
4. Chambers, R., and Zweifach, B. W.: Intercellular cement and capillary permeability. *Physiol. Rev.* 27: 436-463, 1947.
5. Ohta, G.; Sasaki, H.; Matsubara, F.; Tanishima, K., and Watanabe, S.: Heparin-like substances in cement lines of vascular endothelium in guinea pigs. *Proc. Soc. Exper. Biol. & Med.* 109: 298-300, 1962.
6. McGovern, V. J.: Reactions in injury of vascular endothelium with special reference to problem of thrombosis. *J. Path. & Bact.* 69: 283-293, 1955.
7. Riley, J. F.: Riddle of mast cells. *Lancet* 1: 841-844, 1954.
8. Sawyer, P. N., and Pate, J. W.: Bio-electric phenomena as etiological agents in intravascular thrombosis. *Surgery* 34: 491-499; discussion, 499-500, 1953.
9. Sawyer, P. N.; Pate, J. W., and Weldon, C. S.: Relations of abnormal and injury electric potential differences to intravascular thrombosis. *Am. J. Physiol.* 175: 108-112, 1953.
10. Sawyer, P. N., and Pate, J. W.: Electric potential differences across normal aorta and aortic grafts of dogs. *Am. J. Physiol.* 175: 113-117, 1953.
11. Sawyer, P. N.; Harshaw, D. H., and Wesolowski, S. A.: Possible metabolic factors in maintenance of blood intimal interface of blood vessels. *Tr. Am. Soc. Artif. Int. Organs.* 8: 19-22, 1962.
12. Sawyer, P. N.; Suckling, E. E., and Wesolowski, S. A.: Effect of small electric currents on intravascular thrombosis in visualized rat mesentery. *Am. J. Physiol.* 198: 1006-1010, 1960.
13. Sawyer, P. N., and Wesolowski, S. A.: Electric current of injured tissue and vascular occlusion. *Ann. Surg.* 153: 34-42, 1961.
14. Bradham, R. R.: Propagation of induced venous thrombi. *Surg. Gynec. & Obst.* 113: 324-328, 1961.
15. Williams, R. D., and Carey, L. C.: Studies in production of "standard" venous thrombosis. *Ann. Surg.* 149: 381-387, 1959.
16. Sawyer, P. N.; Denis, C., and Wesolowski, S. A.: Electrical hemostasis in uncontrollable bleeding states. *Ann. Surg.* 154: 556-562, 1961.
17. Sawyer, P. N., and Deutch, B.: Use of electrical currents to delay intravascular thrombosis in experimental animals. *Am. J. Physiol.* 187: 473-478, 1956.
18. Schwartz, S. I.: Prevention and production of thrombosis by alterations in electric environment. *Surg. Gynec. & Obst.* 108: 533-536, 1959.
19. Sawyer, P. N., and Pate, J. W.: Bio-electric phenomena as etiologic agent in intravascular thrombosis. *Am. J. Physiol.* 175: 103-107, 1953.
20. Schwartz, S. I., and Richardson, J. W.: Prevention of thrombosis with use of negative electric current. *S. Forum* 12: 46-48, 1961.
21. Engler, H. S.; Christopher, P. E.; Williams, H. G.; Spears, R. S., and Moretz, W. H.: Prevention of thrombus formation in small-artery anastomoses. *A.M.A. Arch. Surg.* 78: 766-772; discussion, 772-773, 1959.

22. Sawyer, P. N., and Valmont, I.: Evidence of active ion transport across large canine blood vessel walls. *Nature* **189**: 470-472, 1961.
23. Sawyer, P. N.; Valmont, I., and Harshaw, D. W.: Effect of anoxia on ion transport across blood vessel walls. *S. Forum* **11**: 167-169, 1960.
24. Sawyer, P. N.; Levine, J.; Mazlen, R., and Valmont, I.: Active ion transport across canine blood vessel walls. *J. Gen. Physiol.* **45**: 181-196, 1961.
25. Wolfson, M. L., and Rice, F. A. H.: Electrophoretic resolution of heparin and related polysaccharides. *J. Am. Chem. Soc.* **69**: 2918-2919, 1947.
26. Moses, C.: Effect of heparin and dicoumarol on thrombosis induced in presence of venous stasis. *Proc. Soc. Exper. Biol. & Med.* **59**: 25-27, 1945.
27. Abramson, H. A.; Moyer, L. S., and Gorin, M. H.: Electrophoresis of Proteins and the Chemistry of Cell Surfaces. New York: Reinhold, 1942, 341 p.; p. 307-319.
28. Abramson, H. A., and Moyer, L. S.: Electrical charge of mammalian red blood cells. *J. Gen. Physiol.* **19**: 601-607, 1936.
29. Davies, D. F.: Electrophoretic mobility of erythrocytes as measure of surface activity of plasma from patients with and without evidence of atheroma. *Clin. Sc.* **17**: 563-573, 1958.
30. Abramson, H. A.: Mechanism of inflammatory process; electrophoresis of blood cells of horse and its relation to leukocyte emigration. *J. Exper. Med.* **46**: 987-1002, 1927.
31. Abramson, H. A.: Possible relationship between current of injury and white-blood cells in inflammation. *Am. J. M. Sc.* **167**: 702-710, 1924.
32. Lozner, E. L.; Taylor, F. H. L., and MacDonald, H.: Effect of foreign surfaces on blood coagulation. *J. Clin. Invest.* **21**: 241-245, 1942.
33. Margolis, J.: Initiation of blood coagulation by glass and related surfaces. *J. Physiol.* **137**: 95-109, 1957.
34. Lüscher, E. F.: Retraction activity of platelets: biochemical background and physiological significance, p. 445-453, *in* Johnson, S. A., and others, editors: Henry Ford Hospital International Symposium; Blood Platelets. Boston: Little, Brown and Co., 1961, 732 p.
35. Schmitz, E. J.; Kanar, E. A.; Sauvage, L. R.; Storer, E. H., and Harkins, H. N.: Influence of diameter disproportion and of length on incidence of complications in autogenous venous grafts in abdominal aorta. *Surgery* **33**: 190-205, 1953.
36. Wesolowski, S. A.; Sauvage, L. R.; Pinc, R. S., and Fries, C. C.: Dynamics of blood flow in graft disproportions and in normal blood vessels. *S. Forum* **6**: 227-233, 1955.
37. Texon, M.: Hemodynamic concept of atherosclerosis. *Bull. New York Acad. Med.* **36**: 263-274, 1960.
38. Wesolowski, S. A.; Fries, C. C., and Sawyer, P. N.: Production and significance of turbulence in hemic systems. *Tr. Am. Soc. Artif. Int. Org.* **8**: 11-18, 1962.
39. Moolten, S. E.; Vroman, L.; Vroman, G. M. S., and Goodman, B.: Role of blood platelets in thromboembolism. *Arch. Int. Med.* **84**: 667-710, 1949.
40. Silberberg, M.: Causes and mechanism of thrombosis. *Physiol. Rev.* **18**: 197-228, 1938.
41. Rose, J. C., and Broida, H. P.: Effects of plastic and steel surfaces on clotting time of human blood. *Proc. Soc. Exper. Biol. & Med.* **86**: 384-386, 1954.
42. Dreyer, B.; Akutsu, T., and Kolff, W. J.: Aortic grafts of polyurethane in dogs. *J. Appl. Physiol.* **15**: 18-22, 1960.
43. Hufnagel, C. A.: Use of rigid and flexible plastic prostheses for arterial replacement. *Surgery* **37**: 165-174, 1955.

44. Donovan, T. J., and Zimmermann, B.: Effect of artificial surfaces on blood coagulability, with special reference to polyethylene. *Blood* 4: 1310-1316, 1949.
45. Hirschboeck, J. S.: Delayed blood coagulation in methyl metacrylate (boilable "lucite") vessels. *Proc. Soc. Exper. Biol. & Med.* 47: 311-312, 1941.
46. Hirschboeck, J. S.: Delayed blood coagulation and absence of clot retraction in collodion lined vessels. *Proc. Soc. Exper. Biol. & Med.* 45: 122-124, 1940.
47. Ross, J., Jr.; Greenfield, L. J.; Bowman, R. L., and Morrow, A. G.: The chemical structure and surface properties of certain synthetic polymers and their relationship to thrombosis, p. 212-223, *in* Meredino, K. A.: *Prosthetic Valves for Cardiac Surgery*. Springfield, Illinois: Thomas Publ., 1961, 586 p.
48. Gortner, R. A., and Briggs, D. R.: Glass surfaces versus paraffin surfaces in blood-clotting phenomena; hypothesis. *Proc. Soc. Exper. Biol. & Med.* 25: 820-821, 1928.
49. Hubbard, D., and Lucas, G. L.: Ionic charges of glass surfaces and other materials, and their possible role in coagulation of blood. *J. Appl. Physiol.* 15: 265-270, 1960.
50. Tocantins, L. M.: Influence of contacting surface on coagulability and anticephalin activity or normal and hemophilic plasmas. *Am. J. Physiol.* 143: 67-76, 1945.
51. Lary, B. G.; Meine, E. L., Jr., and de Takats, G.: Experimental use of steel mesh tubes for replacement of arterial segments. *A.M.A. Arch. Surg.* 72: 69-75, 1956.
52. Mirkovitch, V.; Akutsu, T., and Kolff, W. J.: Polyurethane aortas in dogs. Three-year results. *Tr. Am. Soc. Artif. Int. Org.* 8: 79-84, 1962.
53. Schumacker, H. B., Jr.; Harris, E. J., and Siderys, H.: Pliable plastic tubes as aortic substitutes. *Surgery* 37: 80-93, 1955.
54. Voorhees, A. B., Jr.; Jaretzki, A., III, and Blakemore, A. H.: Use of tubes constructed from Vinyon "N" cloth in bridging arterial defects, preliminary report. *Ann. Surg.* 135: 332-336, 1952.
55. Cohn, R.: Platelet capturing effect of surgical procedures of aorta. *West. J. Surg.* 69: 356-357, 1961.
56. Mirkovitch, V.; Akutsu, T., and Kolff, W. J.: Intracardiac thrombosis on plastics in relation to construction of artificial valves. *J. Appl. Physiol.* 16: 381-384, 1961.
57. Seidel, W.; Akutsu, T.; Mirkovitch, V., and Kolff, W. J.: Mitral valve prosthesis and study of thrombosis on heart valves in dogs. *J. S. Res.* 2: 168-175, 1962.
58. Starr, A., and Edwards, M. L.: Mitral replacement: shielded ball valve prosthesis. *J. Thoracic & Cardiovas. Surg.* 42: 673-682, 1961.
59. Gott, V. L.; Koepke, D. E.; Daggett, R. L.; Zarnstorff, W. C., and Young, W. P.: Coating of intravascular plastic prostheses with colloidal graphite. *Surgery* 50: 382-389, 1961.
60. Sadd, J. R.; Koepke, D. E.; Daggett, R. L.; Zarnstorff, W. C.; Young, W. P., and Gott, V. L.: Relative ability of different conductive surfaces to repel clot formation on intravascular prostheses. *S. Forum* 12: 252-254, 1961.
61. Mirkovitch, V.; and Akutsu, T.: Intracardiac thrombosis on implants of graphite cloth and gold-plated polyurethane. *J. S. Res.*: In press.
62. Glasstone, S., and Lewis, D.: *The Elements of Physical Chemistry*. Princeton, New Jersey: D. Van Nostrand Co., Inc., 1958, 695 p.; p. 566-569.
63. Horan, F. E.; Hirsch, F. G.; Wood, L. A., and Wright, I. S.: Surface effects on blood-clotting components as determined by zeta-potentials. *J. Clin. Invest.* 29: 202-211, 1950.
64. Beck, R. E.; Mirkovitch, V.; Andrus, P. G., and Leininger, R. I.: Apparatus for determination of zeta potentials from streaming potentials. *J. Appl. Physiol.*: In press.