continuing education

Hemostasis

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The term *hemostasis* means prevention of blood loss by processes which inhibit blood flow through (out of) a ruptured vessel. Included in hemostatic processes are vascular spasm, platelet mechanisms, and blood coagulation.

Vascular spasm is the immediate constricting response of the smooth muscle in an injured vessel. Platelets, local myogenic response, and nervous reflexes all contribute to such vasoconstriction. Blood flow through an injured vessel is therefore minimized, allowing time for coagulation reactions to occur before excessive amounts of blood are lost. This vascular response is important and probably accounts for the survival of victims severely traumatized by automobile or other accidents.

Platelets play numerous roles in all hemostatic processes. Contact with collagen, foreign material, or wettable surfaces causes platelets to adhere to such a surface. In doing so, they drastically change their shape and release substances which, in addition to other actions, cause other platelets to become adhesive. Platelet plugs thus formed are often sufficient to temporarily repair the small rents which continually occur in vessels throughout the body (Figure 1).

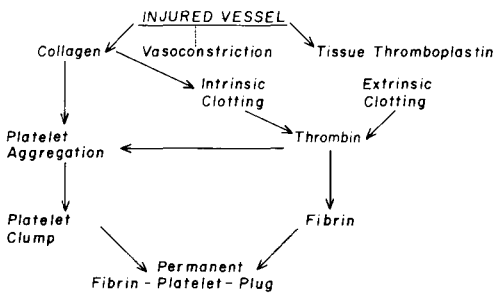


FIGURE 1.

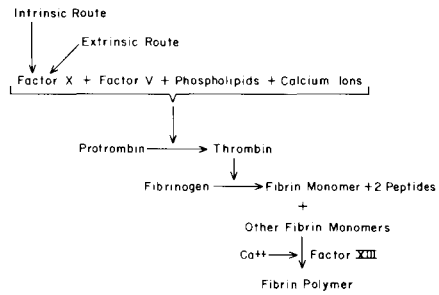


FIGURE 2.

Fig. 1. A diagram of the summary of events immediately following vascular injury showing the relationship of vascular spasm, platelet mechanisms, and blood coagulation in the hemostatic process.

Fig. 2. A diagram of steps leading to coagulation which are common to both the intrinsic and extrinsic processes.

Other substances released by platelets stimulate and/or catalyze hemostatic occurrences. One of these substances, serotonin, is a powerful vasoconstrictor. Phospholipids liberated by platelets are important enzymes for several of the chemical reactions comprising blood coagulation. Platelets also contain large amounts of ATP (adenosine triphosphate) which provides the energy required for final formation of a stable blood clot.

The hemostatic process of greatest interest is *blood coagulation*. The substances involved in blood coagulation are normally present in the bloodstream or tissues, but remain passive until some stimulus converts them to their active forms (Table 1). Once this occurs, a chain of events begins which results in a blood clot. Inherent in the coagulation system are a number of control mechanisms which inhibit abnormal blood coagulation or dissolve blood clots when they are no longer needed.

Ultimately, a blood clot is a mass of fibrin threads with entrapped cells which forms a vascular plug. Coagulation may be initiated through an intrinsic or an ex-

TABLE 1

BLOOD FACTORS AND SYNONYMS

FACTOR	NAME	SYNONYMS
I	Fibrinogen	
II	Prothrombin	
III	Thromboplastin (tissue)	
IV	Calcium ions	
V	Proaccelerin	Labile Factor Plasma Accelerator Globulin (Ac-G)
VI	not assigned	
VII	Proconvertin	Stable Factor Serum Prothrombin Conversion Accelerator (SPCA) Co-thromboplastin Autoprothrombin I
VIII	Antihemophilic Factor (AHF)	Thromboplastinogen Platelet Cofactor I Plasma Thromboplastic Factor A Antihemophilic Globulin (AHG)
IX	Plasma Thromboplastin Component (PTC)	Christmas Factor Platelet Cofactor II Plasma Thromboplastic Factor B Autoprothrombin II
X	Stuart Factor	Stuart-Prower Factor Prower Factor Autoprothrombin Ic
XI	Plasma Thromboplastin Antecedent (PTA)	
XII	Hageman Factor	
XIII	Fibrin Stabilizing Factor (FSF)	
Platelets		Platelet Factor 3

TABLE 1

The coagulation factors by number, with their most common names and synonyms by which they may sometimes be referred in various literature.

trinsic route, but the final steps leading to fibrin formation are the same regardless of the initial stimulating process (Figure 2). These steps involve factor X (Stuart-Prower factor), factor V (proaccelerin), prothrombin, fibrinogen, calcium ions, platelets, and phospholipids. Factor X becomes activated through either the intrinsic or extrinsic pathway and has the ability to directly convert prothrombin to thrombin. However the rate of this conversion is slow, and *factor X usually forms a complex with factor V and phospholipids* which cleaves prothrombin, thereby liberating thrombin. The presence of calcium ions is necessary for this step to occur.

Thrombin, a protein enzyme with proteolytic capabilities, acts on fibrinogen to remove two low molecular weight peptides, resulting in a molecule of *activated fibrin,* also called a *fibrin monomer.* Many fibrin monomers then join to form long chains or polymers. This process is known as *polymerization* and is enhanced by calcium ions and factor XIII (fibrin stabilizing factor). These fibrin polymers form a mesh which traps erythrocytes,

platelets, and plasma. After a few minutes, the fibrin threads shrink and express serum (plasma without clotting factors). This step is called *clot retraction,* utilizes great amounts of ATP from large numbers of platelets, and results in a stable clot.

The difference between the intrinsic and extrinsic systems of coagulation lies in the type of initiating stimulus and the resulting chain of events which precedes the activation of prothrombin (Figure 3). *The extrinsic mechanism is initiated by tissue injury,* as when a blood vessel is cut or ruptured. Vascular spasm occurs as previously described and, in addition, a substance known as thromboplastin is released by the injured tissue. Thromboplastin stimulates extrinsic coagulation by forming a complex with factor VII (proconvertin) and phospholipids in the presence of calcium ions that converts factor X to its active form. In the extrinsic system, the necessary phospholipids are generated from tissue thromboplastin. Factor X, along with the substances described above, subsequently causes prothrombin to be activated which then, of course, leads to the formation of fibrin.

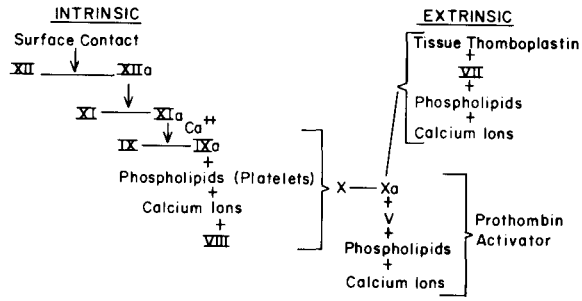


Fig. 3. A diagram of the intrinsic and extrinsic pathways leading to the activation of prothrombin.

The intrinsic mechanism of blood coagulation is thought to be initiated by contact of blood with foreign surfaces. That this system is necessary for normal hemostasis is demonstrated by the fact that deficiency of factor VIII (required only in the intrinsic system) leads to bleeding. Since contact with collagen (contained in the outer layers of blood vessels) is probably the factor which most often stimulates intrinsic coagulation, it is obvious that normal behavior of this system is necessary to prevent bleeding which could be incurred by routine wear-and-tear on the body's vasculature.

However, this tenuous system is also involved in many of the problems encountered by the clinical perfusionist and cardiovascular physician. This system, for example, causes coagulation of blood when it is removed from the body. An extracorporeal circuit is then, by definition, an active stimulus to intrinsic coagulation. Introduction of some lipids, microbubbles, and particulate matter into the vascular system always occurs during open-heart procedures. Implanted prosthetic devices, such as cardiac valves, are also foreign surfaces which can stimulate intrinsic coagulation.

In addition, patients with acquired cardiac or vascular disease often have calcific or atherosclerotic deposits within their heart or vessels. There are also foreign surfaces which may initiate coagulation. Stasis of blood can lead to clot formation through the intrinsic pathway. An example of this event is thrombus formation in the lower limbs of patients on continuous bed rest.

This coagulation system is not completely understood, but is thought to commence when contact with foreign material somehow activates factor XII (Hageman factor). Activated factor XII then converts factor XI (plasma thromboplastin antecedent, PTA) to its active form which, in the presence of calcium ions, subsequently causes factor IX (plasma thromboplastin component, PTC, Christmas factor) to become activated. Activated factor IX, platelet phospholipids, calcium ions, and factor VIII (antihemophilic factor) form a stable macromolecular complex which then converts factor X to its active form. The remaining sequence of events is the same as in extrinsic coagulation.

Whether coagulation occurs through the extrinsic or intrinsic pathway, the clotting process itself stimulates even more clotting, largely due to the powerful and diverse actions of thrombin. The activity of several factors leading to fibrin formation is enhanced by thrombin, so that thrombin accelerates its own generation. Platelet aggregation can be caused by direct action of thrombin, and platelets become tightly packed

under the influence of thrombin. As described previously, aggregated platelets stimulate or participate in several events of coagulation, also contributing to the vicious cycle of clot formation.

In addition, since the enzymes involved in coagulation are constantly present in the blood, it is possible for coagulation to be inappropriately initiated, resulting in abnormal and potentially dangerous clots. Obviously, certain controls are necessary to prevent the coagulation process from occurring throughout the body.

One of the primary factors which ensures against abnormal blood coagulation is the smooth character of vascular endothelium. The innermost lining of blood vessels is not only extremely smooth, but is lined with a monomolecular layer of negatively-charged protein. Clotting factors and platelets are repelled by the negative charge, thereby protecting the vessel wall from clots. However, since even in the "normal" individual, there is some disruption of the smoothness of vascular endothelium, additional protective mechanisms are necessary.

Once a clot occurs, either normally or abnormally, it is inhibited from extending by several factors. The constant flow of blood helps prevent clot extension by diluting the coagulation factors present in the area around the forming blood clot. The substances carried away from the area of clotting by blood flow pass through the liver, where a great quantity of thromboplastin and activated factors IX, X, and XI are removed. About 80% of the generated thrombin is *adsorbed* by fibrin threads as they develop. Excess thrombin is removed from the blood by antithrombin, an alpha globulin normally present in blood. Finally, the generation of thrombin is inhibited by heparin, which is present in small amounts in the bloodstream. The greatest concentrations of heparin are found in the lungs and liver, where blood is exposed to many procoagulant stimuli.

Whether originally functional or not, if blood clots remain in a blood vessel for an indefinite amount of time, the results can be devastating. The fibrinolytic system, which dissolves blood clots, is therefore incorporated into the hemostatic processes to preclude such happenings (Figure 4). Fibrinolysis (clot dissolution) depends upon *plasminogen* (profibrinolysin) which is an inactive precursor substance, a euglobulin normally present in plasma. Euglobulins are those proteins (which include fibrinogen) that precipitate when plasma is diluted in water. Although the specific reaction has not yet been defined, thrombin activity causes plasminogen to be cleaved, yielding plasmin.

A potent proteolytic enzyme, plasmin acts upon fibrin to break it into smaller and smaller fragments, thus digesting clots (Figure 4). The action of plasmin is potentially extremely nonspecific, so that fibrinogen, factors V and VIII, collagen, and several other proteins and polypeptides may be broken down by it. Plasmin action is therefore limited or controlled by circulating antiplasmins which are able to form benign chemical complexes with plasmin.

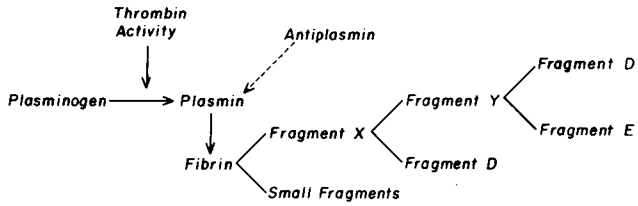


Fig. 4. A diagram of the scheme of fibrinolysis, showing the activation of plasminogen, the action of plasmin upon fibrin, the resulting fibrin degradation products, and inhibition of plasmin by antiplasmin.

The fragments which result from digestion of fibrin or fibrinogen by plasmin are termed *fibrin degradation products or fibrin split products.* The initial reaction between plasmin and fibrin results in one large molecule retaining about 80% of the original molecular weight and several smaller fragments. The large molecule is called fragment X, and is subsequently broken into another large molecule (fragment Y) and a smaller molecule (fragment D). Plasmin continues its operation by cleaving fragment Y into another fragment D and a small fragment E. The end-products of action on fibrin by plasmin are therefore two fragment D's, one fragment E, and numerous tiny fragments.

To summarize the scheme of coagulation (Figure 5), prothrombin becomes activated through the intrinsic or extrinsic pathway; both pathways share the factor X, factor V, phospholipids, and calcium ion complex. Thrombin (activated prothrombin)

then changes fibrinogen into a fibrin monomer, and many fibrin monomers polymerize and then retract to form a stable blood clot. Much of the thrombin is adsorbed onto fibrin threads as they develop, but some of it is washed away by blood flow and the remaining thrombin is counteracted by antithrombin.

Fibrinolysis is apparently initiated by the same stimuli as thrombin activity, commencing with the conversion of inactive plasminogen into active plasmin. Plasmin in turn degrades fibrin into small fragments. Plasmin activity is checked by antiplasmins which normally circulate throughout the bloodstream. Obviously, these complex events comprise a delicate balance, and it is not difficult to fathom the disturbance of such a balance in surgical or other patients.

Inherited or acquired deficiencies of coagulation factors will, of course, disrupt the normal coagulation process. In the case of an open-heart patient or candidate, concern is usually with acquired coagulation deficiencies. Acquired coagulopathies characteristically involve several of the clotting factors and are related to such conditions as oral anticoagulant therapy, liver disease, and chronic intravascular clotting.

Oral anticoagulant therapy is aimed at preventing coagulation in patients with thrombotic tendencies by inhibiting hepatic production of those coagulation factors which require vitamin K for their formation: prothrombin and factors VII, IX, and X. The liver also produces fibrinogen and factor V, for which vitamin K is not necessary. Hepatic disease will therefore lead to depression of *all* of these factors.

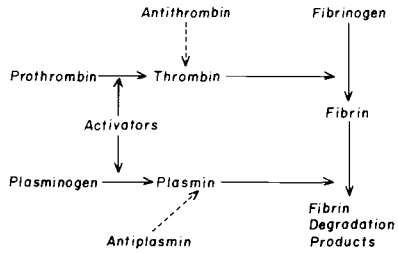


Fig. 5. A diagram of the summary of the coagulation mechanism and the relationship between thrombin and plasmin activity.

Chronic intravascular clotting is often found in the patient with severe cyanotic heart disease, the prime example being tetralogy of Fallot. The marked oxygen demand causes an abnormally increased erythrocyte count, sometimes resulting in hematocrits as high as 60% to 70%. Consequently, the blood of these patients is extremely viscous and sludges in the microcirculation. This sludging often triggers generalized coagulation which consumes clotting factors to the point that functional clotting is impossible.

This is but one example of *disseminated intravascular coagulation (DIC),* a coagulopathy comprised paradoxically of thrombotic and hemorrhagic events. The syndrome commences with the presence of a clot-promoting agent in the general circulation, leading to widespread fibrin deposition within the vascular tree. The source of the thrombotic stimulus is always associated with a primary underlying pathologic state, such as obstetrical events, shock, infection, tumor, trauma, surgery, certain hematological disorders, and extracorporeal circulation—to name just a few (Table 2).

The clots resulting from such incidents often occlude the microcirculation, resulting in local tissue ischemia and/or necrosis. If the process continues, it culminates ultimately in irreversible tissue and organ damage. The ischemic changes may be manifest by blanched areas of the skin, muscle pain, decreased urine output, neurological changes and ulcers of the gastrointestinal tract. Since ischemic or damaged tissues release powerful procoagulant enzymes, the thrombotic cycle may thus become a selfperpetuating one.

As coagulation occurs throughout the body, the supply of clotting factors, including platelets, becomes exhausted. Depletion of these factors causes the blood to become hypocoagulable or incoagulable. At this point, hemorrhagic tendencies develop. There may be spontaneous bleeding from the skin or subcutaneous tissue; intracerebral hemorrhage may occur; profound blood loss from an infarcted organ may arise. The surgical patient will bleed from all sites of incision and venipuncture.

The fibrinolytic system also contributes to the diathesis of DIC. Accelerated coagulation stimulates equally rapid plasmin activity (Figure 6). Action of plasmin is initially

TABLE 2

SOME PATHOLOGICAL STATES ASSOCIATED WITH DIC

SEVERE HEMOLYSIS
- transfusion reaction
- malaria
- hemoglobinopathy
- hemolytic anemia

SEPSIS
- gram-negative septicemia
- tubercle bacilli
- fungi
- viruses
- Rickettsia

OBSTETRICAL STATES
- abruptio placentae
- retained dead fetus
- amniotic fluid embolism
- septic abortion

SURGERY
- cardiac
- other

CARDIOPULMONARY DISORDERS
- pulmonary embolism
- cyanotic congenital heart disease
- Hyaline membrane disease

EXTRACORPOREAL CIRCULATION

IMMUNOLOGIC REACTIONS
- polyarthritis
- glomerulonephritis
- transplant rejection

MALIGNANCY
- tumors
- leukemia

ACIDOSIS
- shock states
- heat stroke
- metabolic

TRAUMA
- burns
- crush syndrome

MISCELLANEOUS
- Malayan Pit Viper
- fat embolism
- acute hemorrhagic pancreatitis
- cirrhosis of liver
- Kasabach-Merritt syndrome

local, confined to the numerous small clots. However, most investigators believe that after these clots have been dissolved, excess plasmin is released into the general circulation. The circulating plasmin acts not only on fibrin, but also on fibrinogen and factors V and VIII, further depleting them. This abundant plasmin activity results in the presence of tremendous amounts of fibrin degradation products within the circulation.

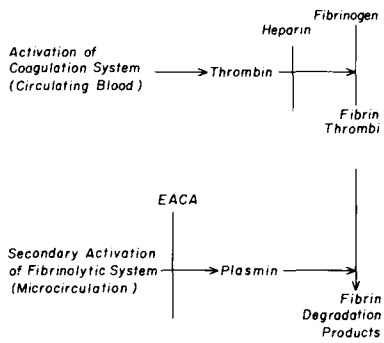
Fibrin degradation products interfere with normal clot formation in several ways. Fragments *X* and *Y* are clottable, but the coagulation reaction involving these fragments requires an unreasonably long time, and the resulting clots are poor because they do not gel properly. These substances, however, compete equally with fibrinogen for any thrombin available. Their resulting action, then, is primarily anticoagulant.

Conversion of fragments *X* and *Y* to fragments *D* and *E* causes the antithrombin activity to cease. However, when fragments *D* and *E* are present during polymerization of fibrin, the result is a severely abnormal clot structure. In addition to all of these effects, fibrin split products also inhibit platelet aggregation. When erythrocytes are forced through the fibrin strands of a clot, damage or destruction often occurs. The stromal material liberated by such hemolysis is a further stimulant to coagulation.

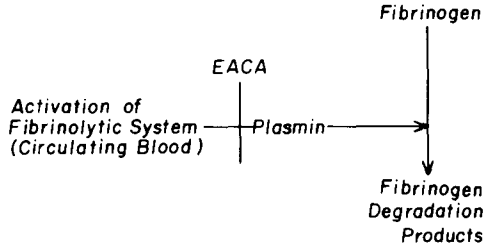
With so many contributing circumstances to the syndrome, diagnosis and treatment of DIC are both extremely problematic, even controversial. Every hemorrhagic anomaly is not DIC and should not be treated as such. Prothrombin time and/or partial thromboplastin time are likely to be abnormal in many types of coagulopathies. Particularly useful in diagnosis of DIC are *assays* of clotting factors and fibrinolysis.

In fulminating DIC (not mild or chronic), platelets are severely depleted, sometimes reaching counts lower than 50,000/cu.mm. The fibrinogen level will be low and the thrombin time is extremely prolonged. Factors V and VIII are reduced, both because of consumption during active coagulation and from action upon them by circulating plasmin. There will usually be no or prolonged clot retraction due to the thrombocytopenia.

Although the opinions of both clinicians and researchers differ, most agree that DIC produces heightened fibrinolysis, as manifest by increased levels of fibrin degradation products and shortened whole blood euglobulin lysis times. The alternate view is that plasmin activity in DIC is local and will not predictably alter either of these parameters.



DISSEMINATED INTRAVASCULAR COAGULATION Figure 6.



PATHOLOGIC FIBRINOGENOLYSIS
Figure 7.

Fig. 6. A diagram of the major occurrences comprising DIC and impedence of the occurrences by heparin and epsilon aminocaproic acid (EACA).

Fig. 7. A diagram of the scheme of pathologic (primary) hyperfibrinolysis and its arrest by epsilon aminocaproic acid (EACA).

As laboratory techniques improve and with more exposure to bleeding problems, additional hypotheses are developing. There are those who believe that DIC as a clinical entity does not exist; but rather that coagulopathies present which involve complex, multiple, and individualized coagulation deficiencies. There are those who believe that some of these cases diagnosed and treated as DIC are, in reality, *hyperfibrinolysis.*

There is evidence to indicate the existence of pathologic fibrinolysis, that is, that bleeding occurs because clots are being lysed faster than they can be formed (Figure 7). Explanations as to how fibrinolysis can be stimulated other than through thrombin activity or circulating kinases are vague or nonexistent. However, the fact remains that there are certain bleeding problems caused by overactive plasmin activity, or hyperfibrinolysis.

In some instances, *pathologic fibrinolysis* is difficult to differentiate from DIC. Some authors state that the platelet count is the most helpful diagnostic aid, since it will not be severely decreased in hyperfibrinolysis as it will in DIC. At least one author has stated that systemic fibrinolysis does not occur in DIC, but is definitely present in pathologic fibrinolysis; in other words, the level of fibrin degradation products will be increased and the euglobulin lysis time will be decreased in pathologic fibrinolysis, but not in DIC. Still another author states that the level of factor VIII should be the deciding factor when diagnosing DIC versus pathologic fibrinolysis: that it will be significantly depressed in DIC, but not in hyperfibrinolysis. This hypothesis would seem to be feasible only in *primary* hyperfibrinolysis (pathologic fibrinolysis apparently unrelated to any other condition). In view of all this, probably the most valuable data is the overall clinical picture combined with the astute judgment of learned and experienced medical staff and supported with a vast amount of laboratory tests.

Specific therapy for any coagulopathy should be begun only after a diagnosis based on the above has been made. The most popular treatment for DIC is heparinization, the theory being to inhibit coagulation until such time as the body can replenish necessary coagulation factors and at the same time protect the tissues from potential damage due to further clotting. Certainly, concommitant blood replacement is mandatory. The therapy for hyperfibrinolysis is administration of epsilon aminocaproic acid (EACA, AMICAR), which inhibits fibrinolysis (Figure 6).

Recently, other modes of therapy for DIC and other coagulation deficiencies have been proposed and attempted which involve replacement of specific depleted coagulation factors. This type of treatment is, of course, supported by those who deny the reality of DIC as a classic clinical entity. Depending upon the coagulation factors which are shown by laboratory analysis to be depressed or absent; fibrinogen, cryoprecipitate, thrombin, packed platelets, packed erythrocytes, fresh frozen plasma, other blood fractions, or any combination of these may be administered.

Of course the most effective ways to combat DIC is to treat or prevent the underlying pathological state. However, immediate heparinization is probably the preferred therapy until the specific coagulation deficit is determined, and specific therapy instituted.