Nonthrombogenic Surfaces: Critical Review

By Edwin W. Salzman

THROMBOSIS IS PREEMINENT among the problems that complicate development of artificial organs. In areas of rapid blood flow, such as the cage of an artificial heart valve or in arterial grafts, the primary difficulty is platelet thrombosis and embolism and, if the surface area is sufficient, thrombocytopenia. In areas where stagnation of blood occurs, as around the sewing ring of a valve or in the reservoir of a pump-oxygenator, the problem is a red fibrin clot.

Although recent years have seen a dramatic expansion of knowledge of plasma coagulation and of platelet aggregation, the physical chemistry of the activation of clotting and the adhesion of platelets to a surface is not well understood. The selection of materials for construction of artificial devices in contact with the blood has therefore been frankly empirical or, when related to theory, has been based on unproved hypotheses.

The degree of blood compatibility that present-day artificial surfaces enjoy is due largely to advances in areas other than surface chemistry, such as fluid mechanics,* and to the use of anticoagulants. For example, implantation of artificial heart valves is a practical clinical procedure, even though the materials these valves are made of are not passive when tested by specific tests for activation of coagulation and platelet alteration in vitro. Their success results in large part from skillful engineering and design, which ensure washing of surfaces by flowing blood and avoid areas of disturbed flow such as stagnation points or recirculating eddies that otherwise might allow buildup of thrombus. Activated clotting factors and altered platelets are swept downstream to be dealt with by natural defenses, and since the surface area of the valve is small, hemostatic elements are not depleted and the economy of the body is not appreciably altered. Subtle changes can be registered, however, from such small areas of blood/surface contact as a heart valve: the survival of platelets is abnormally short in patients bearing artificial heart valves.5,4 If the area of surface contact is large, gross changes may occur. Thrombocytopenia is a regular consequence of extracorporeal cardiopulmonary bypass, although consumption of plasma clotting factors is inhibited by the administration of heparin during the period of artificial circulation.

Supported by National Heart and Lung Institute Grant HE-11127 and Program Project Grant HE-11414.

Edwin W. Salzman, M.D.: Associate Director of the Surgical Service, Beth Israel Hospital, Boston, Mass.; Associate Professor of Surgery, Harvard Medical School, Boston, Mass.; Senior Research Associate, Massachusetts Institute of Technology, Boston, Mass.; Scholar of the John and Mary Markle Foundation.

*The contribution of fluid dynamics to thrombosis and its prevention is treated in detail in several recent reviews.1,2
Other measures to increase the body’s tolerance to nonbiologic materials include the use of agents affecting platelet aggregation, as for example administration of dextran to prevent thrombocytopenia during mechanical circulatory assistance with an intraaortic balloon.\(^5\) Natural processes may also be exploited to achieve long-term blood/surface compatibility. The success of porous or velour-covered vascular grafts and valves lies in their ability to become coated with adherent thrombus, which eventually organizes, and thus to become totally invested in autogenous tissue.\(^6\) Such materials make no pretense of thrombus resistance but are instead designed to acquire a coating layer of well-anchored thrombus, too thin to narrow significantly the lumen of the prosthetic device and too tightly attached to allow embolization. It is possible that conversion to an autogenous cellular lining may be accelerated by preliminary implantation of living fibroblasts or endothelial cells in culture.\(^7\)

**Surface-Induced Thrombosis**

Before reviewing the progress in development of nonthrombogenic materials, one should consider what under normal circumstances maintains the fluidity of blood. Freedom from thrombosis depends only in part on the failure of normal vascular endothelium to activate procoagulant plasma proteins or to induce adhesion and subsequent aggregation of platelets. Natural plasma antithrombins and other inhibitors of coagulation probably contribute, and it is certain that other influences also play a role. In the intact circulation, activated procoagulants are diluted and washed away, altered platelets are dispersed, and the propagation of local thrombotic events is checked by blood flow. In addition, tissue clearance mechanisms in the liver and perhaps other organs appear to provide an important natural defense.

The observation that nonbiologic surfaces induce the blood to clot is not a recent one. Two hundred years ago William Hewson\(^1\) reported that blood within an isolated venous segment remained fluid for hours but quickly coagulated if poured out into a bowl. Lister\(^2\) observed that blood clotted more slowly in a rubber tube than in glass, and Bordet and Gengo&\(^3\) concluded that paraffin was still less clot-promoting. Subsequent workers, too numerous to cite, examined the behavior of blood in contact with other materials. As understanding of the biochemistry of coagulation eventually unfolded, it came to be accepted that blood contains within itself the complete capacity to form a clot, when stimulated to set off the process by contact with an appropriate surface. Upon rereading Hewson’s classic account,\(^4\) one is struck by his observation that even under the most gentle conditions the blood did not remain fluid forever. In isolated venous segments, lined presumably by normal endothelium, small clots were visible within an hour, and a solid cast of the vessel was regularly observed within 2–8 hr. The significance of this finding will be considered below.

The description by Ratnoff and his associates\(^5\) of Hageman factor (factor XII) and its identification as a plasma constituent involved in the initial surface/blood interaction have profoundly influenced the development of artificial materials for contact with blood, it being widely assumed that failure
to activate factor XII is a sine qua non for success as a nonthrombogenic surface.

Activation of factor XII by surface contact presumably involves a major change in the structure of the molecule: a measurable alteration in its sedimentation characteristics has been recorded. Inquiries into the chemistry of materials able to activate factor XII have raised hopes for a sound theoretical basis for fabrication of inert surfaces; e.g., identification of the chemical radicals necessary for activation of factor XII by collagen and demonstration of the activating potency of certain soluble derivatives of tannic acid. Unfortunately, such sophisticated investigations are not numerous. More often, in vitro experiments have been limited to the whole blood clotting time in tubes lined with the materials to be assessed. Such a judgment is patently inadequate for characterization of the behavior of a surface toward coagulation, let alone for prediction of its tendency to induce thrombosis in vivo. In dealing with polymers, the opportunities for artifactual prolongation of the clotting time are frequent, as will be shown. More important, coagulation is only one component of thrombosis, and in vitro studies have tended to ignore the problem of platelet adhesion and aggregation.

Adhesion to foreign surfaces was appreciated as a fundamental property of platelets almost as soon as they were recognized in blood, and adherence to subendothelial tissues is regarded as a basic feature of hemostasis. Much is known of the reactions that follow adhesion of platelets to collagen and other subendothelial tissues: the release of platelet constituents and the subsequent aggregation of platelets into a hemostatic plug or thrombus. Several comprehensive reviews of these phenomena are available.

Of the initial adhesion step, however, little is understood. Sticking of platelets to a foreign surface does not seem entirely equivalent to sticking to other platelets. It is appreciated that divalent cations are required for adhesion of platelets to glass and other nonbiological tissues as well as for subsequent platelet aggregation, but not for adhesion to collagen, which can however be inhibited by structural alterations in the collagen molecule. Adhesion of platelets to a surface appears to involve a protein intermediate. Fibrinogen is known to be active in this respect, but albumin is reported to be without effect in platelet adhesion and, in fact, has been employed as a thromboresistant precoating to inhibit the subsequent adherence of platelets. Early interactions of protein with the surface may account for the period of "conditioning" that has been described before adherence of platelets is demonstrable in an ex vivo flow chamber.

The contribution of surface effects to hemostatic processes and thrombosis has been surveyed in detail in several recent reviews.

Assessment of Nonthrombogenic Surfaces

Characterization of the propensity of a material to induce thrombosis is not a simple problem, and there is little agreement concerning the most appropriate methods of evaluation. Assessment of the patency of prosthetic tubes implanted as intravascular conduits and measurement of the rate of deposition of thrombotic material on a test surface exposed to blood have
obvious relevance to real life, but such in vivo models may be difficult to interpret in terms of detailed mechanisms and are subject to large experimental errors. The ex vivo flow chamber, which provides for microscopic inspection of the developing thrombus,\textsuperscript{23,41,51-53} has some of the same shortcomings and the added criticism that its use is generally restricted to short-term experiments. Despite these limitations, however, and regardless of thrombosis at sites of endothelial abrasion adjacent to these devices that may confound the observations, satisfactory performance in such systems would seem to be a minimum criterion for resistance to thrombosis. In vivo implantation of prosthetic devices also permits one to assess the effects on the organism of chronic exposure to the test material. Measurement of platelet count and assay of specific coagulation factors may provide evidence of consumption of hemostatic elements. Recognition of circulating fibrin monomer and fibrinogen digestion products may also furnish a clue to remote thrombotic events induced by surface contact. Development of sensitive new techniques for this purpose is a subject of current interest in several laboratories.\textsuperscript{54-56} Determination of rate of hemolysis, inspection of red cell morphology, and examination of other blood components afford additional insight.

Valuable information is also to be obtained from studies in vitro, although most in vitro tests were originally designed to reveal defects in hemostasis rather than to recognize induction of activity in hemostatic processes. One cannot understand the mode of action of thrombus-resistant surfaces without assessment in detail of the interaction of materials with plasma clotting factors and with platelets. Activation of factor XII is known to be induced by surface contact under physiologic conditions;\textsuperscript{57} acceleration of the interaction of factors IX and VIII and of factors X and V by altered platelets is also thought to reflect a surface-mediated effect of platelet phospholipids (platelet factor 3).\textsuperscript{24,58} These are the only aspects of the intrinsic coagulation system for which surface effects have been shown to be significant. The former may be tested by demonstration of the ability of surface-contacted plasma to shorten the clotting time of plasma congenitally deficient in factor XII or exhausted of this factor by saturation with celite.\textsuperscript{59} Indirect effects of factor XII activation such as plasma esterase activity or other expressions of the kallekrein system\textsuperscript{50,61} are also subject to experimental assessment. Without such investigation of the influence of surfaces on factor XII, a material cannot be regarded as inert to coagulation. Prolongation of the whole blood clotting time in tubes of the test material is inconclusive in this regard, since adsorption or denaturation of plasma proteins or transfer of an anticoagulant from the surface into the blood also can delay coagulation. By the same token, one cannot expect infinite extension of the whole blood clotting time even in the presence of a passive surface: Air contact is sufficient to trigger coagulation after awhile.\textsuperscript{62} Furthermore, even in Hewson's experiment,\textsuperscript{19} the blood did not stay fluid forever but eventually clotted in an isolated venous segment when deprived of the protective effects of flow and access to natural filtration mechanisms dependent on an intact circulation. (A theoretical treatment of the intrinsic tendency of the blood to clot, attributed to the presence of active procoagulants in the blood under normal circumstances, has been developed by Waugh.\textsuperscript{53,61})
A clotting time much longer than an hour should raise the suspicion of an artifactual delay in coagulation at some step beyond contact activation.

The crucial aspects of platelet function to be examined include adhesion to the test surface, secretion of platelet constituents into the plasma as a consequence of adhesion (the release reaction of platelets), activation of the clot-promoting activity of platelets (platelet factor 3), a feature of the release reaction, and platelet aggregation, which when induced by surface contact is thought to result from the interaction of platelets with the products of the release reaction.

In recent studies by Friedman and co-workers, platelet adhesion in an ex vivo flow chamber occurred on the surface of all materials tested and appeared virtually unaffected by differences in the composition of the substrate surface. It is possible that a feature of platelet/surface interaction more critical than adhesion of platelets is the subsequent induction of the "release reaction" of platelet constituents and resultant platelet aggregation. This might be influenced by the composition of the protein layer that initially coats the surface. There can be no doubt that in many test systems designed to assess platelet "adhesiveness" in vitro, the majority of platelets concerned are involved in aggregation with other platelets rather than in sticking to the nonplatelet test surface. Such tests can be useful for evaluation of surfaces but reflect aggregation as well as adhesion to the surface unless platelet clumping is deliberately prevented by elimination of the divalent cations required for platelet aggregation. Since adhesion to many surfaces also demands divalent cations, the distinction between primary platelet/surface interaction (adhesion) and secondary effects may be difficult even by this technique. The release reaction can be evaluated by examination of plasma for platelet constituents (nucleotides, serotonin, various enzymes, antiheparin activity (platelet factor 4) and released potassium and calcium) and of platelets for clot-promoting activity (platelet factor 3).

Although in vitro studies are economical and versatile, and their vagaries are more completely understood than are in vivo processes, their relevance to the in vivo state cannot be assumed and must be proved in each instance. The tests listed above would seem a reasonable minimum, but they may not prove sufficient in practice to predict the compatibility of a surface with blood for periods of months or years. The molecular events that induce thrombosis on a surface are probably not frequent if the surface is even moderately thrombus-resistant. To recognize such subtle occurrences with techniques available at present may be impossible except in the case of materials doomed to rapid failure in contact with the blood.

**Explorations and Developments**

Development of nonthrombogenic materials has for the most part been empirical or based on theoretical considerations of unproven relevance, for the features of a surface that dictate its compatibility with blood are not established. Innumerable materials have been examined, but attempts to systematize the experimental data have not been entirely successful. An example of a recent study in which in-depth assessment of the effect of a large number
of polymers on the blood could not be correlated with the chemistry of the materials is that of Mason et al. The most comprehensive recent treatment of the physical chemistry of the problem is that of Baier, Shafrin, and Zisman. In this work and in a subsequent publication, the authors develop the thesis that adhesion of a liquid to a solid is a function of the energy of interaction of the molecular species arrayed at the surface of the solid, and that a value for this function can be derived from measurements of the contact angle of a liquid drop resting on the plane solid surface. An analogous hypothesis has been developed by Lyman and associates, who have calculated surface free energy from such measurements. Lyman has postulated that the less the surface free energy, the less is the absorptivity of a surface and the less likely are significant changes in the configuration of adsorbed protein molecules. As a corollary, the less likely would be activation of coagulation and induction of platelet alterations. Considerations of critical surface tension and surface free energy have influenced Lyman and others to develop a variety of hydrophobic polymers, and in practice many of these have proved to retard coagulation and minimize platelet adhesion, at least during short periods of observation.

Such an approach has historic antecedents. Following the work of Lister and Bordet and Gengou, subsequent workers attempted to generalize to a hierarchy of materials classified on the basis of water wettability, the more hydrophilic (e.g., glass) being active in induction of coagulation and the more hydrophobic (e.g., paraffin) being more inert. Later investigators have challenged this scheme on theoretical grounds and because of the failure of certain materials (e.g., celluloid and nylon) to fit into such a pattern, and the issue must be regarded as unsettled. In many early reports, insufficient attention was paid to the complicating effects of protein denaturation at an air-blood interface, and in some studies less than adequate care was taken in selection of homogeneous materials and preparation of scrupulously clean surfaces. Reading these publications today, one is dismayed by a welter of contradictory data. The controversy over the alleged wettability of natural endothelium is illustrative of the problem. Several authors have concluded that the endothelial lining of vessels is water-wettable, but since the estimate is generally made by observing the meniscus after introduction of an air bubble into a living vessel, the issue is of necessity confused by the film of denatured protein that forms at an air blood interface. The problem is further confused by the ability of proteins to bind to hydrophobic surfaces by virtue of lipophilic sites contributed by their apolar groups, and changes in tertiary structure as a result of such attachments would not be surprising. For example, hydrophobic silicone rubber membranes become water-wettable after a brief contact with blood, presumably by adsorption of plasma proteins. Hydrophobic protein/surface bonding may account for the unfavorable characteristics of extreme low-energy surfaces noted by Baier and Dutton. The question of protein interaction with surfaces of high and low energy has been reviewed by Vroman.

In any event, no synthetic material selected on the basis of such considerations has yet achieved permanent blood compatibility in vivo regardless of its
apparently favorable physical surface characteristics. As previously stated, one must question the prospects of prediction of thromboresistance on the basis of gross average physical features, considering the infrequency of the molecular events that may lead gradually to thrombosis after months or years in contact with the blood. Perhaps assessment of surface chemistry may be sufficient to label a material as incompatible with the blood; it is not likely that present-day technology is adequate to establish in advance that a surface is compatible.

Although recent studies have revived earlier concerns about water wettability, the development of strongly hydrophilic gels has cast doubt on the relevance of this characteristic. Several workers have reported preliminary observations on such gels, whose surface is largely water, and extended compatibility with blood has been claimed. Detailed data are limited. The explanation for these apparently paradoxical observations remains to be provided but probably will be found in the specific effects of these materials on the molecular configuration of the plasma constituents that adsorb onto them.

Two other lines of thought have led to materials that have reached clinical trial: surfaces bearing a fixed negative charge and heparin-coated surfaces. In both instances, there is discordance of theory and practice, and the original basis for adoption of these approaches appears to have been based on faulty theory and on data obtained from in vitro experiments of doubtful relevance. These concepts will be reviewed in detail, since they have been widely exploited and have had a germinal effect, and much can be learned from consideration of the experience with them.

In 1953, Sawyer and Pate observed that an electrical potential between electrodes straddling a blood vessel led to thrombosis adjacent to the positive electrode. In a series of reports from Sawyer’s laboratory, a “current of injury” was described at sites of vascular trauma with reversal of the normal negative endothelial surface charge. The relation of transmural potential to streaming potential (or the calculated expression, “zeta potential”) was considered, and it was suggested that endothelium owes its blood compatibility to its negative charge and that thrombosis in vivo results from development of a local positive charge that fails to repel blood elements. These hypotheses proved difficult to reconcile with the observation that all living cells and plasma proteins maintain a net negative surface charge at physiological pH, but only platelets and coagulation factors are involved in thrombosis. Furthermore, it was found that the clot promoting nature of various polymers and other materials was not well correlated with their surface charge, e.g., untreated and siliconized glass each develop a negative streaming potential in relation to flowing blood. In addition, there is evidence that surfaces able to activate factor XII and set off coagulation are negatively charged, that exposure of vessels to a transmural potential of the magnitude employed in Sawyer’s experiments produces denudation of endothelium, that exposure to positively charged or cationic molecules inhibits the activation of the intrinsic clotting system, and that platelets adhere to both negatively charged and positive surfaces. Further confusion has arisen in the literature from failure to distinguish between materials bearing anionic groups at the surface,
such as polyelectrolytes; metallic cathodes; polymers that contain no exposed polar groups but develop a negative zeta potential, e.g., polyethylene; and materials with fixed internal polarization and a negative charge buried within the material but near the surface.

Information obtained by assessment of average total surface charge appears to be insufficient to describe the possible electrochemical interactions of a surface with contiguous molecules. One requires information concerning charge distribution and the nature and physical state of adsorbed molecular species, and the net (average) surface charge as deduced from classical electrokinetic experiments is too crude an index for such an assessment. Nonetheless, selection of materials on the basis of gross surface charge has not been without success. Apposition of a cathode to a site of vascular trauma has been shown to prevent thrombosis and to protect anastomoses of small blood vessels against occlusion. Sawyer has correlated the position of metals in the electromotive series with their tendency to induce thrombosis, the more negative being less thrombogenic; interpretation of these data is difficult because of the possible presence of metallic oxide films with electrochemical properties independent of the base metal. An internal negative charge protected from neutralization in contact with a conductive fluid such as blood can be induced on dielectric polymers by heating and cooling them in a strong electric field, the so-called electret phenomenon. A fixed negative surface charge can also be achieved by other techniques. Such materials adsorb fewer platelets than neutral or positive surfaces and in preliminary experiments have been well tolerated in vivo. Thus, although a negative surface charge at the interface between blood and solid has not been established as relevant to natural processes, it may be found empirically to be effective for prevention of thrombosis on an artificial material, possibly by electrostatic repulsion of cellular and protein elements or by leading to the adsorption of protein species unfavorable to the genesis of a thrombus.

The situation in regard to heparinized surfaces is somewhat analogous. The fundamental observations are those of Gott and associates, who first showed that graphite was thromboresistant. This report has been confirmed in detailed studies and has recently been extended in the development of an interesting new thromboresistant material, pyrolytic carbon. The mechanism of action of colloidal graphite and pyrolytic carbon has not been established. Gott, Whiffen, and Dutton found that inhibition of blood coagulation on a negatively charged graphite surface could be enhanced by adsorption of a cationic detergent followed by ionic bonding of heparin. This graphite-benzalkonium-heparin (GBH) material has been employed in venous grafts, in artificial heart valves, and in subclavian to femoral artery shunts during resection of thoracic aortic aneurysms. Other heparin-coated materials have also been developed, produced for the most part by ionic bonding of heparin to quaternary amines or other cationic groups and also by milling heparin into a polymer base during its fabrication. Long-term tolerance has been erratic, but considerable freedom from thrombosis has been enjoyed for hours to days.

The mode of action of heparinized surfaces has been disputed. Some work-
ers have speculated that endothelium owes its compatibility with blood to a lining of heparin, but evidence to support this imaginative concept is lacking. Although isolation of mucopolysaccharides with weak anticoagulant activity from homogenates of vessel walls has been reported, localization at the endothelial surface remains to be proved. Present evidence suggests that heparin is confined to adventitial mast cells. When dissolved in blood, heparin does not block the activation of factor XII and, unless it is in very high concentrations, does not inhibit the adhesion or aggregation of platelets, except that induced by thrombin.

There is thus no reason a priori why heparinized surfaces should be nonthrombogenic. Furthermore, when ionically bonded to a substrate, heparin gradually leaches into the blood as plasma proteins replace it by ion exchange. A microatmosphere of heparin in solution may thus exist in relation to such heparin-coated surfaces and foil any attempt to establish the effect of the surface-bound heparin, which could simply serve as a heparin reservoir.

Such considerations embarrassed the interpretation of the antithrombotic effects of heparinized surfaces until recently, when development of materials with heparin covalently bonded to the surface showed them to be clot-inhibiting in vitro and free of fibrin in vivo even without desorption of heparin. Above a threshold concentration, the heparin content of these materials does not correlate with their antithrombotic effects, suggesting that the crucial feature is a complete surface coat. Sensitive clotting tests and studies with radioactive heparin have shown the heparin to be tightly bound to such surfaces, whose behavior does not depend on leaching of heparin into the blood. Heparinized surfaces appear to owe many of their properties to an adsorbed coat of protein and perhaps other plasma constituents. Like heparin in solution, surface-bound heparin has been found to complex with plasma proteins including thrombin and other clotting factors. Recent evidence suggests that dissolved heparin may under some circumstances activate Factor XII, but the adsorption of plasma proteins to surface-bound heparin apparently occurs without activation of coagulation. Clotting tests employing factor XII-deficient plasma and assessment of plasma esterase activity indicate that heparinized surfaces fail to activate factor XII, a feature that may be vital to their compatibility with blood.

Despite their favorable behavior in respect to plasma coagulation, present-day heparinized materials are not totally nonthrombogenic. Animals whose blood is circulated past a large heparinized surface become thrombocytopenic, and electron microscopy demonstrates residual platelet thrombi on heparin-coated materials. The situation is analogous with that of heparin in solution. Association of the molecule with platelets has been demonstrated in platelet-rich plasma and it is not surprising that platelets also interact with surface-bound heparin. There is evidence that adhesion of platelets to surfaces requires a protein cofactor, which may be fibrinogen, and heparinized surfaces are no exception. Fibrinogen is known to operate also as a cofactor in platelet aggregation induced by ADP. Preincubation of heparin-coated materials in solutions of albumin inhibits platelet adsorption, perhaps by competition with fibrinogen for surface-binding sites. Exposure of platelets...
to a solution of labeled fibrinogen has been shown to lead rapidly to association of fibrinogen with the platelets; platelet incorporation of albumin did not occur in these experiments.\textsuperscript{134}

The nature and physical state of adsorbed plasma elements probably dictate the behavior of surfaces toward platelets in vivo as well as in vitro. When implanted as intravascular conduits, heparinized materials promptly become platelet-covered, but, with time, the platelet layer disappears, and the surface coat that is left behind appears repellant to other cells; it remains free of thrombus for days or months thereafter, even in such low-shear areas as the infrarenal inferior vena cava.\textsuperscript{40} Identification of this coating layer may provide a means to overcome the initial interaction of heparinized surfaces with platelets, which at present casts a shadow on their favorable behavior toward blood coagulation.

Many fundamental issues remain unresolved: What is the nature of the critical events that occur at a blood-solid interface? Can these be adequately recognized and described by present-day technology? An unsatisfactory surface can often be identified in advance, but what conditions must be satisfied for a material to be nonthrombogenic?

How can one best appraise the thromboresistance of a material? What modes of evaluation are appropriate for prediction of clinical utility, for analysis of mechanisms of action, and to serve as a basis for development of improved devices?

What is the long-term fate of artificial materials in the body and particularly of their interface with blood? Will molecular imperfections lead ultimately to failure in a system without the capacity of biological tissues for self-renewal and repair?

What degree of blood compatibility should one seek in different clinical applications? Is thrombosis at the junction of a vessel with a prosthetic device inevitable despite a totally bland synthetic surface? Can a truly passive material, whose eventual development can be expected, provide perpetual freedom from thrombosis or must active inhibition of coagulation and platelet interaction be provided? A passive material can be no more than inert, and if events in the bulk fluid phase or at a traumatized intimal surface are sufficient to induce changes in plasma proteins or platelets, access to tissue clearance mechanisms and to the cleansing effects of fluid shear and perhaps even pharmacologic inhibition of hemostatic processes may prove indispensable. Further advances in this difficult field await the answers to such questions.

Jamieson et al. (An enzymatic basis for platelet:collagen adhesion. Proceedings, Second Congress of International Society for Thrombosis, Oslo, 1971, p. 220) have recently provided evidence that adhesion of platelets to collagen involves enzyme-substrate interaction between collagen:glucose transferase in platelet membrane and exposed carboxyl groups of collagen.

Acknowledgment

Dr. Frank Hastings kindly made available the Proceedings of the Artificial Heart Conference in a prepublication form. Helpful conversations with Dr. Daniel Deykin, Professor David Waugh, and Professor Edward Merrill are gratefully acknowledged.
Nonthrombogenic Surfaces

REFERENCES


5. Petschek, H.: Personal communication.


84. —, and —: Electric potential difference across the normal aorta and aortic


Nonthrombogenic Surfaces

523


121. von Berlepsch, K.: Personal communication.


Nonthrombogenic Surfaces: Critical Review

EDWIN W. SALZMAN