CURRENT PROBLEMS IN SURGERY

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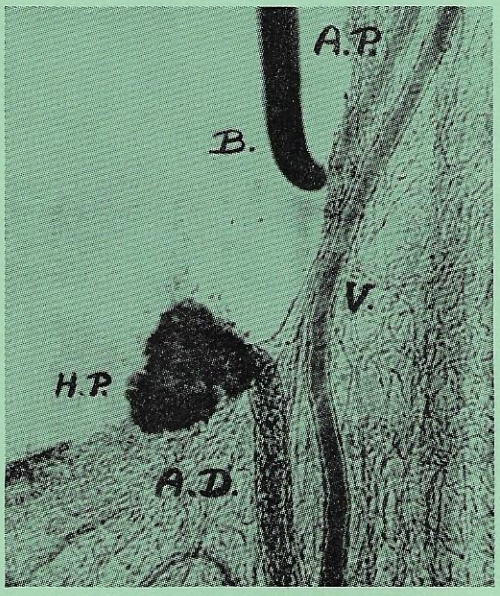
HEMOSTASIS and the SURGICAL PATIENT

Henry Gans



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HEMOSTASIS AND THE SURGICAL PATIENT—*Henry Gans*

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Hemostasis and the Surgical Patient

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Plus ça change,
plus c'est la même chose.
MONTAIGNE

PART I

A NORMAL HEMOSTATIC MECHANISM is required for successful surgery. Although ligatures can control hemorrhage from major vessels, only physiological hemostasis can check bleeding from smaller vessels and the capillary bed. Hence the preservation of vascular integrity and blood fluidity, designated as the hemostatic function, is of major surgical concern. Without a delicately controlled hemostatic mechanism, blood could not carry out its functions of transport, heat regulation and defense against disease, for it would leak from the vessels (hemorrhage) or solidify (intravascular coagulation or thrombosis). Either condition is incompatible with life.

With the advent of technologic adjuncts to surgery, notably the heart-lung machine, the introduction of massive blood replacement, the more extensive surgical procedures and currently the transplantation of organs, it became apparent that the changes induced in blood may become so extensive as to interfere with some of its functions, particularly hemostasis. It therefore became necessary to re-evaluate this function of blood and to determine how these changes could be prevented or minimized.

In surgery, as in other branches of the medical sciences, the progress of knowledge is rapidly outstripping the power of the human mind to assimilate and view it as a whole. Nevertheless, conceptual models must be created in the light of present knowledge, despite its rapid expansion. The fact that current understanding may need re-evaluation more frequently than ever before should not deter the laying of foundations for models that can be retained and supplemented as part of an expanding and more fruitful conception.

This presentation will review the available information on normal hemostasis, evaluate the conditions that interfere with this mechanism, particularly during and after operation, and summarize the advances made in detecting and managing a number of hemostatic defects that occur in the surgical patient.

NORMAL HEMOSTASIS

The requirements for normal hemostasis include an adequate number of functional platelets, a normal coagulation mechanism, normal blood flow and an intact vascular system. The first part of this discussion will summarize pertinent information concerning the vascular wall, the blood platelets and the coagulation mechanism, as it relates to the subject under discussion.

The Vascular Wall

The inner surface of blood vessels that is exposed to blood consists of the endothelial cells and the intercellular functional layer (1). The latter is variably designated as ground substance or intercellular cement (Fig. 1). The endothelial cells are very thin and polygonal in shape. They are not fixed, and freely undergo changes in size and position. They form a smooth semipermeable surface for the exchange of materials between blood and tissue. They are continuously renewed by mitosis and in a very short time cover implanted vascular prostheses. Little is known about the relationship of structure and function of this important layer that is inert to blood and its formed elements as long as its integrity is preserved. This surface, which is thought to carry a negative charge, repels the similarly charged plasma proteins and formed blood elements. The fact that the surface is nonwettable suggests that large numbers of hydrophobic groups protrude from it.

The role of the lining of the vascular system in preserving blood fluidity was first realized by John Hunter who with his associate Hewson showed around 1790 that blood in a segment of vein closed off by ligatures remained fluid (2). Cohnheim subsequently remarked: "As

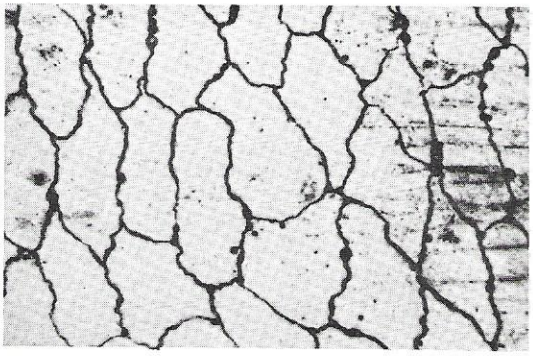


FIG. 1.—Photomicrograph of the endothelium of a normal jugular vein of a dog, stained with 0.4% silver nitrate solution (×550). The silver nitrate stains the intercellular cement and cell nuclei. The white areas represent vascular endothelial cells (1).

long as the endothelium is intact and performs its functions normally, the blood will remain fluid in the vessel" (1889).

Four different types of vessels can be distinguished: arteries, capillaries, veins and arteriovenous shunts, all lined by endothelial cells. The glomus body, which represents an arteriovenous anastomosis, is an exception and is lined by myoepithelial cells, which are modified lining cells many layers deep. Capillaries have only the endothelial layer in addition to a basement membrane. The walls of larger vessels have several layers. All vessels, except capillaries, possess abundant elastic fibers. These fibers can be stretched to resist and accommodate to the distention induced by the blood pressure. The elastic tension is achieved in the vessel wall, without expenditure of chemical energy. It is thought that these fibers, like a coiled spring, have a helical configuration. Arteries have a distinct intima, a media (a layer of smooth muscles that regulates the diameter and the transverse wall tension) and an adventitia connecting the vessel with the surrounding tissues through the nerves and vessels (vasa vasorum) it contains.

The intima of an artery derives its nutrition and oxygen from the passing blood by simple diffusion. In those areas where blood flow is slow, particularly in the veins, this nutritional function may be partially complemented by blood supplied by the vasa vasorum. Intimal damage invariably results from interference with blood flow in the vein and its vasa vasorum as may occur in the deep veins of the legs during prolonged bedrest. The valves are the structures most severely affected by stasis, since they are avascular and derive their nutrition and oxygen solely from the passing blood.

Platelets have an endothelium-supporting function (3). The incorporation of platelets into the endothelial cytoplasm rather than the

intercellular cement, is currently thought to underlie this function. For the synthesis of the intercellular cement, as well as for the maturation of the collagen that constitutes a basic element of the basement membrane, vitamin C is required.

In thrombocytopenic patients it has been suggested that insufficient platelets are available for incorporation into the endothelial cytoplasm. This results in weakening of the cell so that slight trauma is sufficient to force the blood elements through the endothelial lining of capillaries (3).

All mammalian vessels, except capillaries, are contractile. In contrast, changes in size and shape of capillary endothelium are presumably due to deformities secondary to osmotic changes or passive luminal changes, rather than to vasomotor activity. Release of plasminogen activator from the vascular endothelium through autonomic reflex action has been described by Kwaan *et al.* (4). Their observations suggest that stress, hypoxia or orthosympathetic activity facilitate the release of this material.

Trauma elicits a vascular response that is under neurogenic control. A cut with a *sharp* scalpel or a razor blade elicits a poor vasoconstrictive response, presumably because so little pain or irritation occurs. Marked irritation or pain provokes a vasoconstrictive response that plays a significant role in stanching hemorrhage. Precapillary arterioles contract, stopping capillary blood flow and allowing the walls of the capillaries to collapse and adhere. The forces of adhesion exceed the capillary blood pressure, so that when the reflex subsides, hemorrhage rarely resumes (5). Vasoactive amines, e.g., 5-hydroxytryptamine (serotonin) and epinephrine released by platelets, may contribute to this phenomenon. This vasospasm greatly aids the primary hemostasis induced by platelets and the subsequent formation of fibrin.

Severance of an artery with a blunt instrument results in contraction and invagination of the end of the vessel, with spontaneous occlusion, while division with a sharp instrument may fail to elicit this response.

The vasoconstriction of veins, which is much less powerful than that of arteries, is not sufficient to effect hemostasis alone despite the low pressure in these vessels. A hemostatic plug, consisting of platelets and a fibrin clot, is required to control the bleeding.

Blood Platelets

"If one examines the contents of blood vessels with the object immersion lens, one reaches the surprising conclusion that besides red blood cells and white blood cells, elements of a third type circulate within the blood stream. These are extremely thin plate-like structures, shaped like discs with parallel surfaces or more rarely as lentil shaped, round or oval elements, ½ to ⅓ the size of a red blood cell. They are colorless, circulate disorderly

among the other elements of the blood without a specific preference for either the axial or the peripheral blood stream. As a rule they occur distinctly separated, one from the other, not infrequently, however, can they be observed as aggregated in smaller or larger masses. This represents a sign of an induced change in these formed elements.

The circumstance that the platelets (with this name we designate this third formed structure in the blood) are only visible in slowly flowing blood. . . ." (6).

Although not the first observation of these structures, previously noted by Donne (1842), Zimmerman (1846), Schultze (1865) and William Osler (1874), this description by Guilio Bizzozero, which appeared in 1882, summarizes the knowledge concerning these formed elements for the next half century (6). Only after the introduction of more refined technics, particularly electronmicroscopy and immunochemical and analytic assays, was renewed interest focused on the complex morphology of these fascinating organelles in an attempt to establish a relationship to their many and diverse functions.

MORPHOLOGY.—Platelets are the smallest of the formed elements of the circulating blood and were the last to be recognized. They are "sticky" particles that tend to adhere to many surfaces such as yeast cells, glass and many other materials. They derive from the cytoplasm of megakaryocytes in bone marrow and possibly in the lungs. They are spheroidal; their size minute, ranging from 2 to 4μ in diameter. Small as they are, they are complex little bags that play a significant role in transport, defense, regulation of blood flow, hemostasis and possibly other physiologic processes. Their membrane, rich in adenosine triphosphatase (ATPase) activity, encloses a cytoplasm called hyalomere, containing tubules and microvesicles, and from 50 to 100 granules called granulomeres (7) (Fig. 2). The latter sometimes found aggregated in the center of the cell, may be mistaken for a nucleus. However, the granules can be readily distinguished morphologically in

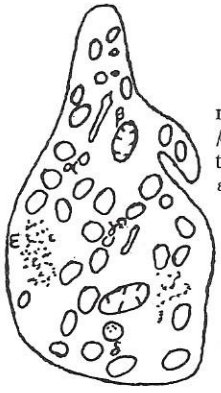


FIG. 2.—Diagrammatic representation of a normal human platelet: α—dense granules; β—mitochondria; γ—clear elements (vacuoles, tubules, microvesicles); δ—cytosome; and ε—glycogen granules (7).

electron micrographs as differing structures, and recently it has been possible to ascribe particular functions to some of these structures. They are rather arbitrarily classified into the following 5 categories.

Alpha granules or dense granules, oval in shape, representing lysosomes. Approximately 50–80 of these elements occur per platelet. They contain platelet factor 3, a phospholipoprotein essential for the generation of the clotting process (as evidenced by the requirement of its presence for the thromboplastin generation test), and possibly cathepsin, a proteolytic enzyme capable of dissolving a platelet plug.

Beta granules or mitochondria are less numerous; only 2 or 3 can be seen per cross-section. They contain relatively few cristae, representing the folds of the inner membrane that are covered with "packages" of enzymes. These play a role in glycolysis, cellular respiration, oxidative phosphorylation and a number of other processes.

Gamma granules are clear elements consisting of vesicles or vacuoles that represent products of endocytosis (pinocytosis and phagocytosis).

Delta granules or siderosomes are ferritin-containing vesicles. They presumably represent phagosomes.

Epsilon granules represent dark-stained granules that contain glycogen.

Following the action of thrombin all granules except the mitochondria disappear from the platelet.

In addition to the granules, one can distinguish stacks of tiny flattened sacs, "saccules" or microtubules. These form the Golgi apparatus, named after Camillo Golgi, the Italian microscopist who in 1898 discovered these structures in nerve cells. Their membranes are rich in proteins. Their function is closely associated with the formation of mucoproteins that form the surface coat of the platelet. Whether they also provide support to the platelet structure is not known.

Platelets are approximately 60% protein, 25% lipid and 8.5% carbohydrate. Although lacking a nucleus (and DNA) and despite their minute size and deceptive simplicity, the platelets are compact, actively metabolizing cells. Enzymes for the Emden Meyerhof and Krebs cycle, cellular respiration, oxidative phosphorylation and other processes can be readily demonstrated. The content of adenosine triphosphate in platelets is greater than in skeletal muscle.

IN VIVO TURNOVER.—The normal platelet count of human blood ranges from 150,000 to 300,000 cells per mm. (3). In the storage depots, particularly the spleen and lungs, this number is considerably higher. In contrast, lymph is poor in platelets. Regulation of platelet production appears to depend on the number of circulating platelets as suggested by Cronkite *et al.* (8), who showed that thrombopoetic activity in rats rendered thrombocytopenic by irradiation was much greater after platelet-free plasma or saline infusion than following the

infusion of fresh platelets. Although platelets are found in the bone marrow, Kaufman *et al.* (9) calculated from data obtained during right heart catheterization in 23 patients that 7–17% of the total number of platelets may derive from the lung.

Platelet destruction takes place in the reticuloendothelial system. Platelets damaged by freeze thawing or extracorporeal circulation are cleared by the Kupffer cells (10). Antibody coated platelets, as in drug-induced purpura, idiopathic thrombocytopenic purpura or post-transfusion purpura, are cleared by the spleen. Aster and Jandl (11) showed that platelets coated with small amounts of isoantibodies are predominantly cleared by the spleen whereas hepatic removal played a more important role in the presence of large quantities of antibody. Similarly platelets heavily damaged by EDTA were predominantly cleared by extrasplenic phagocytes. Increased platelet destruction is associated with the release of platelet constituents in the blood. Although Oski and associates failed to demonstrate that free clot accelerates phospholipid or platelet factor 3 activity, definite increase in acid phosphatase, also a platelet constituent, was noted (12).

The half-life of platelets, longer than that of leukocytes but much shorter than that of erythrocytes, ranges from 7 to 10 days. The survival curve of labeled young platelets is identical with that of a mixed platelet population (13). This finding suggests that aging appears to play little part in platelet destruction. Data obtained by other investigators tend to confirm the impression that platelet destruction presumably does not occur by aging but by random utilization (14). Since platelets play a significant role in hemostasis, in coagulation and in clot retraction, through processes intimately involved in preserving vascular integrity and blood fluidity, their life span seems to depend on the rate at which they are utilized in these various processes.

ROLE OF PLATELETS IN HEMOSTASIS.—The vascular endothelium constitutes the first line of defense against bleeding or clotting. Injury to the intimal layer that is in contact with the blood results in a curious chain of events. Platelets adhere to the denuded collagen at the site of injury, as if to seal off the area (Fig. 3). Additional platelets accumulate, forming a loose platelet aggregate. As a result of hypoxia, platelets adhere to the intercellular cement and to areas denuded of endothelial cells (1, 15).

The adherence of platelets to the collagen underlying damaged intimal surfaces and to each other is related to the action of adenosine diphosphate (ADP) (16), a nucleotide derived from the high energy phosphate compound ATP by an enzyme present in platelets (ATPase) (17). The source of the ATP is presumably the platelet (18).

Besides adhesion, platelets undergo changes designated as *aggregation* and *viscous metamorphosis*. Morphologically the outline of a platelet, which is originally spheroidal, undergoes drastic changes,

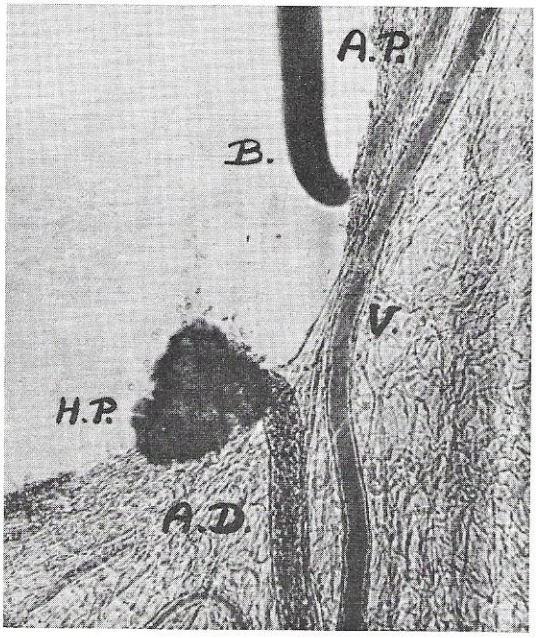


FIG. 3.—Hemostasis after transection of a mesenteric arteriole. Discrepancy between the arrests of bleeding at both ends of a transected artery. (*A.P.*, proximal end of the transected vessel (notice the moniliform vasoconstriction); *B*, site of active bleeding; *H.P.*, hemostatic plug having closed *A.D.*, the distal end of the artery 2 minutes and 30 seconds after the division of the vessel; *V*, the corresponding vein. This photograph was taken at the tenth minute of the hemorrhage (20).

forming numerous pseudopodia with fusion of the platelets and accumulation of the granules in the center of the cell. Some of the lysosomes appear to be extruded from the platelets, a process known as the "release reaction" (19). Released are a number of hydrolytic enzymes, serotonin and other vasoactive substances as well as platelet factor 3. The last is required for the coagulation of blood. It has been suggested that the serotonin slows the blood flow through its vasoconstricting properties, thereby aiding hemostasis. Shortly after the release of platelet factor 3, fibrin appears. It is not inconceivable that the lysosomal enzymes, released from the cell, affect the surface characteristics of the platelet membrane, increasing its permeability which causes swelling and subsequently lysis of the cell.

Initially aggregation is a reversible process, especially in rapidly flowing blood where aggregates readily break up with the return of the platelets into the circulating blood. Quite soon, however, the platelet membranes lyse and the friable platelet plug fuses, forming a more durable plug. For the normal process of aggregation and viscous meta-

morphosis, divalent ions, particularly the Ca^{++} and Mg^{++} ions of blood, are required in addition to thrombin, traces of fibrinogen and adenosine diphosphate. The role of these materials in the process of viscous metamorphosis is not presently known.

The described process whereby platelets accumulate and coalesce, constitutes the *primary hemostatic response*. In this manner hemorrhage from the capillaries and the small arterioles of a surgical incision is initially controlled. Although vascular injury presumably constitutes the most significant cause of platelet aggregation, especially for the surgeon, a similar response with platelet aggregation and release of lysosomes has been observed when certain materials enter the circulation, presumably in amounts exceeding physiologically tolerable quantities. These include endotoxin, epinephrin, norepinephrin, fatty acids, thrombin, trypsin, serotonin, tryptamine, antigen-antibody complexes, viruses and a host of other substances. Under these circumstances the platelet aggregation produces not a sessile clump on collagen fibers but circulating masses of platelets. The release of serotonin and platelet factor 3 under these conditions may initiate vascular and coagulative responses that may assume considerable clinical significance.

The primary hemostatic response is relatively short lived. After 3–4 hours, a platelet plug breaks down, presumably as a result of the action of proteolytic enzymes present in platelets or tissues.

ROLE OF PLATELETS IN COAGULATION.—Roskam (20) postulated the presence of a dense layer of coagulation factors on the platelet, and this has recently been confirmed for factors XI and XII by Iatrides and Ferguson. The adsorption of factor V onto the platelet surface has also been substantiated. It is absent in platelets from patients deficient in factor V (21). Platelets act like a sponge by binding virus particles, bacteria and soluble antigen-antibody complexes. Besides factors V, XI and XII, a number of other substances associated with the coagulation mechanism have been found on or in the platelets. Among these are fibrinogen (22), factor XIII, plasminogen, antiplasmin and antiheparin (23). Of particular significance is platelet factor 3, a phospholipoprotein fraction required for the completion of the clotting sequence. Whether this material is derived from the dense granules (24) or from the endoplasmic reticulum (25) has not been definitely established. Although its place in the clotting sequence has been determined with certainty, its role in the chain reaction is not precisely defined. In its absence, however, prothrombin consumption is markedly impaired. As a result such blood may contain large amounts of prothrombin at a time when all of the prothrombin of normal blood would have been consumed. Hence the prothrombin consumption test is frequently used to assess the availability of platelet factor 3.

ROLE OF PLATELETS IN PRESERVING CAPILLARY WALL INTEGRITY.—Johnson's studies (3) suggest that the thrombocytopenic lesion of the

vascular wall represents an abnormality of the capillary endothelial cells rather than of the intercellular cement. The latter remained impenetrable to blood cells even in pronounced thrombocytopenia when erythrocytes were found to escape freely through the intact vessel wall into the interstitial fluid. The escape of erythrocytes, observed in the buccal mucosa of thrombocytopenic guinea pigs, was noted to occur through the endothelial cytoplasm and, as the endothelial cytoplasm closed behind the erythrocytes, they accumulated in the basement membrane prior to their escape into the interstitial fluid. Thoracic duct lymph, normally virtually free of platelets and erythrocytes, can assume a pink hue in severe thrombocytopenia. The hue is due to the presence of large numbers of erythrocytes. The possible role and the mechanism of action of platelets in preserving endothelial function is not presently known.

ROLE OF PLATELETS IN CLOT RETRACTION.—A normal blood clot shrinks, with the expression of serum from the clot. Clots prepared from platelet-poor plasma shrink slightly as a result of the syneresis of the fibrin gel. Platelets are required for firm clot retraction, which results in a 50–60% reduction in the volume of the clot. The presence of a contractile protein in platelets similar to muscle actinomyosin has been demonstrated by Bettex-Galland and Lüscher (26). For its action this material requires Ca^{++} ions, ATP, glucose and a presently unidentified plasma co-factor.

The physiologic role of clot retraction was previously regarded as an atavism from an evolutionary period when the primitive platelet constituted the sole hemostatic constituent of blood, since it was felt that the force exerted in this process was too feeble to aid in hemostasis. This concept has undergone new scrutiny. Lüscher's work suggests that clot retraction, by providing a retracting bridge between the edges of a severed vessel, plays a significant role in stanching the flow of blood. In addition, patients with normal platelets but impaired clot retraction may have hemorrhagic disorders. In these instances the clot retraction test is abnormal.

THE CLOTTING MECHANISM

The central process of blood coagulation consists of the activation of prothrombin to thrombin. The proteolytic enzyme, thrombin, initiates platelet aggregation, induces fibrin formation and aids in the activation of another enzyme, fibrinase (factor XIII) that initiates intramolecular disulfide bonding within the fibrin molecule, "zipping up" the fibrin into a tight and solid structure.

The clotting mechanism, once regarded as a treacherous labyrinth that few cared to enter, has in the past few years been reduced to the

concept that it represents a sequence of enzyme reactions not unlike and certainly not much more complex than some other biochemical processes, notably the activation of the complement system, or glycolysis, or the "Na pump." Whereas glycolysis and the Na pump operate within cells and concern enzyme activities that remain localized to specific areas within the cell, the clotting mechanism and the complement system operate in blood and lymph. For the operation of the clotting mechanism to be safe as well as meaningful, several mechanisms are required to localize the thrombin activity. When they fail or break down, however, generalized or disseminated intravascular coagulation ensues.

Several features of the process leading to prothrombin activation are of importance.

1. It involves a sequence of integrated enzyme reactions (Fig. 4).
2. These enzymes are present in the extracellular fluid in their inactive form.
3. The activation sequence occurs stepwise and has been conveniently compared to a series of falling dominoes; if one tips over it will tumble the adjacent one, and so on down the line.

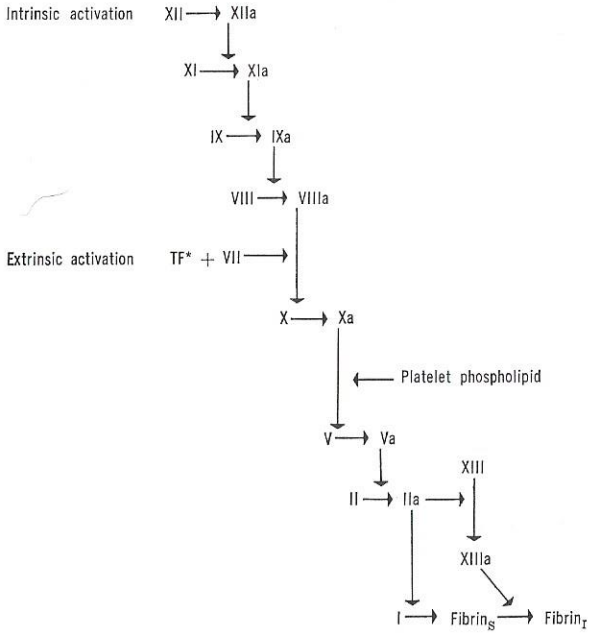
If each of the dominoes represents an inactive proteolytic enzyme precursor, activation of the first in the sequence will in step-wise fashion activate each subsequent plasma protein into an active proteolytic enzyme. In the clotting sequence, the site of action of Ca^{++} and phospholipid derived from the platelets has been elucidated, although their role is not entirely clear.

Several of the proteins concerned in the coagulation mechanism appear to be closely related. Those concerned are indicated by the term "prothrombin complex." This relates in particular to the plasma proteins that require vitamin K for their synthesis (factors II, VII, IX and X). These proteins also behave similarly in the plasma fractionation procedures in common use today. The exact nature of their relationship is presently unknown. It is conceivable, as suggested by Seegers (27), that each one represents a part of one and the same protein molecule, or that each constitutes a different active group on such a molecule, or that they represent only slightly modified forms of the same basic protein structure.

Built into the coagulation sequence (as depicted below in Fig. 6) is the feature of amplification (28). Compared to the minute quantities of factor XII (contact factor) present in plasma, staggering amounts of factor I (fibrinogen) are available. The protein concentrations increase as one proceeds down the clotting sequence; hence it would appear that the process of coagulation represents a snowballing type of reaction. The large number of stages in the coagulation sequence represents, then, steps of amplification.

The two pathways to thrombin activation have been recognized to

A



B

Factor I	Fibrinogen; Fs = urea-soluble fibrin Fi = urea-insoluble fibrin.
Factor II	Prothrombin; IIa = Thrombin.
Factor III	Thromboplastin.
Factor IV	Ca^{++}.
Factor V	Labile factor (Quick), Proaccelerin (Owren).
Factor VI	Obsolete.
Factor VII	Proconvertin (Owren) VIIa = convertin.
Factor VIII	Antihemophilic globulin (AHG).
Factor IX	Christmas factor (Biggs).
	Plasma thromboplastin component or R.T.C. (Aggeler).
	Autoprothrombin II (Seegers).
Factor X	Stuart factor (Hougie).
Factor XI	Plasma thromboplastin antecedent (PTA) (Rosenthal).
Factor XII	Contact or Hageman factor (Ratnoff, Haanen).
Factor XIII	Fibrin-stabilizing factor (Laki-Lorand); profibrinase (Loewy).

FIG. 4.—The clotting sequence (28). *A*, the clotting process is activated on contact of blood with tissue (extrinsic activation) or with glass or other foreign materials (intrinsic activation). During intrinsic activation factor XII is converted into an active, proteolytic enzyme that converts factor XI, an inert plasma fraction, into its active form and so on down the line. Extrinsic activation which accompanies the interaction of blood with tissue factor results in activation of factor X. The final stages in both activation sequences are identical, namely the activation of prothrombin (factor II) with formation of thrombin; conversion of fibrinogen (factor I) to urea-soluble fibrin. Fibrin becomes urea insoluble by formation of additional intramolecular cross-linkages which occur through the action of fibrinase (factor XIIIa). The precursor for this enzyme (factor XIII) also requires thrombin for its activation.

B, this table shows common synonyms and explanations of the factors.

be the extrinsic and the intrinsic, depending on the event that starts the activation sequence. One process is triggered not only on contact of blood with a sizable wettable surface, such as the wall of a test tube, a vascular prothesis or the surface of an artificial organ and its connecting tubing (for instance, those used in open heart surgery or hemodialysis), but also in arteries extensively involved by atherosclerosis. The contact initiates the so-called *intrinsic* pathway with the activation of factor XII (Hageman factor) (29), which presumably effects an unfolding of this protein molecule on its contact with a foreign surface. This change in structural configuration results in activation of its proteolytic activity. In contrast, the *extrinsic* process is initiated by tissue damage, with release of components of tissue (so-called tissue factor) into the circulation. This occurs after burns, trauma (especially hip fractures), sepsis and operation, particularly if during operation necrotic tissue is sequestered in the body cavities or in the operative wounds. The tissue factor initiates the *extrinsic* pathway. The terminal events are identical in both pathways.

The intrinsic pathway is triggered by activation of the "contact" factor (factor XII), presumably from the contact of blood with a wettable surface that carries a charge different from that of the normal intima. Once the process is triggered, a chain reaction of 9 or more steps ensues. The extrinsic pathway is activated when tissue is injured and material from injured cells reaches the circulation. On contact with blood, this material activates factor VII, bypassing the first 4 steps of the intrinsic activation process. The extrinsic pathway is identical to the intrinsic pathway in its last 4 steps. Both processes require Ca^{++} and phospholipid (derived from platelets) and involve activation of the prothrombin activator (factor V), which in turn triggers the activation of prothrombin (factor II) to thrombin.

The conversion of fibrinogen (factor I) to fibrin, the final step in the blood coagulation sequence, is a complex but orderly reaction (30). Thrombin cleaves the long fibrinogen molecule at a specific arginine-glycine bond, freeing two peptides from the molecule (fibrinopeptide A and B) (31). One of these fibrinopeptides, resulting from the action of thrombin on fibrinogen, is a vasoactive substance (32) (Fig. 5).

The resultant protein molecule (fibrin monomer) remains soluble till a number of fibrin monomer units polymerize to form a large hydrogen-bonded aggregate. This structure remains soluble in urea or guanidine HCl, agents that disrupt hydrogen bonds. Finally, covalent bonds are formed within the fibrin polymer, a process requiring factor XIII (fibrinase, an enzyme with transaminase activity), with formation of a stable molecule (33). The fibrin cross-linking reaction has considerable significance for wound healing. The nature of the relationship is not presently known. Evidence for its existence is derived

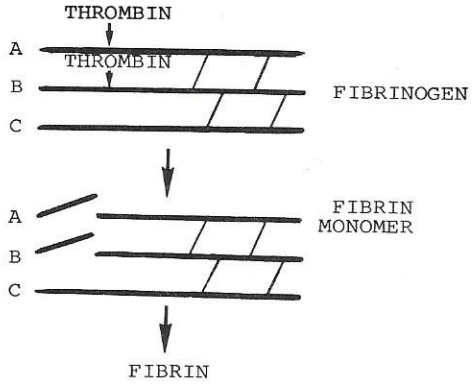


FIG. 5.—Effect of thrombin on fibrinogen. Thrombin cleaves off polypeptides from two of the three chains that constitute the fibrinogen molecule. The resultant material, fibrin monomer, polymerizes by end to end and subsequently by side to side aggregation to the macromolecular structure: fibrin. In addition, one of the fibrinopeptides which is formed, acts as a vasodilator (32).

from the observation that patients with fibrinase deficiency suffer from postoperative hemorrhage and from defective wound healing, and are particularly prone to wound dehiscence (34, 35).

Of the 9 different proteins that have been defined as operating in the clotting sequence, all but the antihemophilic globulin (factor VIII) are formed by the liver. An additional requirement is a phospholipid, derived from platelets. At present, opinions differ as to whether clotting takes place continuously within the confines of the vascular system. There are those who feel that such a process is a prime requirement for the preservation of vascular integrity. To support them is the observation that defects of the coagulation mechanism result in what appears to be a loss of vascular integrity, as manifested by leaking of blood through an apparently intact vascular wall. However, the mechanism whereby vascular integrity is preserved by clotting has not been adequately explained. Also, long-term heparinization does not appear to appreciably affect the turnover rate of fibrinogen or platelets. Whatever the role of clotting in preserving vascular integrity may be, if this process does indeed occur continuously, mechanisms must be present to eliminate the fibrin as fast as it is formed, for without them the vascular system would eventually be obliterated.

At present three mechanisms are recognized to serve this purpose (Fig. 6). The first, operating in the reticuloendothelial system, clears activated coagulation products from the blood as it passes by through the liver, spleen and lungs. By this mechanism free circulating thromboplastin (36), thrombin (37), fibrin (38) and platelets aggregates (10) are rapidly cleared from the circulation. Another mechanism consists of the natural anticoagulants, particularly those that neutralize thrombin activity or interfere with fibrin formation. A number of antithrombins serving such a function have been defined in plasma and serum. One of these is the heparin co-factor, a plasma or serum factor activated by heparin (39). Another is in fibrin itself, which like a

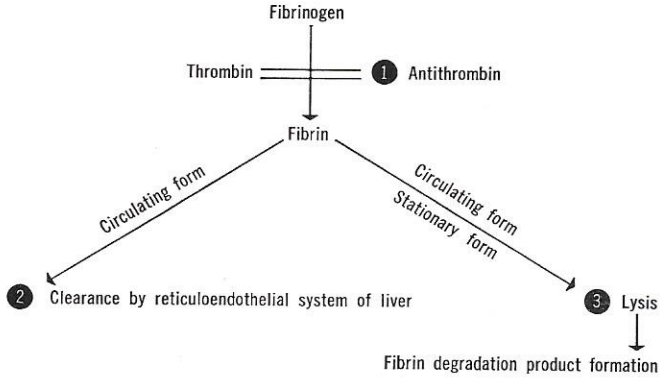


FIG. 6.—Defense mechanisms against intravascular coagulation: formation of antithrombin; clearance of fibrin, thrombin and thromboplastin by the reticuloendothelial system, and fibrinolysis, the enzymatic breakdown of fibrin (83). The intravascular conversion of fibrinogen to fibrin by thrombin is counteracted by several mechanisms. The rapid dilution of thrombin in flowing blood and its inactivation by the antithrombins of plasma constitute the first line of defense. In addition, both active as well as inactive thrombin are rapidly taken up by macrophages, predominantly the Kupffer cells. The clearance of active thrombin probably occurs within one passage.

A second line of defense deals with the removal of fibrin. Circulating fibrin is rapidly cleared by phagocytosis. The fibrin that accumulates in the tissues (e.g., lobar pneumonia) or vessels (thrombi) is predominantly eliminated by local phagocytosis and by proteolysis. The proteolysis products of fibrin have anticoagulant activity.

sponge, can absorb considerable quantities of thrombin (40). The natural antithrombins of blood reside in clearly defined plasma fractions; one occurs in the alpha$_1$-antitrypsin (41); another is associated with the alpha$_2$-macroglobulin fraction of plasma (42). Finally, the fibrinolytic enzyme system constitutes a mechanism capable of breaking down large quantities of fibrin.

THE FIBRINOLYTIC ENZYME SYSTEM

A blood clot incubated under favorable conditions dissolves spontaneously. This observation, made by Denis more than a century and a half ago, led to an investigation in von Liebig's laboratory to determine the factors that promote the process of clot dissolution. The study continues at present.

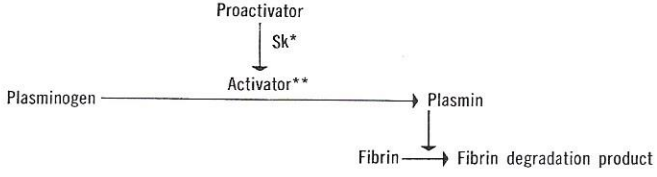
Today more people die from intravascular clots than from malignant neoplasms. There is ample evidence to support the thesis that thrombosis and its sequelae are not only the most prevalent cause of death, but also one of the major sources of disability, imposing heavy socioeconomic burdens on society.

From the globulin fraction of the plasma of mammals a protein, plasminogen, can be isolated. This protein is the inactive precursor of the proteolytic enzyme, *plasmin*. Besides fibrin, plasmin will break down fibrinogen, glucagon, ACTH, somatotropic hormone, a component of complement and the clotting factors V and VIII (43). By its ability to destroy fibrin, it could provide a potential weapon for preventing or treating intravascular thrombosis. Unfortunately, it is not yet known how this process can be utilized to the best advantage.

The activation of plasminogen (Fig. 7) involves a loss of a protein moiety, and there is evidence to suggest that the plasmins obtained by different modes of activation may vary in composition. The different activators can be divided into those that occur naturally, such as urokinase in urine, trypsin, streptokinase (from hemolytic streptococci) and staphylokinase (from coagulase positive staphylococci), and pharmacologic agents that induce activity after their intravenous injection, such as protamine, nicotinic acid, epinephrine and acetylcholine. Pyrogens elicit a similar effect.

Naturally occurring activators have been found to circulate in the blood under various conditions, such as after stress, hypoxia (44), electric shock (45), cancer of the prostate (46), cirrhosis of the liver (47), leukemia (48) and operation (49), especially extensive pulmonary (50), hepatic (51) and cardiovascular procedures (52). Poor wound healing and the breakdown of barriers against infection with subsequent dissemination may, in part, be the result of excessive plasmin activity. Some tissues are rich in activator. The lung is one such organ. Extensive manipulation of the lung during operation may, for that reason, result in a severe fibrinolysin-induced hemorrhage. The high activator concentration of the lung might also explain why lobar pneumonias usually resolve. Moreover, the lung, as a blood filter, for substances derived from the peripheral vascular bed, is furnished with the means to break down considerable amounts of fibrin. Failure of

FIG. 7.—The plasminogen-plasmin system (83). Plasminogen, the inactive globulin precursor of plasmin, is activated by a number of materials, e.g., by a urine component (urokinase), a tissue component (tissue activator) and by thrombin (thrombin esterase). Streptokinase acts through the activation of a proactivator in plasma, predominantly present in human plasma.



* Sk: streptokinase, an enzyme produced by beta-hemolytic streptococci

** Common activators are tissue factor, thrombin, urine factor (urokinase), etc.

this function may well be responsible for some of the pulmonary changes observed after a variety of conditions that are frequently associated with some degree of disseminated intravascular coagulation, particularly during and after shock.

The kidneys, too, are richly supplied with plasminogen activator. Urine contains large quantities; hence the inhibition of its activity with epsilon amino caproic acid after transurethral resection has greatly reduced the amount of blood lost from the prostatic fossa.

On the other hand, there are organs, such as the liver, whose plasminogen activator activity is much more limited. It has been implied that this may be one of the reasons why the liver heals with excessive scar formation, as it does in cirrhosis (53). Marked fibrinolytic activity has been noted after manipulation of the liver. The enhanced fibrinolytic activity observed after hepatic resection and liver transplantation presumably results from a defect in the clearance of the plasminogen activator by the liver, a phenomenon previously also observed following extracorporeal circulation (54).

The tissue activators are undoubtedly involved in the activation of the plasminogen of *blood* during tissue injury in instances where tissue components escape into the blood stream. Under those circumstances the clotting and the fibrinolytic enzyme system are simultaneously activated. A quite specific function of tissue activator appears to reside in its ability to activate plasminogen locally. It acts on the plasminogen adsorbed onto the fibrin that is deposited on the site of vascular injury and serves to limit the amount of fibrin formed under these circumstances. In contrast to its local effect, its systemic effect is limited. Consequently, rarely can free plasmin activity be demonstrated; this is because of the protective action of the naturally occurring antiprotease activities in blood. If all the plasminogen of blood were to be activated, there would not be enough plasmin generated to overcome the inhibitory level. This is why in normal individuals the activation of all plasminogen is seldom associated with free plasmin activity because of the excess of inhibitor present in blood. Only when the plasminogen concentration is markedly increased or the inhibitor level is markedly decreased, can a situation characterized by free plasmin activity occur. We have come to distinguish two groups of antiproteinases, the naturally occurring and the synthetic inhibitors. Of the former, one is associated with an $alpha_1$-globulin fraction (the $alpha_1$-antitrypsin fraction, previously implicated as an antithrombin [see p. 17]) (41). Its concentration was found to be markedly reduced in patients with homozygous $alpha_1$-antitrypsin deficiency and pulmonary emphysema. Subsequently its absence was also observed in patients with infantile liver cirrhosis (55). The other inhibitor is associated with an $alpha_2$-globulin fraction; it represents the $alpha_2$-macroglobulin fraction. Recurrent thromboembolism has on occasion been found to be associated with

increased fast antiplasmin levels (56). Increased alpha$_2$-macroglobulin values are occasionally observed in these patients (57). This finding suggests also that the antithrombins and antiplasmins are identical. The alpha$_2$-antiplasmin appears to be the more important plasmin inhibitor because it rapidly neutralized plasmin activity *in vivo*. Besides these natural inhibitors, several synthetic inhibitors have been developed, e.g., soybean trypsin inhibitor, various amines (methylamine, laurylamine, quaternary amines), basic amino acids (epsilon amino caproic acid, lysine and arginine esters), kalikrein inhibitor (Trasylol) and several others (Amcha, etc.). The antiplasmins undoubtedly constitute a significant mechanism for localizing the action of the fibrinolytic enzyme system.

Fibrinogen and plasminogen are physically so closely associated that fibrinogen, free of plasminogen, is difficult to prepare. Elaborate procedures are required for their separation. The physiologic role of the fibrinolytic enzyme system is thought to be mediated predominantly through the activators. Fibrin, besides its affinity for thrombin, which localizes the effect of clotting in blood, also readily adsorbs plasminogen activator. These activators convert the plasminogen present in the clot into the active enzyme.

The degradation of fibrin by plasmin is a continuous process, in contrast to the one-step action of thrombin on fibrinogen. During the plasmin induced digestion, a number of different-sized peptides are formed, termed fibrinogen split or degradation products (F.D.P.). As the digestion proceeds, the fragments become smaller and lose their clottability with thrombin as well as their antigenic determinants of the parent fibrinogen molecule (58).

Some of these fragments interfere with the thrombin-fibrinogen interaction through their incorporation into the growing fibrin polymer, thereby reducing the rate of polymerization sufficiently to effect prolonged thrombin times (59). Not only is the polymer slow in forming, it is also abnormal in structure and physical characteristics.

Fibrin split products complex readily with fibrinogen, factor VIII, factor V, fibrin monomer and each other, to form proteins that precipitate below 32 C. or on addition of heparin or protamine sulfate. These precipitable proteins are indicated as cryofibrinogen or cryoglobulin. They occur in patients with collagen diseases, particularly in patients with Waldenström's macroglobulinemia, following treatment with fibrinolytic agents and after disseminated intravascular coagulation. The increased viscosity of the blood observed in these patients may result in producing localized vasospastic or microcapillary occlusive disease and leg ulceration (60).

Besides these effects on clotting, fibrin degradation products profoundly affect platelet aggregation. The practical significance of fibrinolysis is in the manner in which it induces bleeding. It does this by

several mechanisms, first the breakdown of fibrin that was laid down to provide hemostasis, second by delaying clot formation to a marked degree ("anticoagulant effect" from incorporation of F.D.P. in fibrin which results in a clot with poor physical characteristics (friable clot) and third by inhibiting platelet aggregation (61), thus interfering with primary hemostasis.

PART II

DEFECTS IN HEMOSTASIS

The requirements for normal hemostasis include an intact vascular system, an adequate number of functional platelets and a normal coagulation mechanism. Abnormal hemostasis, either as an increased bleeding tendency or extensive thrombosis, results from platelet defects, coagulation disorders or from vascular defects.

VASCULAR DEFECTS

Defects in hemostasis, resulting from vascular abnormalities occur in two broad categories, those that cause bleeding and those that cause thrombosis. The latter predominate, although vascular abnormalities that result in bleeding (purpura) occasionally occur. In those patients in whom platelets are normal in both number and function, petechiae and ecchymoses suggest the presence of abnormalities of the vascular system. That the recognition of the different etiologies in purpura is not of very recent date is evidenced in a statement made in 1883 by Krauss: "In the cases of purpura haemorrhagica in children, a striking decrease and finally a disappearance of the platelets was found at the height of the illness; with the recovery these cells reappeared." To differentiate this capillary purpura from other causes he added: "In the case of purpura with joint involvement this relationship is not present" (62). Since the majority of the causes of bleeding from vascular defects represent conditions that rarely confront the surgeon, these will only be briefly indicated.

DEFECTS IN THE SUPPORTING TISSUES OF VESSELS

(1) Atrophy of subcutaneous tissues: purpura senilis, purpura cachectica.
(2) Fragility and hyperelasticity of connective tissues: Ehlers-Danlos syndrome, Cushing's syndrome, Marfan's syndrome.

DEFECTS IN THE VESSEL WALL

(1) Congenital: Hereditary familial purpura simplex.
(2) Hyperglobulinemia, dysproteinemia, cryoglobulinemia, hyperfibrinogenemia and other conditions that cause sludging and capillary hypoxia.

(3) Infectious: Meningococcemia, subacute bacterial endocarditis, smallpox, diphtheria, measles, typhoid fever, staphylococcemia, scarlet fever, rheumatic fever, Rocky Mountain spotted fever.
(4) Allergic: Purpuras of Henoch and Schönlein, DNA hypersensitization, autoerythrocyte sensitization.
(5) Metabolic: Scurvy, diabetes.

Platelet Defects

Platelet defects account for a considerable number of clinical problems. Their main manifestation is bleeding, because a platelet abnormality may affect the vascular endothelium as well as the coagulation of blood.

The nature of the various platelet defects is quite diverse. First the number of platelets may be decreased, as in *thrombocytopenia.* Inadequate platelet production, implicating abnormalities of the bone marrow or an enhanced turnover rate, e.g., from a rapid consumption, as in clotting or in immune reactions, are not uncommon. The number of platelets may be normal but their function defective, affecting aggregation (thereby interfering with primary hemostasis) or interfering with their function in the coagulation of blood, as in *thrombopathy.*

Thrombocytopenias are well tolerated up to a certain point. Below an average of 20–60,000 platelets per cubic mm., however, bleeding develops. Hemorrhage may occur anywhere; yet it seems to affect particularly the subcutaneous tissues, intestine, the urinary tract and the central nervous system. Patients with thrombocytopenias, of which the cause is not readily apparent, require at least a peripheral blood smear for leukemia, an L.E. clot test to eliminate the possibility of lupus erythematosus, biopsy of enlarged lymph nodes to rule out lymphoma or sarcoidosis, and a bone marrow biopsy to determine the number and the functional status of the megakaryocytes and to rule out bone marrow invasion or replacement by leukemia, metastatic carcinoma or multiple myeloma.

Depression of bone marrow function may follow radiation therapy or drug treatment, especially with antimetabolites or chemotherapeutic agents. These drugs affect platelet production by damaging the megakaryocytes. They also frequently produce anemia and leukopenia. Drugs can also enhance platelet destruction by inducing sensitivity reactions. In those instances leukopenia and anemia are less frequently observed, and the manifestations bear no relationship to the dose of the drug used.

Agents known to elicit thrombocytopenia are summarized below:

Sedatives: Meprobamate, phenobarbital, allylisopropyl-barbituric acid, allylisopropylacetylurea (Sedormid).

Cinchona alkaloids: Quinine and quinidine.

Antibiotics: Oxytetracycline, chloramphenicol, streptomycin, ristocetin, para-aminosalicylic acid.

Antibacterial sulfonamides: Sulfasoxazole (Gantrisin), sulfadiazine, sulfamethoxypiridazine (Kynex), sulfathiazole, sulfadimidine, sulfamethazine.

Other sulfonamide derivatives: Tolbutamide (Orinase), chlorothiazide (Diuril), acetazolamide (Diamox), chlorpropamide (Diabinese).

Other agents: Dinitrophenol, gold, mercurials, bismuth and arsenicals, potassium iodide, digitoxin, estrogens, ergotrate, thiourea.

It is thought that in a sensitivity reaction, the drug (hapten) in combination with the platelet serves as an antigen that stimulates antibody formation. The antigen-antiplatelet antibody reaction would result in the aggregation and lysis of platelets. In many respects this is similar to the hemolysis noted in acquired (Coombs-positive) hemolytic anemias. In several instances the incriminating agent or drug (e.g., quinidine and sedormid) (64) can indeed be shown to induce the *in vitro* aggregation and lysis of platelets following its *in vitro* addition to the patient's blood. The administration of a drug to such a previously sensitized individual may result in a fulminating thrombocytopenia. Usual manifestations are chills, fever, lethargy, pruritus, gum bleeding, epistaxis, petechiae, shock and occasionally death from cerebral hemorrhage.

Autoimmune hemolytic anemias may be accompanied by leukopenia and thrombocytopenia (65). Purpura is not an uncommon complication. Thrombocytopenia is also occasionally seen after multiple or massive blood transfusions. This may be dilutional, following replacement with platelet-poor blood, or it may result from intravascular coagulation or the formation of isoantibodies. Mechanical factors may reduce platelet survival. Following insertion of a prosthetic cardiac valve and after extracorporeal circulation, rapid breakdown and utilization of platelets may lead to thrombocytopenia. Thrombocytopenia has also been noted in a number of infants with hemangiomas (66). On regression of the tumor, either spontaneously, after radiation therapy or following excision, the thrombocytopenia disappears. Sequestration of platelets in the tumor has been demonstrated with Cr^{57}-labeled platelets and related to the thrombocytopenia (67).

With burns, thrombocytopenia may develop within several hours after injury and may be associated with purpura. Thrombocytopenia has also been described after snake and insect bites (68). Thrombocytopenia should invariably bring to mind the possibility of autoimmune diseases, notably sarcoidosis and lupus erythematosus. An L.E. clot test should be performed in instances of observed thrombocytopenia. Idiopathic thrombocytopenic purpura (I.T.P.) is also an autoimmune disease in which platelet agglutinins, immunoglobulins of the 7S variety, can usually be demonstrated in the blood or plasma. This type of thrombocytopenia is characterized by an abnormal mor-

phology of the platelet observed in the peripheral blood smear, a decreased platelet life span, a bizarre megakaryocyte in the bone marrow, with megakaryocytic hyperplasia. It may present in an acute form, with sudden onset of purpura, usually seen in children some weeks after an infection—particularly rubella, but also as simple an infection as a common cold. Of these, 80–90% have spontaneous remissions. In contrast, the same disease in young women tends to become chronic, not uncommonly it starts as a mild purpuric state, to increase gradually in intensity. Usually exacerbations and remissions characterize its course. If it persists for longer periods, despite corticosteroid treatment, e.g., if no spontaneous remission occurs after a 6-month period, splenectomy is warranted.

The platelet itself may elicit an antibody response. Hence, patients can become immunized to isologous platelet transfusions. Isoimmunization with the rapid destruction of transfused platelets has been noted to occur after 1 previous transfusion (69). This suggests that platelets, like erythrocytes, possess different serologic types (70). Adequate methods for platelet typing are presently not available.

Thrombocytopenia when present in blood with low fibrinogen and prothrombin levels in patients with otherwise normal liver function tests should suggest the possibility of *disseminated intravascular coagulation*. When accompanied by a Coombs negative hemolytic anemia, fever, gastrointestinal or genitourinary hemorrhage, headache, mental changes, seizures, paresis, aphasia or other evidence of focal central nervous system involvement, it should suggest the possibility of thrombotic thrombocytopenic purpura (71).

There is also a group of patients with normal platelet count but demonstrable abnormalities in the participation of platelets in the process of aggregation or in the coagulation mechanism *(thrombopathy)*. These are the result of defects in aggregation or in the release reaction. Abnormalities in aggregation affect primary hemostasis, whereas a deficiency of platelet factor 3, present in both conditions, interferes with a normal clotting process. The thrombopathies, especially those that are congenital, are poorly understood. Acquired and reversible forms of thrombopathy are seen in patients with uremia (the result of dialyzable metabolites), in patients with dysproteinemia (e.g., multiple myeloma, lupus erythematosus) as a result of platelet coating by abnormal proteins and in patients with renal or liver disease, presumably because of an acquired platelet factor 3 deficiency.

The congenital forms of thrombopathy consist of Glanzmann's disease (thrombasthenia), a bleeding disorder characterized by nonadhesive platelets and factor VIII and IX deficiency (72), and the more common von Willebrand's disease (73), which is inherited as an autosomal dominant trait characterized by factor VIII deficiency and a deficiency of a presently unknown plasma factor which seems to be

essential for normal platelet adhesiveness. Platelet count is normal but bleeding time is prolonged. A variety of platelet enzyme deficiencies have been described in thrombasthenia, including reduced activity of glyceraldehyde 3 phosphate dehydrogenase, pyruvate kinase and glutathione reductase. There is defective clot retraction and a failure of platelets to aggregate by ADP, decreased platelet factor 3 availability and an impairment in their adhesiveness to glass bead columns. From this it is quite evident that special studies are required to establish the diagnosis.

Thrombocytosis is less well defined, but equally common. It is not uncommonly observed following trauma. In patients with fractures of the hip platelet counts may be found to be increased from 20 to 200%. Patients with neoplasms also frequently have thrombocytosis with platelet counts in excess of 400,000. Similar changes have been noted following surgical operations. The maximal rise occurs somewhere between the 6th and 21st postoperative day. Splenectomy and splenic vein thrombosis may be followed by a 5- to 10-fold rise.

Acute blood loss, as from upper gastrointestinal hemorrhage, may cause thrombocytopenia. The drop in platelets is probably dilutional. During convalescence, however, thrombocytosis is not an uncommon finding.

Persistent elevation of platelet count is most frequently associated with polycythemia vera, chronic leukemia, Hodgkin's disease and occasionally is found in patients with collagen diseases.

Coagulation Disorders

Most clotting disorders are acquired. Of the congenital abnormalities, hemophilia is by far the most frequent and to the surgeon, one of the most frustrating disorders to deal with.

Hemophilia has a fascinating history. The earliest description of the characteristic sex-linked mechanism of transmission of this bleeding disorder with its prolonged clotting time was that of John C. Otto in the Medical Repository of 1803, entitled "An Account of An Hemorrhagic Disposition Existing in Certain Families." Subsequently Lassen, in an article in the Deutsche Zeitschrift für Chirurgie in 1877, wrote, "Women transmit the disease but they do not manifest any of the symptoms. Only the men are bleeders." The characteristic genetic defect of the disease is carried by females but is manifest almost exclusively in males. This observation was recorded even earlier, as was shown by Rothschild (1882), when he pointed out that in the second century A.D. the following directive can be found in one of the Talmudic scriptures: "If a woman has had two sons who bled to death following circumcision, the third one should not be circumcised." At

that time it was unusual to place emphasis on the mother rather than on the father, whose task it is, according to Jewish custom, to see that his sons are circumcised.

Toward the end of the 19th century hemophilia gained considerable notoriety through the famous novel by Ernst Zahn, *Die Frauen von Tanno (The Women of the Tanno Valley),* which gave a detailed description of a Swiss family affected by an hereditary form of a tendency to bleed as a result of a failure of their blood to clot. Also its manifestations in Queen Victoria's offspring and in Alexei, son of the last Russian Czar, Nicholas II, made the disease generally known. The relationship of the Czarist family to Rasputin, which has been attributed directly to the Czarevich's illness, has become a part of modern history (74). It is less well known that prior to the engagement of Princess Elizabeth of England and Philip Mountbatten, both great-grandchildren of Queen Victoria, it was established by determining the factor VIII concentrations of their blood that their future children would not be regal bleeders.

Classic hemophilia (factor VIII deficiency) or deficiency of the antihemophilic globulin (AHG deficiency) is the most important, most common and one of the most serious bleeding disorders. Approximately 1 in every 10,000 persons is affected by the disease. Brinkhous estimated the magnitude of occurrence to be between 20,000 and 100,000 cases in the U.S. in 1964 (75). Less than one-half present with the serious form. Since factor VIII forms an important link in the chain reaction that constitutes the intrinsic clotting sequence, *but not of the extrinsic clotting mechanism,* a prolonged thromboplastin generation time or partial thromboplastin time and normal prothrombin time may be expected. Since platelet function is not affected, primary hemostasis and the control of bleeding from capillaries and smaller arterioles are, as a rule, not greatly disturbed. Since the extrinsic pathway is not affected, blood clots readily on contact with tissues. Hence massive clots form as a result of the continuous extravasation of blood into the tissues. The function of these clots in hemostasis is insignificant since they remain unrelated to the defect in the vessel wall. Consequently, trauma and operation result in hemorrhage.

The functional reserve capacity of the coagulation mechanism is truly amazing. A hemophilic patient rarely bleeds if his factor VIII is 5% or greater. This suggests that the amount of this factor present in blood is approximately 20 times greater than that required to provide normal hemostasis. In the hemophiliac, however, factor VIII levels may be found below 1%. Few of these patients survive infancy or childhood, since they usually succumb to uncontrollable cerebral and gastrointestinal hemorrhage. In contrast, the moderate (AHG level, 1–5%) or mild (5–25%) hemophiliac may only present with recur-

rent joint swelling or soft tissue hematomas and manifest a bleeding tendency only after trauma or operation.

In detecting the disease, the significance of a careful history, which should always include a family history, cannot be overemphasized. A history of bleeding following circumcision or from cuts and bruises and tongue bites or lip injuries is common. By contrast, prolonged nose-bleeding is quite rare. In the past, operations and dental extractions have led to exsanguination. Bleeding into joints and tissues is common. These bleeding episodes may appear unrelated to trauma, since they may become manifest as long as a week later. This has been related to breakdown of the platelet thrombi that provide the initial arrest of hemorrhage (primary hemostasis) in the absence of fibrin required to maintain hemostasis (defect of secondary hemostasis).

Hemophiliacs, like all other patients with serious congenital bleeding disorders and those on anticoagulants, should carry an identification bracelet, indicating the nature of their disorder so that proper measures can be taken immediately in case of accidents. Trauma not sufficiently severe to cause bleeding in normal individuals may cause serious hemorrhages in the hemophiliac.

By far the most common lesion is hemarthrosis, especially bleeding into and around the knee joint. The joint may become very large and so painful as to require local treatment (splinting and aspiration) and the administration of blood products and analgesics.

Bleeding into the muscles (e.g., psoas, gluteal and thigh muscles) is also not an uncommon complication. The hemophilic pseudotumors in muscles may become quite large; blood cysts are residues of large hematomas that failed to resorb or organize. If they erode through the underlying bone they may cause pathologic fractures. Following erosions through the skin, they become infected. The organized, thick cyst wall has, as a rule, extensive ramifications. Hematomas of calf and forearm muscles usually resolve with factor VIII infusion, local heat and immobilization. But wide, radical excision, and occasionally even amputation may be required to eliminate the chronic hematomas of thigh, buttocks or psoas muscle.

Surgical treatment of hemophilic cysts was extremely hazardous until a few years ago. Fifteen of 24 cases cited by Hall and co-workers (1962) died after aspiration, incision or biopsy (76). Major surgery in hemophilia has become safer with the development of effective concentrates of antihemophilic globulin, but one should not conclude that it now has become simple. It still poses many problems, particularly of recurrent bleeding. The reason is that for normal hemostasis and wound-healing factor VIII levels should be over 25%; in the first few days after trauma or surgery levels of 40–80% are preferred (77). Since these levels are not easily attained, the tendency to conservative management persists.

Pseudotumors of the bone also occur. They represent subperiosteal hemorrhage that gradually calcifies. Local areas of bone destruction are invariably associated with these hematomas. The tumors should be let alone whenever possible.

Britten and Salzman reviewed the management of the acute abdomen in patients with hemophilia (78). Since more hemophiliacs die from unnecessary operation than from neglected appendicitis, and because the majority of symptoms are due to bleeding into retroperitoneal structures and mesentery and may also produce pyrexia, tachycardia and leukocytosis, they stress that careful observation of the patient and a regimen of bed-rest and administration of factor VIII, intravenous fluids and antibiotics are indicated in those instances in which the diagnosis is uncertain. It should be mentioned that the finding of factor VIII levels in excess of 5–10% would rule out the likelihood of bleeding as a cause of the observed abnormalities. Hence, the necessity for immediate study of the factor VIII level of blood in addition to the usual screening procedures.

Intracranial hemorrhage may occur spontaneously in hemophiliacs. However, in about half of the cases it results from trauma. Its prognosis is poor. In one collective series the mortality was greater than 70%. Diagnostic lumbar puncture as well as cerebral arteriography can safely be performed, especially if specific transfusion therapy is started immediately.

For treating or for preparing a hemophiliac for operation, concentrated factor VIII fractions obtained from fresh frozen plasma have become available. A cold-insoluble fraction of human plasma, the so-called cryoprecipitate fraction, is rich in fibrinogen and factor VIII activity (79). The precipitate fraction from one unit of plasma can be infused in as little as 15–25 ml. of saline. A glycine-precipitated factor VIII fraction also provides a stable, potent source of antihemophilic globulin for clinical use. Both fractions provide more factor VIII and in significantly less volume than plasma or AHF-rich fibrinogen. Because of their low total protein content and small volume their use is not associated with overtransfusion and heart failure, not an uncommon complication of infusion of the large volumes of plasma required for effective prolonged therapy. Transfusion reaction, serum hepatitis and development of circulating anticoagulants, however, continue to pose a threat.

Following its administration approximately one fourth to one half of the infused factor VIII activity disappears within 3–6 hours, presumably as a result of its equilibration with the interstitial fluid. Subsequently a steady state is reached, whereafter the material decays linearly at a rate ranging from 7 to 10% per hour.

Rate of utilization or daily requirements for factor VIII vary, de-

pending on the severity of the hemostatic defect, the patient's temperature, the concentration of the active coagulation factors present in the cryoprecipitate fraction, its rate of utilization, especially in the process of hemostasis and the presence or absence of inhibitors of factor VIII activity. The severity of the defect is established by determining factor VIII assays or by performing thromboplastin generation or partial thromboplastin times. Others have advocated the use of the thromboelastograph for this purpose. The effect of therapy must be gauged several times daily by one of these laboratory procedures.

Resistance to human AHG may develop after multiple transfusions as an immune response to foreign protein. Inhibitor to factor VIII develops in about 5% of treated hemophiliacs. Such inhibitors are detected by the laboratory because factor VIII levels fall to zero. Transfusion therapy is ineffective. Steroids have not been successful in correcting this condition. Bidwell has suggested that under these circumstances transfusions with porcine or bovine factor VIII may be of benefit (80). If these materials are used, it should be determined first that they do not induce thrombocytopenia. Particularly bovine AHG has been found to contain agglutinins against human platelets.

Operation can be safely performed when the factor VIII level is greater than 25%. Preoperative loading with cryoprecipitate, which may contain in 250–300 ml., the pooled concentrate fractions of 10–30 units of plasma, can be done relatively rapidly (Table 1).

During operation, primary hemostasis is secured by direct pressure on the bleeding area, the administration of factor VIII, meticulous surgical technic and the use of hemostatic agents such as thrombin, gelfoam and oxycel. Blood losses are replaced with fresh, whole blood. The excessive tissue necrosis from cautery should be avoided as should the drainage of wounds or internal structures for fear of infection and

TABLE 1.—Relationship between Severity of Lesion in Hemophilia and the Blood Levels of Factor VIII Necessary to Secure Hemostasis

Type of Lesion	Posttreatment Hemostatic Level (%)	Dose of Factor VIII per 24-hour (U/kg.)
Superficial injuries; hemarthroses; hematuria; single tooth extraction; serious hematomata; multiple dental extractions; minor surgery.	20 (2–5)	10 (plasma)
	40 (10)	20–25 (human AHG)
Major surgery; large infected wounds.	100 (25)	60–80 (animal AHG)

Note.—The figures in brackets in column II indicate the levels 24 hours after the immediate postinfusion level. Column III indicates the dose required to achieve these levels and the type of material usually employed (after Macfarlane: *Scientific Foundations of Surgery*, C. Wells and J. Kyle (eds.) (New York: American Elsevier, 1967).

hazards of a draining wound. Hematoma formation contributes to secondary hemorrhages.

Sustained levels of 40–80% of factor VIII for at least 10 days after operation are required to provide hemostasis. This will necessitate transfusions of the cryoprecipitate fraction collected from 5 to 25 units of fresh frozen plasma, several times daily. Its effect should be followed by the partial thromboplastin test. Immobilization of the wound area, care in the change of dressings and transfusion immediately prior to removal of sutures will obviate untoward hemorrhage. Soft tissue defects and their attendant bleeding can be brought to healing with the use of skin grafts. Bleeding from the donor site is not likely to pose a serious problem.

The same regimen should be instituted for the control of the more serious hemorrhagic complications seen after severe trauma and during bleeding into critical areas. Why so few hemophilic patients develop serum hepatitis, despite massive transfusions, remains to be clarified. Many supposed hemophiliacs do not suffer from hemophilia but from factor IX deficiency. In fact, the subjects of Zahn's novel, referred to above, were suffering from this malady. Factor VIII deficiency occurs anywhere from 3 (Switzerland) to 10 times as frequently (England) as factor IX deficiency. Clinically factor IX deficiency is indistinguishable from hemophilia. Factor IX concentrates prepared from human plasma are also available.

FACTOR XIII DEFICIENCY.—Although quite rare, this condition is of particular significance to the surgeon because it results in defective wound healing. Since Duckert's original report, cases of congenital and acquired factor XIII deficiency have been recorded. The acquired form has been observed in patients with hyperfibrinogenemia and in patients with liver disease. The defect in fibrin clot polymerization results in excessive bleeding, usually 24–36 hours after operation. It can be prevented by preoperative administration of blood or plasma.

PART III

PREDICTION OF BLEEDING

The requirements for normal hemostasis include an adequate number of functional *platelets,* a normal *coagulation* mechanism and an intact *vascular* system. Hemostasis, however, has a truly impressive functional reserve capacity. As abnormalities in liver function become detectable only if large numbers of functional liver cells become involved, so bleeding as an expression of a deranged hemostatic function occurs only when the involvement of one or more of the three mentioned factors has exceeded certain limits. Thus patients with more

than 2–3% of factor VIII (hemophilia) bleed only after trauma or operation.

In contrast to a single enzyme determination for establishing liver or heart disease, a single test to detect abnormalities of the hemostatic mechanism is currently not available. Reliance cannot be placed on the clotting time, which is normal in many conditions associated with a markedly deranged coagulation mechanism. However, tests are available to detect practically every conceivable abnormality of the hemostatic mechanism. A defect can almost always be corrected once its nature has been established.

The prevention of a surgical or postoperative bleeding starts while the patient's history is being taken, for if this is done carefully it will frequently reveal past or familial bleeding tendencies. A detailed history, carefully taken, is the single most important screening approach for determining the hemostatic status (81). This history must specifically include direct questions concerning operations particularly circumcision, tonsillectomy and adenoidectomy, dental extraction or loss of deciduous teeth, excessive bleeding or hematoma formation following trauma and postoperative bleeding. Any bleeding or hematoma formation that occurred or continued for 12–24 hours after any of the above should be cause for suspicion. If this bleeding has necessitated transfusion, then a coagulation disorder should be presumed to be present until proved otherwise (82).

Epistaxis and abnormalities involving menstrual flow, because of their physiologic nature and wide variation in normal individuals, are not included in the above list. Yet questions concerning bleedings in these areas should form a part of the background information and must be evaluated concomitantly with other historical data. A positive history is diagnostic of a coagulation abnormality, especially when unusual bleeding has been observed on more than one occasion. Once the first suspicion of an abnormality has been aroused, continued questioning should invariably be followed by a more detailed study of the patient's hemostatic mechanism.

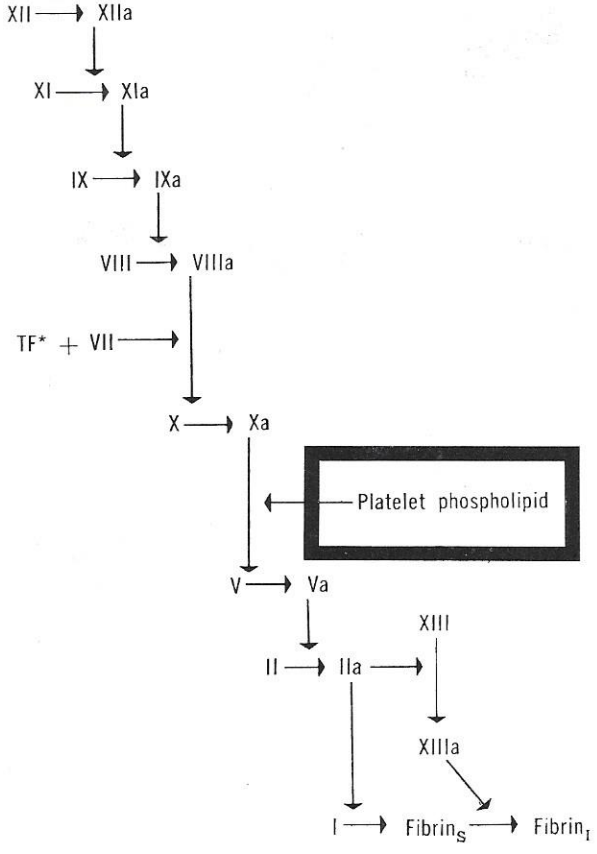
Once a bleeding has developed, however, treatment is usually resorted to before blood is obtained for proper studies. *It should be routine to collect blood for adequate testing before any treatment is given.* For proper collection, a clean venipuncture and the use of plastic syringes are important requirements. Prolonged constriction of the arm with a tourniquet should be avoided because the blood collected from vessels distal to such an obstruction often has increased fibrinolytic activity. A clean venipuncture is required to avoid the contamination of blood by tissue factor. The tubes containing the blood are placed in ice water containers before being transferred to the hematology laboratory. This diminishes *in vitro* decay of plasminogen activator, which occurs rapidly at room temperature.

Screening Tests of Plasma Factors

Screening for clotting abnormalities can be done rapidly with maximal efficiency by performing a partial thromboplastin time, a one-stage prothrombin time and a thrombin time determination. These tests are performed on platelet-free plasma samples (83).

The reaction for the partial *thromboplastin time* (PTT) is shown in Figure 8 and represents patients' plasma and partial thromboplastin + Ca^{++} = clot (in x seconds). "X" for normal plasma (in the kaolin

FIG. 8.—Partial thromboplastin time (PTT). Material in the box and CA^{++} are added to the patient's platelet-poor plasma and the clotting time is recorded in seconds. If kaolin is also added (activation of factor XII), normal value for the clotting time of this system = 35–45 seconds, which is the time required for completion of the entire reaction sequence (83).



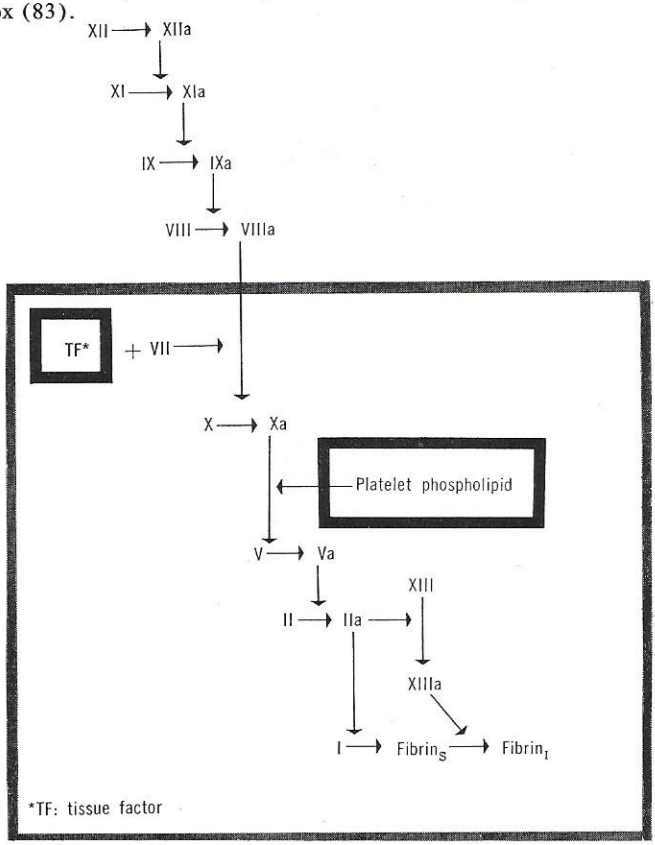
*TF: tissue factor

PTT, whereby the kaolin activates factor XII) ranges from 35 to 45 seconds. This is the time required for completion of the activation sequence from factor XII to factor II in the intrinsic pathway. The partial thromboplastin supplies the phospholipid normally contributed by the platelets.

In the *prothrombin time* determination the reaction as shown in Figure 9 is: patients' plasma + complete thromboplastin + Ca^{++} = clot (y seconds). Y for normal plasma ranges from 12 to 13 seconds. The complete thromboplastin used in this assay is derived from rabbit brain, while the platelet substitute in the PTT is an acetone extract of this preparation.

In patients with markedly prolonged PTT and normal prothrombin

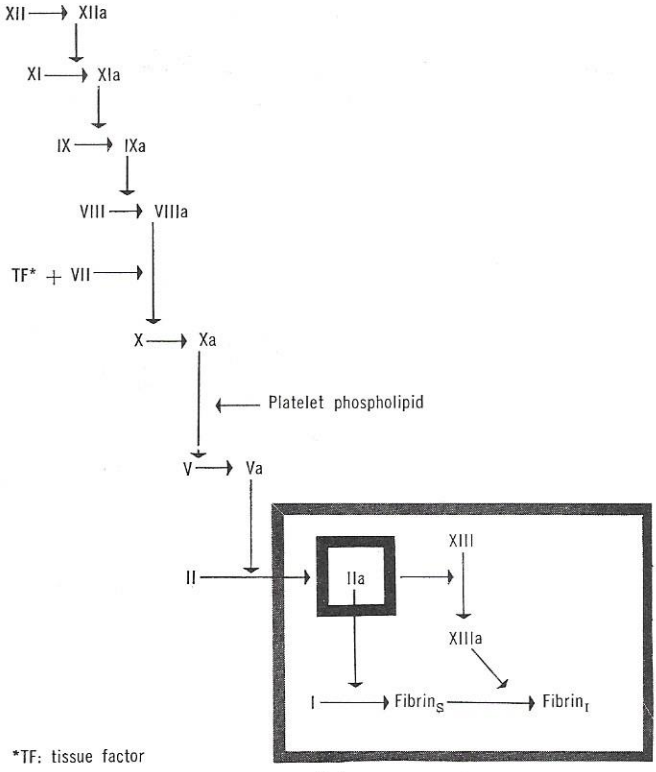
FIG. 9.—Prothrombin time. Material in the two small boxes and Ca^{++} are added to the patient's platelet-poor plasma and the clotting time is recorded in seconds. Normal value for the clotting time of this system = 12 to 13 seconds, which is the time required for completion of the reaction sequence enclosed in the large box (83).



time, the defect involves either factor VIII, IX, XI or XII. The cause most often encountered in such an abnormality is hemophilia, which on the average is 10 times more frequent than factor IX deficiency (Christmas disease), the second most common congenital clotting abnormality. If the prothrombin time is also prolonged, abnormality in the activation of factor V and X must be ruled out by more specific testing. A normal PTT in a patient whose prothrombin time is prolonged suggests that the intrinsic pathway of activation is normal. In this circumstance the abnormality involves factor VII only. Factor VII is the first factor to be affected by a vitamin K deficiency, and isolated factor VII deficiencies are not rare. Patients with biliary tract disease, sprue or jejunal diverticula and infants with cystic fibrosis or several other conditions may present such a defect. These patients have normal PTT and thrombin time but prolonged prothrombin time.

If no clot is formed in the PTT or prothrombin time, the amount of

FIG. 10.—Thrombin time determination. Material in the small box (thrombin) is added to the patient's platelet-poor plasma in an amount that will give a clotting time with normal plasma of 15 seconds. This is the time required for completion of the reaction sequence enclosed in the larger box (83).



available fibrinogen is assumed to be very small indeed. The presence of an anticoagulant is suggested if a clot is formed in either assay only after several minutes.

The *thrombin time reaction* (Fig. 10) is: patient's plasma + thrombin = clot (in z seconds).

This test is performed in plastic or siliconized tubes, because of the tendency of thrombin to be adsorbed onto glass (84). Prolongation of the thrombin time suggests the presence of an antithrombin. Heparin is the anticoagulant if the addition of small amounts of protamine to the reaction mixture corrects the thrombin time abnormality. Similarly, in these circumstances a patient's bleeding diathesis can be promptly corrected by administering small amounts of protamine sulfate until the clotting time has returned to normal values (85). If the thrombin time prolongation does not respond to the addition of protamine, further testing is necessary to determine whether the anticoagulant activity results from enhanced fibrinolytic activity or whether the material represents one of the acquired anticoagulants. Such an anticoagulant has been noted in patients with disseminated lupus erythematosus and interferes with the activation of factor X. Another anticoagulant has been observed in a patient with acute hemorrhagic pancreatitis receiving multiple blood transfusions; it interfered with factor V activation.

These abnormalities, as well as deficiencies in individual clotting factors, can be detected by tests designed to assess the presence or absence of such factors. The principle depends on how well the patient's plasma (as compared to normal plasma) can correct the defect in plasma of patients with known factor deficiencies. For example, if the patient's plasma corrects the abnormal PTT of hemophiliac plasma, it is obvious that the patient himself has no hemophilia or factor VIII deficiency. If, however, the patient's plasma will not correct the abnormally long PTT of factor IX-deficient plasma, the patient himself has factor IX deficiency. In this way, it is possible to test for the presence or absence of every individual coagulation factor.

Screening Tests of Platelets

Platelet abnormalities can be determined by several methods. In the absence of purpura or ecchymoses, a tourniquet test is performed by applying to the upper arm a blood pressure cuff, which for 5 minutes is kept inflated halfway between diastolic and systolic pressure. In a positive test, petechiae appear in the skin, their number and size being roughly proportional to the hemorrhagic diathesis. Increased capillary fragility indicates vascular disease or platelet abnormalities. The former occurs in patients with scurvy or infections (measles, flu, scarlet fever); the latter is seen in thrombocytopenia, uremia and several

other conditions. If the platelet count is normal but the bleeding time is prolonged, this suggests (if the vascular wall is not involved), an abnormality in the adhesive or aggregating properties of platelets. Specialized technics are required for this diagnosis. Few of these tests are done routinely; the majority are currently performed only in the research laboratories. Tests use platelet-rich plasma and include determination of platelet adhesiveness, platelet factor 3 activity, the ADP concentration required for aggregation, platelet lifespan, clot retraction and platelet morphology as determined by phase contrast microscopy and electron microscopy.

The simplest of these tests is undoubtedly the clot retraction test. It is found to be abnormal in patients with thrombocytopenia, abnormal platelet function (e.g., uremia), the presence of plasma proteins in larger than normal quantities (particularly of fibrinogen or globulins) or the presence of abnormal proteins (dysproteinemia, cryoglobulinemia, etc.). Abnormalities in clot retraction have been observed in patients with multiple myeloma, hyperglobulinemia, cryofibrinogenemia, liver cirrhosis and lupus erythematosus.

Detection of Increased Fibrinolysis

Evidence of increased fibrinolytic activity can be obtained from a whole blood or plasma clot incubated in a 37 C. water bath. The time required for lysis of the clot is recorded and compared with that for normal blood or plasma. Results can be obtained more rapidly with the euglobulin clot lysis time determination (86). In addition, a number of other tests have been worked out to assess this activity of this plasma enzyme. These include determination of plasminogen, concentration of plasminogen activator and antiplasmin activity and more recently of fibrinogen split products (86).

These tests can be performed on a routine basis. Three or 4 technicians trained to perform 5 or 6 procedures, or a division of work, whereby one studies clotting, another platelet function, and a third performs fibrinolysin studies, could provide an invaluable service provided surgeons availed themselves of it at the first suspicion that abnormalities of the hemostatic mechanism may be developing.

Fortunately, it is rarely necessary to perform all these tests in every patient. The decision on which test to perform in an individual case depends on the information obtained with the basic clotting (PTT, prothrombin and thrombin time) and platelet tests (platelet count, bleeding time and clot retraction test). This information, which can be fed into a computer, provides the technologist with advice on what procedure to do next.

This work is eminently suited for performance by technologists who

TABLE 2.—Complete Range of Tests for Bleeding Disorders (96)

Platelet Tests	Clotting Tests	Tests for Fibrinolysis
Platelet count	P.T.T.	Euglobulin clot lysis time
Bleeding time	Protime	Plasma clot lysis time
Platelet adhesiveness	Thrombin time	Plasminogen concentration
Platelet factor 3 activity	Fibrinogen	Plasminogen activator activity
ADP aggregation test	Cryofibrinogen	Antiplasmin concentration
Platelet lifespan	Prothrombin consumption	F.D.P. concentration
Clot retraction	Factor analysis	
Platelet morphology	(VIII, IX, XIII, etc.)	

have ready access to a small, compact computer. Modern technology has made it possible systematically to collate extensive data, commensurate with what is known on each diagnostic hematologic profile, and to associate prognosis and treatments with each specific profile. This information, accommodated in the store of a computer, can be updated and periodically re-evaluated. This is especially feasible since in the process of evaluation a diagnosis of a defect is derived by the process of elimination whereby each step is taken in a logical sequence, determined solely by what is found in a preceding step. This may seem to diminish the "art" of making a diagnosis of a hemostatic defect but increases the accuracy and decreases the time required.

One technologist, adequately trained to perform approximately 15–25 routine hematologic procedures, or 2 or more persons who would divide this task into several groups of procedures as shown in Table 2, can, with the aid of a computer, arrive at a diagnosis of any bleeding disorder, using one blood sample.

The computer not only would record the diagnosis and elaborate on how it was arrived at, but could also advise on the management of the patient's disorder in a report typed out on a slip of paper that, transmitted immediately to the nursing station, can be rapidly attached to the patient's chart. Such a computer could be made available through telephone connections to every hospital of an entire area.

MANAGEMENT DECISIONS

The majority of diagnostic problems can be solved with intelligent use of the screening tests that are available in most hospitals. When it has been shown that a specific hemostatic defect accounts for the observed bleeding episode, the question of management arises.

Let us assume that bleeding has resulted from an abnormality in either number or function of platelets. The logical treatment would be to administer fresh platelets. This is done by replacing the lost blood

with fresh blood obtained in siliconized or plastic containers. Similar results can be expected from the use of platelet-rich plasma. The finding of an abnormally long PTT in a patient who has a normal prothrombin time might indicate hemophilia. Operations or dental extractions should be delayed and the patient referred to a hematologist who has the laboratory facilities that enable him to make an accurate diagnosis.

The presence of anticoagulants, as detected by the prolongation of all the plasma screening tests and the failure to correct fully the defect on addition of normal plasma, is a possibility. If this defect cannot be corrected in the test tube by protamine sulfate, heparin is not the cause of the bleeding. If, in addition, the euglobulin clot lysis time is shortened, the patient may be clotting intravascularly or lysing his own plasma proteins or both. Intravascular coagulation occurs often enough to present a threat to patients with hemorrhagic pancreatitis, extensive burns, shock from any cause, ulcerative and pseudomembranous colitis, hemangiomas, hemolytic crises, incompatible blood transfusion, liver cirrhosis, polycythemia, malaria, viral and rickettsial diseases, cryofibrinogenemia, neoplastic disease, septicemia, eclampsia, amniotic fluid embolism, infected abortion, hydatidiform mole, cyanotic congenital heart disease, Waterhouse-Friderichsen syndrome, infantile diarrhea, and a number of other conditions. If intravascular coagulation is present, one may expect to find thrombocytopenia, decreased fibrinogen, decreased factor V concentration and a low or high factor VIII activity. In the chronic form, heparin therapy will alleviate the condition. Prompt treatment is imperative; every effort should be made to overcome the clinician's resistance to the use of heparin, the only form of treatment for this severe bleeding problem. Following heparin therapy, bleeding will continue till all clotting abnormalities have resolved. Hence blood replacement will have to be continued for 1 or 2 days after starting heparin treatment.

The fibrinolysis which often accompanies these cases is treated with intravenous administration of epsilon amino caproic acid or one of the related inhibitors every 2–3 hours in doses ranging from 1.5 to 3 Gm. This drug should never be used alone in treating patients with increased fibrinolytic activity and evidence of intravascular coagulation because it may result in massive thrombosis (87). In the absence of intravascular coagulation, however, epsilon amino caproic acid is the drug of choice.

Unfortunately, epsilon amino caproic acid may fail to elicit a response in patients with fibrinolysis who have bled for some time, especially when large amounts of fibrinogen degradation products have been formed. These split products, which interfere with platelet aggregation (61) and act as anticoagulants (59), have a long in vivo half-life (38), and no specific agent is available to counteract their activity

in vivo. Consequently, the only resource available is the use of whole blood.

Massive transfusion frequently results in further bleeding. Adequate supplies of labile clotting factors (V and VIII) and platelets, both of which are virtually absent in bank blood, are available in fresh blood, especially when collected in silicone-treated glassware or plastic containers. Every attempt should be made to obtain fresh blood when it becomes apparent that the volume required to replace the losses will approach the patient's blood volume.

The use of aged plasma, free of hepatitis virus, to restore blood volume, is briefly mentioned. This plasma is not only devoid of the labile clotting factors but also lacks part of its fibrinogen after a 6-month storage. This has been found to result from fibrinogen breakdown (88). Hence aged plasma should not be used to restore blood volume during or immediately after a bleeding episode, because the breakdown products present in such plasma greatly enhance any bleeding tendency that may exist.

Ionized Ca^{++} is required for the normal coagulation of blood and should be used after blood transfusions whenever large quantities of citrate are given rapidly (e.g., massive blood transfusions) when mobilization of calcium from the bone is delayed (e.g., osteoporosis) or in instances where normal citrate metabolism is interfered with (e.g., liver disease, hepatectomy or liver transplantation). It is usually given as calcium chloride or calcium gluconate (89).

Abnormalities in prothrombin time in patients with normal PTT and thrombin time result from deficiency of vitamin K-dependent factors, particularly factor VII. The use of vitamin K or its water-soluble derivative can help to correct this defect.

Deficiency of a specific coagulation factor, once thought to be rare, is no longer an unusual finding. For correction of inborn or acquired defects, fresh whole blood, fresh frozen plasma or protein fractions can now be obtained. Factor VIII-rich cryoprecipitate and the glycine precipitated fraction of fresh plasma have become great assets in the treatment of hemophilia.

Preoperative Management

The preoperative management of patients with hemophilia or defects of the vascular wall or platelet function has been briefly outlined. However, the treatment of several acquired abnormalities requires further discussion.

For patients with *chronic, idiopathic, thrombocytopenic purpura* who require splenectomy, the preoperative administration of steroids and fresh blood or platelet transfusions may be indicated to correct

extensive preoperative abnormalities in the bleeding time and prothrombin consumption test.

The incidence of complications after operation in patients with *polycythemia vera* is high, particularly in those in whom the disease is uncontrolled, and whose hemoglobin and hematocrit values are greater than normal. Gilbert and Wasserman (91) noted complications in 40–50% of their operated patients. The complication rate was 80% in uncontrolled cases and was less than 30% in those that were controlled. Complications consisted of hemorrhage (65%), thrombosis (25%) and infection (20%). Postoperative mortality was also high (15–20%). Clotting studies showed multiple defects including a decreased concentration of several clotting factors, a poor organization of the clot, platelet factor 3 deficiency and an anticoagulant effect associated with thrombocytopenia but also with antiplasmin deficiency and fibrinolysis.

Administration of myelosuppressive agents should be continued in patients with polycythemia vera for as long as necessary to achieve and maintain a normal blood count. In case of emergency operation, repeated phlebotomies are performed to reduce red cell volume to normal. Fresh blood is administered in case of postoperative hemorrhage.

The incidence of postoperative bleeding, thrombosis and infection in patients with *myelofibrosis, leukemia* and *lymphoma* is also markedly increased (91). This has been related to quantitative and qualitative platelet defects and to abnormalities of the plasma proteins, specifically the coagulation proteins. Elective surgical procedures should be avoided in these patients; however, when operation is required, correction of the hemostatic defect should be attempted with vitamin K, platelet transfusions and fresh blood or plasma.

Obstructive jaundice, prolonged use of broad-spectrum antibiotics, sprue, intestinal fistula and upper gastrointestinal obstructions are frequently associated with prothrombin deficiency. This is easily corrected by parenteral administration of vitamin K. Patients with *liver cirrhosis* may exhibit deficiency of prothrombin and other vitamin K-dependent factors and at times enhanced fibrinolytic activity (47). This was found to respond favorably to antifibrinolytic agents such as epsilon amino caproic acid (92) or Trasylol. Functionally abnormal platelets or thrombocytopenia secondary to congestive splenomegaly may also occur. In the severe alcoholic with nutritional deficiencies and hypovitaminosis, abnormal vascular fragility and easy bruising are not uncommon findings. Therefore, treatment with vitamin K may not be sufficient to alleviate bleeding or to prepare the patient for operation. Under these circumstances the use of fresh blood, vitamin K_1 oxide, multivitamins and antifibrinolytic agents should not be omitted.

In patients with *uremia* the accumulation of metabolic products interferes with the normal function of platelets (93). Control of uremia

with hemodialysis reverses this abnormality. Occasionally patients start to bleed several hours after completion of hemodialysis in spite of what may be considered as adequate heparin neutralization. Heparin "rebound" may be implicated when thrombin times are found to be prolonged and when the defect can be corrected in the test tube with small amounts of protamine. In these instances the bleeding can be readily controlled with intravenously administered protamine.

Mismatched blood transfusions are prevented only by adequate care in blood grouping and cross-matching technics and by meticulous care in all clerical work connected with transfusion therapy. Incompatible blood transfusions in the pre- or postoperative period are frequently associated with severe pain in the back, a feeling of constriction in the chest, dyspnea and shock. Death may supervene rapidly.

The first stage is often initiated by a bleeding tendency, characterized by thrombocytopenia, hypoprothrombinemia and hypofibrinogenemia. In fact, during operation the characteristic features are uncontrollable oozing, tachycardia and the development of shock. In either circumstance, the first objective should be maintenance of the blood pressure and urinary output. Hence after a urinary catheter is inserted in the bladder, sufficient fresh, newly typed and cross-matched blood and glucose and electrolyte solutions are administered to maintain these two functions. Heparin therapy should be instituted early in the treatment of this condition since its late use is of no value. Only if anuria develops should the input be reduced to match the patient's urinary output.

If the patient survives, free hemoglobin may accumulate in plasma and urine with the later development of jaundice. This second phase is frequently associated with renal damage, oliguria, azotemia, anuria and hyperkalemia.

The hemorrhagic diathesis observed in patients with *cyanotic congenital heart disease* is related to secondary polycythemia. Although

TABLE 3.—Extent of Pre-existing Clotting Defects in Patients with Congenital Heart Defects (96)

Parameters Studied (Their Normal Range)	No. Cases Studied: Total	Cases with Normal Values	Cases with Abnormal Values	Range of Abnormal Values
Platelet count (200,000-400,000)	71	62 (88%)	9 (12%)	90,000-150,000
Lee White clotting time (12-22 min.)	49	45 (92%)	4 (8%)	25-35 min.
Prothrombin time (13/13-16/13 sec.)	73	54 (74%)	19 (28%)	16/13-35/13 sec.
Thrombin time (20-30 sec.)	43	29 (67%)	14 (33%)	50-180 sec.

thrombocytopenia or abnormal platelet function, hypofibrinogenemia, reduction of the prothrombin complex and increased fibrinolytic activity occur more than occasionally (Table 3), in general, preoperative phlebotomies will greatly reduce the incidence of postoperative hemorrhage. This procedure is sometimes poorly tolerated, especially if it provokes transient hypotension and increased cyanosis.

Shock, regardless of its cause, will affect the hemostatic mechanism if allowed to persist for some time. Septicemic shock, especially from the endotoxins of gram-negative organisms, induces intravascular coagulation (94). This is particularly pronounced in those instances in which recurrent bouts of septicemia occur to mimic closely the experimental Shwartzman reaction.

Operative Bleeding

Cardiopulmonary bypass.—During cardiac bypass the blood is exposed to considerable trauma. The effect of the trauma on the cellular and plasmatic components of blood was experimentally determined by recirculating freshly drawn human blood through a pump oxygenator. Destruction of significant numbers of platelets and erythrocytes was found. The first alteration could be determined directly. The second was inferred from the finding of a rise in plasma hemoglobin concentration.

As a result of cellular injuries, significant shortening of the recalcification and thrombin generation time became apparent during these experiments. The extent of the changes indicated the development of a state of marked hypercoagulability (Table 4). When cell-free plasma instead of whole blood was used for recirculation, no changes in recalcification time and thrombin generation time were present. It was con-

TABLE 4.—Effect of Perfusion on Blood during in Vitro Studies (96)

Findings		Remarks
Platelet count	Decreased	The longer the perfusion, the more marked the decline in platelet number
Fibrinogen concentration	Unaltered	
Plasma hemoglobin concentration	Increased	The longer the perfusion, the greater the rise in plasma hemoglobin concentration
Recalcification time	Shortened	Marked shortening occurs after 30-45 min. of perfusion
Thrombin generation time	Shortened	Marked shortening occurs after 30-45 min. of perfusion

cluded that the alteration of blood cells was causally related to the hypercoagulability changes observed in blood (95).

These in vitro changes find their counterpart in patients undergoing open heart operations. In addition to evidence of blood cell destruction, the extent of which increases as the time of bypass becomes longer, a decline in fibrinogen and prothrombin complex is noted. These changes presumably result from intravascular coagulation (96).

Shortly after the initiation of cardiopulmonary bypass, considerable plasminogen activator activity can be found in plasma. The degree of this activity can be related to the duration of cardiac bypass (97). In addition, the in vivo half-life value of plasminogen activator activity becomes prolonged after extended cardiopulmonary bypass procedures. Since plasminogen activator is presumably cleared by phagocytosis, prolonged half-life values can then be ascribed to impairment of reticuloendothelial function (98).

GENERAL CONSIDERATIONS.—The exact incidence of operative bleeding is not known, for criteria that delineate normal from abnormal blood loss are not sharply defined. The experienced surgeon, however, senses immediately that something is amiss when oozing occurs.

Blood loss can be related to the patient, the surgeon, the anesthesiologist, the type of operative procedure and many other factors. The handling of the tissues and the time and care taken to achieve adequate mechanical hemostasis are not only factors that determine blood loss but are also reflected in other operative or postoperative complications.

The extent and nature of the blood replacement, the anesthetic agent used, the adequacy in maintaining blood pressure and tissue oxygenation are also of significance in determining the incidence of operative and postoperative hemorrhage.

Bleeding that occurs as a generalized oozing from the time of the first incision should be cause for serious concern. The patient's history and laboratory data should be reviewed. If they are unavailable on the patient's chart, any further surgical intervention should be deferred and the patient's hemostatic mechanism studied to rule out congenital or acquired abnormalities before serious and irreversible changes in hemostasis occur.

In the absence of known abnormalities and with normal values for the screening tests on the chart, however, it is advisable to question the anesthesiologist concerning the nature of the anesthetic agent, whether the blood pressure is normal and whether the patient is adequately oxygenated. If the patient is receiving blood, it should be checked to rule out the possibility of errors that may have led to a mismatched transfusion.

The abnormal bleeding tendency occasionally observed with the use of cyclopropane and halothane has been ascribed to elevations in central and peripheral venous pressure (99). A variety of mechanical

factors, such as an airway obstruction, increased intrathoracic pressure during positive pressure breathing and overtransfusion may also lead to increased venous pressure and bleeding. Hypoventilation affects bleeding, presumably through the effects of hypercarbia and hypoxia on venous pressure and through its hypertensive effect.

Blood replacement should keep pace with blood loss. The need for accurate determination of blood loss by the weighing of sponges and packs and the estimation of blood loss in towels and drapes as well as the measurement of the effluent in suction bottles has become generally accepted. Nevertheless, inadequate replacement of blood loss remains the most common cause of operative hypotension.

Hypotension initially promotes clotting. Prolonged hypotensive episodes, however, result in severe derangements of the coagulation mechanism which rapidly assume magnitudes that defy any form of therapy (100).

The knowledge that certain conditions predispose to hemorrhage should be of help in properly preparing the patient and anticipating excessive blood loss. Extensive surgical resections for cancer, especially of the prostate (101), lung, breast and pancreas, and also pulmonary resections (102) and hepatic lobectomies (57) have occasionally been associated with rapid development of clotting abnormalities. Intravascular coagulation and fibrinolysis have been associated with the surgical procedures for these diseases. The sequestration of devitalized tissue, whether by extensive third degree burns induced by the electric current of the Bovie apparatus or by ligating more tissue than the bleeding vessel alone, adversely affects the hemostatic mechanism, if not during operation then within the first postoperative week. The extensive dissection that results in large raw surfaces from which serum and tissue factor are readily resorbed in more than usual quantities and the extensive clotting required to effect hemostasis of such a surface may be contributing factors. Whatever the cause, however, the decision as to how to manage the patient who starts to ooze during operations should not be delayed, for it cannot await time-consuming laboratory procedures.

Packing the bleeding surfaces with moist, warm packs, oxycel or gelfoam in thrombin under application of local pressure and the administration of freshly drawn blood, fresh frozen plasma, and vitamin K_1 oxide, are innocuous, exceedingly useful measures and may suffice. Before any blood is administered, however, blood samples are obtained for examination by the hemotologist.

If these measures fail to control the hemorrhage, or if no hematologist is available, a small amount of thrombin can be added to a tube of the patient's blood. If this blood does not clot or if it results only in a tiny, flimsy clot, indicating absence of fibrinogen or presence of antithrombin, the chance that the bleeding results from extensive intra-

vascular coagulation with or without associated fibrinolysis is sufficiently great to warrant vigorous treatment with heparin, epsilon amino caproic acid, fresh blood, fibrinogen and platelet transfusions in an attempt to control a bleeding disorder which may be life-threatening. Failure to use heparin under these circumstances may precipitate a renewed episode of intravascular coagulation. Heparin will seriously affect hemostasis only if adequate numbers of platelets are not present to maintain primary hemostasis.

Postoperative Bleeding

Postoperative hemorrhage from wounds or chest tubes results probably more often from inadequate surgical hemostasis than from inadequate physiologic hemostasis. The failure to ligate a vessel that continues to bleed manifests itself in exactly the same manner as a deranged hemostatic mechanism, that is, as bleeding from the incision. In emergency situations it is frequently difficult to determine the exact cause of the bleeding. The presence of purpura, either as petechiae or ecchymoses, is a tell-tale sign. Yet, its absence does not absolve the hemostatic mechanism, nor for that matter does a normal bleeding or clotting time. To ascribe postoperative bleeding to inadequate surgical hemostasis is unwise and inappropriate. Bleeding postoperatively often occurs after certain types of operation, particularly open heart, prostatic or pulmonary, but bleeding following an appendectomy, tonsillectomy or dental extraction is unusual and demands investigation.

Drug-induced hemorrhages, liver disease, defective protein synthesis and increased blood proteolysis frequently occur during the postoperative period to account for postoperative hemorrhage.

Postoperative thrombocytopenia, as a result of severe infection or massive blood transfusion, is not rare. *Proper testing is required to determine the cause of the bleeding.*

In addition, the postoperative period is characterized by a hypercoagulability state. As long as the mechanisms that localize thrombin activity remain intact, diffuse intravascular coagulation probably does not develop to a clinically significant degree. In those vessels in which the blood is permitted to pool, however, localized clotting may result in the development of venous thrombosis.

CHANGES IN BLOOD COAGULABILITY

In 1915 Walter Cannon observed that pain, hunger, fear and rage enhance the coagulability of blood (103). He related these changes to the release of adrenalin. Since then a host of agents has been found to affect the coagulability of blood, either increasing or decreasing it.

While a hypocoagulability state is usually associated with deficiency of coagulation factors or follows anticoagulant therapy, hypercoagulability of blood results from changes in the colloidal state of fibrinogen either in the degree of hydration or in electric charge. Such alterations are thought to contribute to the sludging of blood cells. Hypercoagulability has also been associated with the presence of the active and intermediate products of coagulation in blood. Presumably these are normally absent from circulating blood but may form intravascularly or be released from tissues. Occasionally they overcome the clot-inhibiting capacity of the blood and the ability of the reticuloendothelial system to clear the blood, thus inducing diffuse intravascular coagulation. Agents that depress reticuloendothelial activity (104), materials that aggregate and degranulate platelets (19) (serotonin, endotoxin, histamine, adrenalin, thrombin, etc.), but also serum and free, nonesterified, long-chain saturated fatty acids (105) (in contrast to unsaturated fatty acids) are some of the presently recognized agents that can induce blood hypercoagulability.

The relationship of the hypercoagulability of blood to specific disease entities is presently far from clear. It is not unlikely, however, that future studies in this area may modify our concepts of several diseases, particularly atherosclerosis.

PART IV

THE DEFIBRINATION SYNDROME

A number of agents can induce platelet aggregation following entry into the circulation. The exact mechanism whereby this occurs is not known. Endotoxin, the lipopolysaccharide fraction of the membrane of gram-negative bacteria, induces the aggregation of platelets as do thrombin, epinephrine, serotonin, adenosine diphosphate and the phagocytosis by platelets of antigen-antibody complexes. The platelet aggregates are filtered off in the microvascular bed of the liver, lung and kidneys where, following the release of serotonin, vessels constrict, and after the release of platelet factor 3, coagulation proceeds with the formation of fibrin.

The coagulation process that is activated in the peripheral vascular bed exerts clinical manifestations. These have been designated as the "syndrome of disseminated intravascular coagulation," and "defibrination syndrome." It has stimulated considerable interest because of its prevalence, for it is the most frequently acquired hemostatic defect. Several conferences and a number of books have recently been devoted to the subject (106).

Defibrination (acquired a- or hypofibrinogenemia) rarely results

from a defective fibrinogen production. Instead, it is due to rapid utilization of fibrinogen by intravascular coagulation or its destruction by fibrinolysis. Not infrequently both processes occur simultaneously.

Intravascular Coagulation

Several mechanisms have been implicated in triggering intravascular coagulation. The most obvious occurs when "tissue factor" enters the circulation inducing activation of the extrinsic clotting mechanism. Intravascular coagulation is implicated in shock, hemolysis, surgical trauma, hemorrhagic pancreatitis, certain malignancies, chronic homograft rejection, arterial reconstructive operations, fat embolism, septicemia, giant hemangioma (Kasabach-Merritt syndrome), incompatible blood transfusions, liver cirrhosis, extracorporeal circulation and many other conditions. The "intrinsic" coagulation mechanism can also be activated through "contact" activation. Any condition associated with endothelial damage (e.g., viral and rickettsial diseases), exposure of blood to foreign surfaces (e.g., the implantation of vascular prostheses) or following extracorporeal circulation of blood (e.g., hemodialysis and cardiopulmonary bypass) activates the coagulation mechanism.

Some of the vagaries of the defibrination syndrome must be ascribed to the involvement of different organs in different patients. The localization of fibrin, according to McKay (107), relates to the amount and differences in potency of procoagulant released in the blood and to the duration of the clotting episode. For example, endotoxin is much more potent in inducing clotting than is incompatible blood. In the dog, rapid intravenous administration of incompatible blood is sometimes followed by death from right heart failure with widespread fibrin deposition in the lungs. Intra-aortic administration of similar quantities, however, rarely affects the animal. Treatment with steroids and ACTH or adrenergic stimulation greatly enhances the deposition of fibrin, while blockade of alpha adrenergic pathways with dibenzyline or dibenamide reduces this effect.

Intravascular fibrin often disappears. Thus intravascular coagulation induced in dogs by slow infusion of thrombin is well tolerated. Little or no fibrin is found at autopsy, even though the animals are completely or nearly completely defibrinated (108). In contrast, the addition of epsilon amino caproic acid to thrombin or pretreatment of the animal with carbon to induce reticuloendothelial blockade is rather poorly tolerated. It results in death of one fourth to one half of the animals. At autopsy intravascular fibrin can now readily be demonstrated with definite morphologic evidence of organ damage (87). Similarly, endotoxin injection into rabbits in *sublethal* doses induces a full-blown Shwartzman reaction if the endotoxin is combined with either epineph-

rine, steroids or carbon (or other inhibitors of phagocytosis). Intravascular fibrin, formed under those circumstances, tends to persist for longer periods of time (109).

Only a few years ago, the diagnosis of intravascular coagulation was not accepted if fibrin could not be demonstrated. Now it is generally conceded that fibrin may be absent at biopsy or autopsy because of its susceptibility to proteolytic enzymes, particularly those derived from leukocytes, macrophages, vascular endothelium and organ cells.

It cannot be overemphasized that normothermic ischemia is tolerated for only a very short time. Ischemic brain damage follows an arterial occlusion of only a few minutes. Liver injury, severe enough to result in death, develops after arterial occlusion of 15–20 minutes. Hence long-term presence of fibrin is not required to inflict serious damage to tissues or organs. The degree of tissue injury merely relates to the extent of the vascular occlusion and to the degree of collateral circulation. Extensive vascular occlusion is poorly tolerated, *even for a very short time,* if the organ lacks an adequate collateral circulation.

The physiologic effects include severe acidosis, characterized by a marked base deficit. Hyperkalemia occurs which closely reflects the extent of tissue damage. It represents a defect of the sodium pump, an ATPase type, membrane-bound enzyme system responsible for maintaining high intracellular potassium levels and for the removal of excess sodium from the cell. Serum sodium levels decline as sodium escapes into the damaged cells. Platelet count and fibrinogen levels fall, at times to the extent that blood becomes unclottable. Respiratory distress in the severe cases is pronounced and indistinguishable from that observed in hyaline membrane disease, septicemia or hemorrhagic and traumatic shock or in patients with pseudomembranous enterocolitis, fat embolism or after cardiopulmonary bypass. The distress is characterized by dyspnea, orthopnea and occasionally by cyanosis. The development of pulmonary edema frequently precedes circulatory collapse from right heart failure. In less severe form, it presents a patchy pneumonitis with evidence of mild to moderate functional impairment.

Clinically renal involvement ranges from hematuria to oliguria or anuria. Microscopic evidence of fibrin thrombi in the capillary tufts of glomeruli is frequently present. The anuric patient rapidly develops uremia with its concomitant metabolic derangements of acidosis, hyperkalemia and hyponatremia. These abnormalities are also invariably found in patients who have serious hepatic ischemia; it is then associated with progressive jaundice and chemical evidence of liver cell damage. The extent of the involvement is closely reflected in elevation of the hepatocellular enzymes in the blood, e.g., glutamic oxalic transaminase, glutamic pyruvic transaminase, ornithine carbonyl transaminase, lactic dehydrogenase and others. In the presence of both renal and hepatic failure, the patient develops hepatorenal syndrome.

Intestinal manifestations of erosive gastritis and hemorrhagic enterocolitis have been described. It is of note that this type of upper gastrointestinal hemorrhage, ischemic in nature, in contrast to many forms of stress ulcers, rarely responds to vagotomy and pyloroplasty. Hemorrhagic adrenal necrosis, formerly specifically identified with meningococcus septicemia (Waterhouse-Friderichsen syndrome), has also been noted in conditions associated with diffuse intravascular coagulation and consumption coagulopathy.

Several abnormalities have been noted in the blood and plasma of these patients. Besides the coagulation changes (to be discussed in more detail), there are changes in the erythrocyte morphology and the development of cold precipitable proteins.

The plasma of patients with disseminated intravascular coagulation contains varying quantities of cryoglobulins, proteins which, in vitro, form gelatinous precipitates in the cold. Following addition of heparin fibrinogen also tends to precipitate under these circumstances (heparin precipitable fraction). This material represents a fibrinogen altered by the partial action of thrombin and possibly also plasmin. Cryofibrinogen in vivo sensitizes the patient to cold. Exposure to cold may range from a plantar ulcer to a pulseless limb or gangrenous toe. Hence the use of hypothermia, to combat hyperpyrexia, under these circumstances is not a harmless procedure as we had the occasion to observe in several patients. Heparin, which will precipitate these proteins in vitro, blocks the further formation of cryoglobulins in vivo when administered in doses ranging from 100 to 175 units per kg. body weight every 4 hours.

Also, injury to the blood cells, particularly the erythrocytes, has been found in patients during the defibrination syndrome. Fragmentation of erythrocytes becomes recognizable in a peripheral blood smear. Schistocytes, including helmet cells, burr cells, triangular shaped cells, irregular contracted cells and other fragmented forms, can be readily seen. Dacie and his associates have postulated that interaction of erythrocytes with fibrin strands results in hemolysis and red cell fragmentation (110).

Irrespective of the mode of activation of the coagulation mechanism, the ultimate effect is determined largely by the *rate* and the *degree of defibrination* of the blood. The slow development of thrombin is probably tolerated to a certain degree since plasma contains a number of mechanisms designed to localize and neutralize thrombin activity. Only when these mechanisms break down as a result of a deficiency in the antithrombin system, depression of reticuloendothelial activity or defects of fibrinolysis is intravascular coagulation expected to develop. Hence, minor episodes of intravascular coagulation are, as a rule, well tolerated and remain unrecognized. The microemboli that are formed presumably block relatively *few* arterioles or capillaries, with rapid

lysis of the fibrin and reopening of the vessels. Rapid and extensive microembolization, on the other hand, is poorly tolerated. It results in severe tissue hypoxia, acidosis, edema formation, hemorrhage and shock and in impairment or failure in function of one or several of the filter organs (lungs, liver, kidney). Because of its profound depletion of coagulation factors it is invariably associated with a serious bleeding diathesis.

The critical issue in the management of patients with defibrination syndrome is to recognize the condition and to establish the diagnosis early when it is potentially curable.

The consumption coagulopathy that results is the most evident and lucid clinical manifestation of this syndrome. It is characterized by hypofibrinogenemia or afibrinogenemia, thrombocytopenia and hypoprothrombinemia. Following the entry of tissue factor into the blood stream, or in the presence of contact activation, increased proteolytic activity of blood frequently occurs, presumably from activation of plasminogen by tissue activators. Shortened euglobulin clot lysis times, prolonged thrombin times, increased quantities of fibrin and/or fibrinogen degradation products and cryofibrinogenemia can then be readily demonstrated. Whether fibrinolysis accompanies every episode of intravascular coagulation is not clear. Recently Sherry described a case of chronic intravascular coagulation without associated fibrinolysis. Wherever proteolysis is associated with this condition, however, fibrin and fibrinogen degradation products are released. These products of proteolysis exert marked anticoagulant activity (59). Since they are also adsorbed onto platelets more tightly than fibrinogen they extensively interfere with platelet aggregation (61). Hence, the fibrinogen degradation products, in interfering with hemostasis, promote a hemorrhagic diathesis. Unfortunately there are no antidotes for these effects. *Hence, screening tests must be performed at the first suspicion that defibrination may be taking place. Only in this way is it possible to establish an early diagnosis and to prevent further extension of the disease.*

Two distinctive forms of the intravascular coagulation syndrome can be recognized: an *acute* form which, like the Sanarelli Shwartzman reaction, results from the release of endotoxin with, in its extreme form, the clinical manifestations of the hemorrhagic, hemolytic, uremic syndrome and a *chronic* condition associated with evidence of insidious intravascular coagulation. *Acute* intravascular coagulation episodes occur in patients during shock, heat stroke, acute hemorrhagic pancreatitis, xenograft rejection or transplantation across major blood groups, incompatible blood transfusion, obstetric defibrination (abruptio placentae, dead fetus-in-utero syndrome, amniotic fluid embolism), snake bites, fat embolism, septicemia and surgical trauma. *Chronic* intravascular coagulation is observed in patients with giant hemangiomas (Kasabach-Merritt syndrome), arterial diseases (athero-

sclerosis, periarteritis), malignancies, cyanotic heart disease, systemic lupus erythematosus, liver cirrhosis, insertion of heart valve prosthesis, amyloidosis and many other conditions.

As a result of previous exposure to endotoxin reticuloendothelial function is impaired. Further release of such materials will result in another bout of platelet aggregation and fibrin formation. The delayed clearance of the reaction products results in their accumulation in peripheral vessels predominantly of the kidneys and lungs. Clinically, uremia and a hemorrhagic diathesis are striking characteristics. The prolonged contact of erythrocytes with fibrin results in their lysis, hence the term *hemolytic uremic syndrome*. Once this condition has developed, no further evidence of intravascular coagulation may be noted. This condition requires a different management than its chronic counterpart. Only few patients survive an acute, massive intravascular coagulation episode. Although fibrinolysin therapy has been utilized either as activator (streptokinase or urokinase) or as the active enzyme plasmin (streptokinase activated human plasminogen) in an attempt to lyse the fibrin, acute ischemia for 30–45 minutes results in irreparable damage of most of the major organs. Hence the treatment of an *acute* intravascular coagulation episode is in its prevention. Any patient who has minor coagulation defects, notably slight prolongation of prothrombin time, minimal to moderate thrombocytopenia and an abnormal partial thromboplastin time, presents us with a warning of what might be an impending disaster. As more experience is gained with this condition we will undoubtedly learn to read these danger signs and heed them. The following patients represent examples of such an acute episode.

CASE 1.—A 60-year-old male developed "declamping" shock following resection and replacement of an abdominal aortic aneurysm. He died shortly after from right heart failure and intractable hemorrhage which did not respond to multiple blood transfusions. Extensive platelet and fibrin thrombi were noted on microscopic examination of the lungs. This patient had not been heparinized prior to cross-clamping the aorta.

CASE 2.—Another example of acute defibrination is presented by a 36-year-old female who sustained a 30% 2d- and 3d-degree burn. On the 16th hospital day she received a blood transfusion. Afterwards the patient complained of backache and heavy feeling in chest. She vomited blood-stained mucus later that day. Blood samples obtained at this time were unclottable. The plasma showed gross evidence of hemolysis. Presumptive diagnosis of incompatible blood transfusion was made.

She developed anuria, became progressively jaundiced and died 6 days later with a full-blown hepatorenal syndrome. At autopsy, the kidney showed bilateral cortical necrosis. The glomeruli were filled with fibrin. There was yellow atrophy of the liver.

In contrast, protracted episodes of defibrination are amenable to successful treatment as would appear from the following case reports:

CASE 3.—A 15-year-old girl presented with giant hemangioma of the right thigh and buttock and a history of easy bruising, ecchymoses and frequent nose bleeds. Referred by a dentist who requested consultation prior to dental extraction, the diagnosis of Kasabach-Merritt syndrome was made on finding a platelet count of 55,000, a fibrinogen concentration of 120 mg./100 ml. and a prothrombin time of 19 seconds (control 11 seconds). The patient was heparinized and following treatment all abnormal values rapidly returned to normal. Following excision of approximately three-fourths of the tumor and skin grafting, symptoms did not recur; coagulation values remained normal and the patient has remained free of symptoms. She subsequently underwent tooth extractions without difficulty.

CASE 4.—A 56-year-old male with a history of chronic alcoholism, hepatosplenomegaly and impaired liver function (albumin 2.8 Gm./100 ml., bilirubin 1.8 mg./100 ml. direct), protime 18.4 (control 11 seconds), platelet count 60,000 and fibrinogen concentration 125 mg./100 ml. presented with several large ecchymoses over the back, buttocks and legs, and a history of hemoptysis 2–3 days prior to admission. The patient was heparinized with 25 units of heparin/kg./hr. Within 24 hours fibrinogen concentration was 250 mg./100 ml., platelet count 190,000, protime 13 seconds. The euglobulin clot lysis time which had been 10 minutes was over 1 hour. These findings indicated that the changes in the coagulation mechanism did not result from hypersplenism or inadequate production of coagulation factors as is consistent with liver failure and portal hypertension. Instead the rapid regeneration of coagulation factors suggested that liver function was much better than had been anticipated.

These observations suggest that treatment must center around the interruption of the mechanisms that trigger the intravascular coagulation process. Successful treatment of the underlying disease will arrest the process of intravascular coagulation. This includes the successful management of shock, surgical and antibiotic therapy of infectious diseases, particularly those caused by gram-negative bacteria, the operative removal of hemangiomata, the operative or cytostatic therapy of the underlying tumor, etc.

For the *chronic* form heparin therapy has been used extensively and with considerable success since Good and Thomas (111) and Cluff and Berthrong (112) provided experimental evidence for its ability to prevent the Shwartzman reaction in the rabbit, one of the first recognized and documented examples of the defibrination syndrome. Heparin doses of 30 units/kg./hr. are given to adults with normal hepatic and renal function. In the presence of liver or renal disease, these doses must be drastically reduced. On the other hand doses as high as 50 units/kg./hr. may be required for children from 1 to 12 years of age to obtain adequate anticoagulation. Much higher doses are also required in acidotic patients since, as was shown by Hardaway (113), in acidosis, heparin is much less effective in producing adequate anticoagulation. Following heparin therapy, it has been shown that the fibrinogen levels usually rapidly rise with gradual disappearance of fibrinogen degradation products.

Since most patients with chronic defibrination syndrome have increased proteolytic activity in the blood, the findings obtained in the past have occasionally been mistaken for primary fibrinolysis. Management of these patients with antifibrinolytic agents alone, without heparin, has served to aggravate the condition (87).

The next case report may serve as an example of the deleterious effect of epsilon amino caproic acid if administered to a patient with disseminated intravascular clotting and secondary fibrinolysis (125).

CASE 5.—A 66-year-old woman had a resection of an abdominal aneurysm and replacement of the terminal aorta by a preclotted dacron graft. Following the release of the vascular clamps, severe bleeding through the graft occurred. Because of low fibrinogen values and active clot lysis, the patient received 8 Gm. fibrinogen and 5 Gm. EACA. Bleeding decreased, urine output diminished and 5 hours postoperatively complete anuria developed. The patient had a cardiac arrest 14 hours postoperatively. At autopsy, bilateral renal cortical neurosis was found. Extensive fibrin thrombi were present throughout the glomeruli of both kidneys.

Frequently it is difficult to tell whether the patient suffered from intravascular clotting, primary fibrinolysis or the combined effect of both conditions. A case reported by Ratnoff (114) in 1952 exemplifies the problems in reaching a diagnosis.

CASE 6.—A 42-year-old woman with adenocarcinoma of the pancreas developed during exploratory laparotomy a generalized oozing from the serosal surfaces. The operation was interrupted when the patient became hypotensive from an uncontrollable generalized bleeding without evidence of specific bleeding points. Despite multiple transfusions the patient died 5 hours later. Five liters of unclottable blood had collected in the peritoneal cavity. Blood obtained during the bleeding episode was unclottable. Platelet count was 68,000, fibrinogen 105 mg. and clots prepared from the plasma lysed in 11 minutes. The conclusion that clotting was not observed in the whole blood because the fibrin lysed as quickly as it formed, seems justified.

Table 5 presents the features that may aid in reaching a differential diagnosis between primary fibrinolysis, defibrination from intravascular coagulation or intravascular clotting associated with fibrinolysis (so-called secondary fibrinolysis).

If the diagnosis is made too late, the patient invariably exsanguinates. Necropsy findings may show the agonal changes associated with circulatory failure. However, the prolonged course of the disease prior to the patient's death frequently makes it difficult to determine how the process started and to assess its effect. Microemboli may be found. They certainly do not always present a striking feature, however, probably because of their disappearance as a result of post-mortem autolysis. In patients with chronic intravascular coagulation, besides the formation of fibrin thrombi a focal thickening of the glomerular basement membrane has occasionally been noted. This represents the deposition of a granular material on the luminal side of the capillary tufts. Part of

TABLE 5.—Differential Diagnosis between Primary Fibrinolysis, Defibrination from Intravascular Coagulation or a Combination of Both Processes

Diagnostic Tests	Primary Fibrinolysis	Intravascular Clotting	Intravascular Clotting and Fibrinolysis
Platelet count	Normal	Low	Slightly decreased
Plasminogen level	Low	Normal	Slightly decreased
Soluble fibrin monomer complex (cryoglobulin level)	Not present, or present in small amount	Present in large amount	Present in small to moderate amount
F.D.P. level	High	Normal	High
Thrombin time	Prolonged	Normal	Prolonged
Heparin thrombin time	Prolonged	Normal, prolonged or shortened	Prolonged
Erythrocytes *(peripheral blood smear)*	Normal	Schistocytes, burr, helmet and triangular-shaped cells	Schistocytes, but not as pronounced as intravascular clotting alone

this material is also found taken up by the endothelial cells. This material is immunochemically identifiable as fibrin and probably represents a partially polymerized fibrin. It has been observed in otherwise normal kidneys as well as in homografted kidneys undergoing chronic rejection.

The diagnosis of the chronic defibrination syndrome is made by demonstrating a hypofibrinogenemia or afibrinogenemia and a decreased number of circulating platelets, and in the presence of FDP (fibrin degradation products) a prolonged thrombin time which is not fully corrected by protamine. All patients with a defibrination syndrome have thrombocytopenia, decreased factor V and VIII activity, low plasma fibrinogens and prolonged prothrombin times. In addition, if activation of the fibrinolytic enzyme system occurs shortened euglobulin clot lysis times, prolonged thrombin times and the presence of fibrin degradation products and cryofibrinogen are demonstrable. Shortly after an *acute* defibrination episode markedly elevated factor VIII and fibrinogen levels, as a rebound phenomenon, are not an uncommon finding.

Definite evidence for the presence of chronic intravascular coagulation is obtained from an in vivo study of the turnover rate of a purified, undenatured, labeled human fibrinogen preparation. Clinical evidence, albeit indirect, is derived from observations made following heparinization of the patient. Heparin therapy, alone or in combination with fresh blood, fibrinogen and antiproteolytic agents, will alleviate the

condition. Prompt treatment is imperative to prevent the accumulation of larger quantities of fibrin degradation products. Every effort should be made to overcome the resistance so frequently encountered against the use of heparin as the only form of treatment for this severe bleeding problem.

The problems of chronic intravascular coagulation have gained increasing significance as their relationship to other surgical problems is being elucidated. It is of particular importance in cardiac surgery, the use of artificial organs and organ transplantation.

Heart valve replacement is still associated with injury to the blood. Some degree of hemolysis is almost invariably present in patients with artificial heart valves. The degree of blood injury, however, varies considerably among individuals. The presence of foreign material in immediate contact with blood, and the intravascular coagulation that results either locally in thrombus formation or more generally in defibrination, characterized by thrombocytopenia and fibrinogenopenia, is presently associated with a relatively high incidence of thromboembolic complications.

Studies of the effect of cardiopulmonary bypass on the hemostatic mechanism have established, beyond any doubt, the development of intravascular coagulation. Besides an activation of the coagulation mechanism impairment of phagocytic activity could be demonstrated after extracorporeal circulation. These factors as well as injury to the blood by pumps and by its exposure to foreign surfaces are still severe enough to limit the long-term use of artificial organs for temporary replacement of the function of heart, lungs, kidneys and possibly the liver.

Several bridges that link various immunologic reactions to the coagulation mechanism have been found. Some operate through damage of vascular endothelium, which is presumably complement induced. Others occur through the aggregation and degranulation of platelets which develop during the phagocytosis of antigen-antibody complex. A few affect the coagulation mechanism in some other manner. Research in organ transplantation has uncovered the great similarity of xenograft rejection or rejection of homografts in the presence of major histoincompatibility (e.g., grafting across major blood groups) and mismatched blood transfusions. Such a similarity is not surprising in view of the fact that both conditions represent extremely rapid rejection reactions characterized in part by the development of extensive intravascular coagulation. The resulting interference with blood flow leads to an accelerated "rejection," which is in effect no rejection but rather an infarction.

Irrespective of the mode of activation of the coagulation mechanism, however, its repercussions for the patient may be serious indeed. The factors that determine the severity are the duration and the extent of

its involvement. Invariably the effects are fatal if the induced changes persist long enough or assume sufficient magnitude.

The long-term use of anticoagulants required for prevention of activation of the coagulation mechanism is not without hazards and is not always effective. Heparin in therapeutic doses does not greatly affect platelet aggregation. Hence, several other avenues are being explored in attempts to overcome the aversion of blood to foreign surfaces. Chan (115), Reid (116), and others, predominantly in England, are exploring the use of Arvin, the defibrinating fraction prepared from the venom of the Malayan pit viper (Angkistrodon rhodostoma). This material causes long-term defibrination supposedly by its effect on fibrinogen. The failure of the fibrin formed by moderate doses of Arvin to cause circulatory obstruction may be because the clot formed is much softer and much more fragile than normal clot. It is presumably fragmented as it circulates. That fibrinolysin plays a significant role in its elimination appears from the fact that when Arvin is given with E.A.C.A., death resulted. Indeed, fibrinolytic activity is noted in animals receiving the venom. The fibrin has no appreciable effect on the function of the lungs. Resistance to blood flow occurs only temporarily, without effect on the systemic organs as judged by renal plasma flow. Experience with this material is still limited. Another approach is taken by Gott (117), Salzman (118), Leininger (119) and others, who are exploring the use of heparin-coated surfaces for use in heart valves, tubing and eventually in artificial organs. Liotti and DeBakey (120) promote a firmer attachment of fibrin by allowing it to form on a velour-covered surface. Others, notably Zucker (121), Salzman (122), O'Brien (123) and Mustard and associates (124), explore avenues that permit interruption of platelet adhesion or aggregation by pharmacologic means following the contact of blood with foreign surfaces or during immunologic reactions (Table 6).

In order to be able to transplant liver, lung or heart successfully, increasing reliance will have to be placed on organs of optimal quality and on availability of artificial organs to sustain life during or following rejection till a suitable donor becomes available. The main limitations for the general use of artificial organs has been their adverse effect on

TABLE 6.—MATERIALS WHICH INHIBIT PLATELET AGGREGATION

EXPERIMENTAL AGENTS	PHARMACOLOGIC AGENTS
Sulfhydryl inhibitors	Antihistaminics
Fibrinogen degradation products	Dextrans
Chelating agents	Acetylsalicylic acid
Arginine methyl esters	Butazolidine
Adenosine and its analogues	Reserpine
Cocaine	

blood—particularly on platelets and some of the coagulation proteins through the induction of intravascular coagulation. The attempts to solve these problems represent one of the most significant challenges in surgery today.

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