Hemostasis and blood coagulation

The term hemostasis means prevention of blood loss. Whenever a vessel is severed or ruptured, hemostasis is achieved by several mechanisms: (1) vascular constriction, (2) formation of a platelet plug, (3) formation of a blood clot as a result of blood coagulation, and (4) eventual growth of fibrous tissue into the blood clot to close the hole in the vessel permanently.

Vascular Constriction

Immediately after a blood vessel has been cut or ruptured, the trauma to the vessel wall itself causes the smooth muscle in the wall to contract; this instantaneously reduces the flow of blood from the ruptured vessel. The contraction results from (1) local myogenic spasm, (2) local autacoid factors from the traumatized tissues and blood platelets, and (3) nervous reflexes. The nervous reflexes are initiated by pain nerve impulses or other sensory impulses that originate from the traumatized vessel or nearby tissues. However, even more vasoconstriction probably results from local myogenic contraction of the blood vessels initiated by direct damage to the vascular wall. And, for the smaller vessels, the platelets are responsible for much of the vasoconstriction by releasing a vasoconstrictor substance, thromboxane A2. The more severely a vessel is traumatized, the greater the degree of vascular spasm. The spasm can last for many minutes or even hours, during which time the processes of platelet plugging and blood coagulation can take place.

Formation of the platelet plug

If the cut in the blood vessel is very small—indeed, many very small vascular holes do develop throughout the body each day—the cut is often sealed by a platelet plug, rather than by a blood clot.

Platelets (also called thrombocytes) are minute discs 1 to 4 micrometers in diameter. They are formed in the bone marrow from megakaryocytes, which are extremely large cells of the hematopoietic series in the marrow; the megakary ocytes fragment into the minute platelets either in the bone marrow or soon after entering the blood, especially as they squeeze through capillaries. The normal concentration of platelets in the blood is between 150,000 and 300,000 per microliter. Platelets have many functional characteristics of whole cells, even though they do not have nuclei and cannot reproduce.In their cytoplasm are such active factors as (1) actin and myosin molecules, which are contractile proteins similar to those found in muscle cells, and still another contractile protein, thrombosthenin, that can cause the platelets to contract; (2) residuals of both the endoplasmic reticulum and the Golgi apparatus that synthesize various enzymes and especially store large quantities of calcium ions; (3) mitochondria and enzyme systems that are capable of forming adenosine triphosphate (ATP) and adenosine diphosphate (ADP); (4) enzyme systems that synthesize prostaglandins, which are local hormones that cause many vascular and other local tissue reactions; (5) an important protein called fibrin-stabilizing factor; and (6) a growth factor that causes vascular endothelial cells, vascular smooth muscle cells, and fibroblasts to multiply

and grow, thus causing cellular growth that eventually helps repair damaged vascular walls. The cell membrane of the platelets is also important. On its surface is a coat of glycoproteins that repulses adherence to normal endothelium and yet causes adherence to injured areas of the vessel wall,especially to injured endothelial cells and even more so to any exposed collagen from deep within the vessel wall. In addition, the platelet membrane contains large amounts of phospholipids that activate multiple stages in the blood-clotting process. Thus, the platelet is an active structure. It has a half- life in the blood of 8 to 12 days, so that over several weeks its functional processes run out. Then it is eliminated from the circulation mainly by the tissue macrophage system. More than one half of the platelets are removed by macrophages in the spleen, where the blood passes through a latticework of tight trabeculae.

Platelet repair of vascular openings is based on several important functions of the platelet itself. When platelets come in contact with a damaged vascular surface, especially with collagen fibers in the vascular wall, the platelets themselves immediately change their own characteristics drastically. They begin to swell; they assume irregular forms with numerous irradiating pseudopods protruding from their surfaces; their contractile proteins contract forcefully and cause the release of granules that contain multiple active factors; they become sticky so that they adhere to collagen in the tissues and to a protein called von Willebrand factor that leaks into the traumatized tissue from the plasma; they secrete large quantities of ADP; and their enzymes form thromboxane A2. The ADP and thromboxane in turn act on nearby platelets to activate them as well, and the stickiness of these additional platelets causes them to adhere to the original activated platelets. Therefore, at the site of any opening in a blood vessel wall, the damaged vascular wall activates successively increasing numbers of platelets that themselves attract more and more additional platelets, thus forming a platelet plug. This is at first a loose plug, but it is usually successful in blocking blood loss if the vascular opening is small. Then, during the subsequent process of blood coagulation, fibrin threads form. These attach tightly to the platelets, thus constructing an unyielding plug. The platelet-plugging mechanism is extremely important for closing minute ruptures in very small blood vessels that occur many thousands of times daily. Indeed, multiple small holes through the endothelial cells themselves are often closed by platelets actually fusing with the endothelial cells to form additional endothelial cell membrane. A person who has few blood platelets develops each day literally thousands of small hemorrhagic areas under the skin and throughout the internal tissues, but this does not occur in the normal person.

Blood coagulation

The third mechanism for hemostasis is formation of the blood clot. The clot begins to develop in 15 to 20 seconds if the trauma to the vascular wall has been severe, and in 1 to 2 minutes if the trauma has been minor.Activator substances from the traumatized vascular wall, from platelets, and from blood proteins adhering to the traumatized vascular wall initiate the clotting process.The physical events of this process are shown in Figure 1. Within 3 to 6 minutes after rupture of a vessel, if the vessel opening is not too large, the entire opening or broken end of the vessel is filled with clot. After 20 minutes to an hour, the clot

retracts; this closes the vessel still further. Platelets also play an important role in this clot retraction.
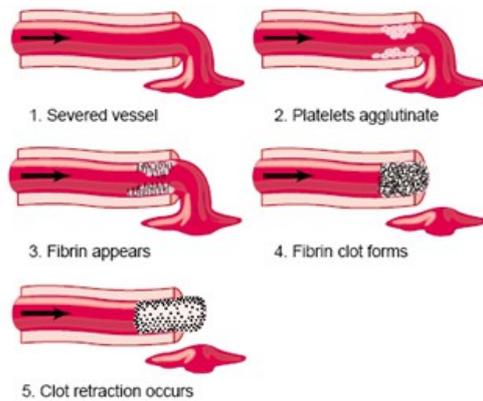
Figure 1 Clottting process in a traumatized blood vessel

Once a blood clot has formed, it can follow one of two courses: (1) It can become invaded by fibroblasts, which subsequently form connective tissue all through the clot, or (2) it can dissolve. The usual course for a clot that forms in a small hole of a vessel wall is invasion by fibroblasts, beginning within a few hours after the clot is formed (which is promoted at least partially by growth factor secreted by platelets). This continues to complete organization of the clot into fibrous tissue within about 1 to 2 weeks. Conversely, when excess blood has leaked into the tissues and tissue clots have occurred where they are not needed, special substances within the clot itself usually become activated.

Mechanism of blood coagulation

More than 50 important substances that cause or affect blood coagulation have been found in the blood and in the tissues—some that promote coagulation, called procoagulants, and others that inhibit coagulation, called anticoagulants. Whether blood will coagulate depends on the balance between these two groups of substances. In the blood stream, the anticoagulants normally predominate, so that the blood does not coagulate while it is circulating in the blood vessels. But when a vessel is ruptured, procoagulants from the area of tissue damage become "activated" and override the anticoagulants, and then a clot does develop.

All research workers in the field of blood coagulation agree that clotting takes place in three essential steps: (1) In response to rupture of the vessel or damage to the blood itself,a complex cascade of chemical reactions occurs in the blood involving more than a dozen blood coagulation factors. The net result is formation of a complex of activated substances collectively called prothrombin activator. (2) The prothrombin activator catalyzes conversion of prothrombin into thrombin. (3) The thrombin acts as an enzyme to convert fibrinogen into fibrin fibers that enmesh platelets, blood cells, and plasma to form the clot.
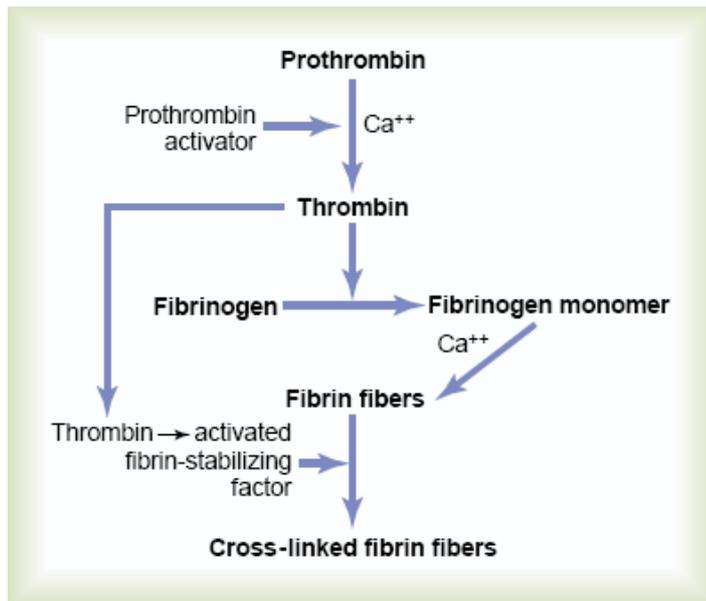
Figure 2 Schena for conversion of prothrombin to trombin and transformation of fibrinogen to fibrin

First, prothrombin activator is formed as a result of rupture of a blood vessel or as a result of damage to special substances in the blood. Second, the prothrombin activator, in the presence of sufficient amounts of ionic Ca^{++}, causes conversion of prothrombin to thrombin (Figure 2).Third, the thrombin causes polymerization of fibrinogen molecules into fibrin fibers within another 10 to 15 seconds.Thus, the rate-limiting factor in causing blood coagulation is usually the formation of prothrombin activator and not the subsequent reactions beyond that point, because these terminal steps normally occur rapidly to form the clot itself. Platelets also play an important role in the conversion of prothrombin to thrombin because much of the prothrombin first attaches to prothrombin.

Prothrombin is a plasma protein, an alpha2-globulin, having a molecular weight of 68,700. It is present in normal plasma in a concentration of about 15 mg/dl. It is an unstable protein that can split easily into smaller compounds, one of which is thrombin, which has a molecular weight of 33,700, almost exactly one half that of prothrombin. Prothrombin is formed continually by the liver, and it is continually being used throughout the body for blood clotting. If the liver fails to produce prothrombin, in a day or so prothrombin concentration in the plasma falls too low to provide normal blood coagulation. Vitamin K is required by the liver for normal formation of prothrombin as well as for formation of a few other clotting factors. Therefore, either lack of vitamin K or the presence of liver disease that prevents normal prothrombin formation can decrease the prothrombin level so low that a bleeding tendency results.

Fibrinogen is a high-molecular-weight protein (MW = 340,000) that occurs in the plasma in quantities of 100 to 700 mg/dl. Fibrinogen is formed in the liver, and liver disease can decrease the concentration of circulating fibrinogen, as it does the concentration of prothrombin, pointed out above. Because of its large molecular size, little fibrinogen normally leaks from the blood vessels into the interstitial fluids, and because fibrinogen is one of the essential factors in the coagulation process, interstitial fluids ordinarily do not

coagulate. Yet, when the permeability of the capillaries becomes pathologically increased, fibrinogen does then leak into the tissue fluids in sufficient quantities to allow clotting of these fluids in much the same way that plasma and whole blood can clot.

Table 1 Clotting factors and synonyms

Fibrinogen	Factor I
Prothrombin	Factor II
Tissue factor	Factor III; tissue thromboplastin
Calcium	Factor IV
Factor V	Proaccelerin; labile factor; Ac-globulin (Ac-G)
Factor VII	Serum prothrombin conversion accelerator (SPCA); proconvertin; stable factor
Factor VIII	Antihemophilic factor (AHF); antihemophilic globulin (AHG); antihemophilic factor A
Factor IX	Plasma thromboplastin component (PTC); Christmas factor; antihemophilic factor B
Factor X	Stuart factor; Stuart-Prower factor
Factor XI	Plasma thromboplastin antecedent (PTA); antihemophilic factor C
Factor XII	Hageman factor
Factor XIII	Fibrin-stabilizing factor
Prekallikrein	Fletcher factor
HMWK kininogen (high-molecular-weight) kininogen	Fitzgerald factor
Platelets	

Thrombin is a protein enzyme with weak proteolytic capabilities. It acts on fibrinogen to remove four low-molecular- weight peptides from each molecule of fibrinogen, forming one molecule of fibrin monomer that has the automatic capability to polymerize with other fibrin monomer molecules to form fibrin fibers. Therefore, many fibrin monomer molecules polymerize within seconds into long fibrin fibers that constitute the reticulum of the blood clot. In the early stages of polymerization, the fibrin monomer molecules are held together by weak noncovalent hydrogen bonding, and the newly forming fibers are not cross-linked with one another; therefore, the resultant clot is weak and can be broken apart with ease. But another process occurs during the next few minutes that greatly strengthens the fibrin reticulum.This involves a substance called fibrin-stabilizing factor that is present in small amounts in normal plasma globulins but is also released from platelets entrapped in the clot. Before fibrin-stabilizing factor can have an effect on the fibrin fibers, it must itself be activated. The same thrombin that causes fibrin formation also activates the fibrin-stabilizing factor. Then this activated substance operates as an enzyme to cause covalent bonds between more and more of the fibrin monomer molecules, as well as multiple crosslinkages between

adjacent fibrin fibers, thus adding tremendously to the three-dimensional strength of the fibrin meshwork.

The clot is composed of a meshwork of fibrin fibers running in all directions and entrapping blood cells, platelets, and plasma.The fibrin fibers also adhere to damaged surfaces of blood vessels; therefore, the blood clot becomes adherent to any vascular opening and thereby prevents further blood loss.

Clot retraction—serum

Within a few minutes after a clot is formed, it begins to contract and usually expresses most of the fluid from the clot within 20 to 60 minutes. The fluid expressed is called serum because all its fibrinogen and most of the other clotting factors have been removed; in this way, serum differs from plasma. Serum cannot clot because it lacks these factors. Platelets are necessary for clot retraction to occur. Therefore, failure of clot retraction is an indication that the number of platelets in the circulating blood might be low. Electron micrographs of platelets in blood clots show that they become attached to the fibrin fibers in such a way that they actually bond different fibers together. Furthermore, platelets entrapped in the clot continue to release procoagulant substances, one of the most important of which is fibrin-stabilizing factor, which causes more and more cross-linking bonds between adjacent fibrin fibers. In addition, the platelets themselves contribute directly to clot contraction by activating platelet thrombosthenin, actin, and myosin molecules, which are all contractile proteins in the platelets and cause strong contraction of the platelet spicules attached to the fibrin. This also helps compress the fibrin meshwork into a smaller mass. The contraction is activated and accelerated by thrombin as well as by calcium ions released from calcium stores in the mitochondria, endoplasmic reticulum, and Golgi apparatus of the platelets. As the clot retracts, the edges of the broken blood vessel are pulled together, thus contributing still further to the ultimate state of hemostasis.

Once a blood clot has started to develop, it normally extends within minutes into the surrounding blood. That is, the clot itself initiates a vicious circle (positive feedback) to promote more clotting. One of the most important causes of this is the fact that the proteolytic action of thrombin allows it to act on many of the other blood-clotting factors in addition to fibrinogen. For instance, thrombin has a direct proteolytic effect on prothrombin itself, tending to convert this into still more thrombin, and it acts on some of the blood-clot- ting factors responsible for formation of prothrombin activator. Once a critical amount of thrombin is formed, a vicious circle develops that causes still more blood clotting and more and more thrombin to be formed; thus, the blood clot continues to grow until blood leakage ceases.

Initiation of coagulation: formation of prothrombin activator

Now that we have discussed the clotting process itself, we must turn to the more complex mechanisms that initiate clotting in the first place. These mechanisms are set into play by (1) trauma to the vascular wall and adjacent tissues,(2) trauma to the blood,or (3) contact of the blood with damaged endothelial cells or with collagen and other tissue elements outside the blood vessel. In each instance, this leads to the formation of prothrombin activator,which then causes prothrombin conversion to thrombin and all the subsequent clotting steps.

Prothrombin activator is generally considered to be formed in two ways, although, in reality, the two ways interact constantly with each other: (1) by the extrinsic pathway that begins with trauma to the vascular wall and surrounding tissues and (2) by the intrinsic pathway that begins in the blood itself. In both the extrinsic and the intrinsic pathways, a series of different plasma proteins called blood-clotting factors play major roles.Most of these are inactive forms of proteolytic enzymes. When converted to the active forms,their enzymatic actions cause the successive, cascading reactions of the clotting process. Most of the clotting factors,which are listed in Table, are designated by Roman numerals. To indicate the activated form of the factor, a small letter "a" is added after the Roman numeral, such as Factor VIIIa to indicate the activated state of Factor VIII.
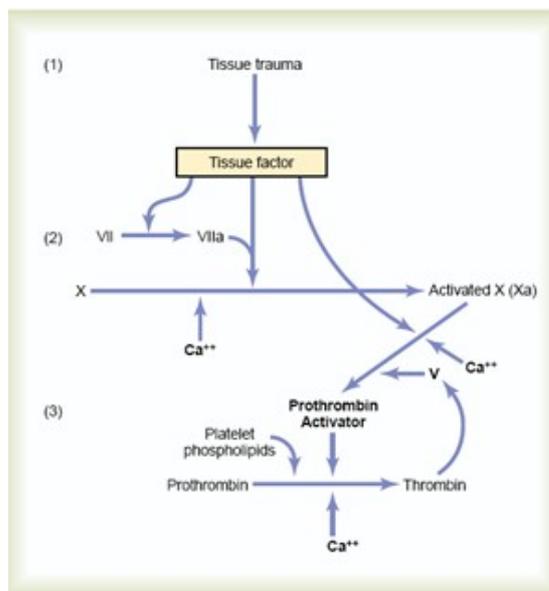
Figure3 Extrinsic pathway for initiating clotting

The extrinsic pathway for initiating the formation of prothrombin activator begins with a traumatized vascular wall or traumatized extravascular tissues that come in contact with the blood. This leads to the following steps, as shown in Figure 3:

1. Release of tissue factor. Traumatized tissue releases a complex of several factors called tissue factor or tissue thromboplastin. This factor is composed especially of phospholipids from the membranes of the tissue plus a lipoprotein complex that functions mainly as a proteolytic enzyme.

2. Activation of Factor X—role of Factor VII and tissue factor. The lipoprotein complex of tissue factor further complexes with blood coagulation Factor VII and, in the presence of calcium ions, acts enzymatically on Factor X to form activated Factor X (Xa).

3. Effect of activated Factor X (Xa) to form prothrombin activator—role of Factor V. The activated Factor X combines immediately with tissue phospholipids that are part of tissue factor or with additional phospholipids released from platelets as well as with Factor V to form the complex called prothrombin activator. Within a few seconds, in the presence of calcium ions (Ca^{++}), this splits prothrombin to form thrombin, and the clotting process proceeds as already explained. At first, the Factor V in the prothrombin activator complex is inactive, but once clotting begins and thrombin begins to form, the proteolytic action of thrombin activates Factor V. This then becomes an additional strong accelerator of prothrombin activation. Thus, in the final prothrombin activator complex, activated Factor X is the actual protease that causes splitting of prothrombin to form thrombin; activated Factor V greatly accelerates this protease activity, and platelet phospholipids act as a vehicle that further accelerates the process. Note especially the positive feedback effect of thrombin, acting through Factor V, to accelerate the entire process once it begins.

Intrinsic pathway for initiating clotting

The second mechanism for initiating formation of prothrombin activator, and therefore for initiating clotting, begins with trauma to the blood itself or exposure of the blood to collagen from a traumatized blood vessel wall. Then the process continues through the series of cascading reactions shown in Figure 4.
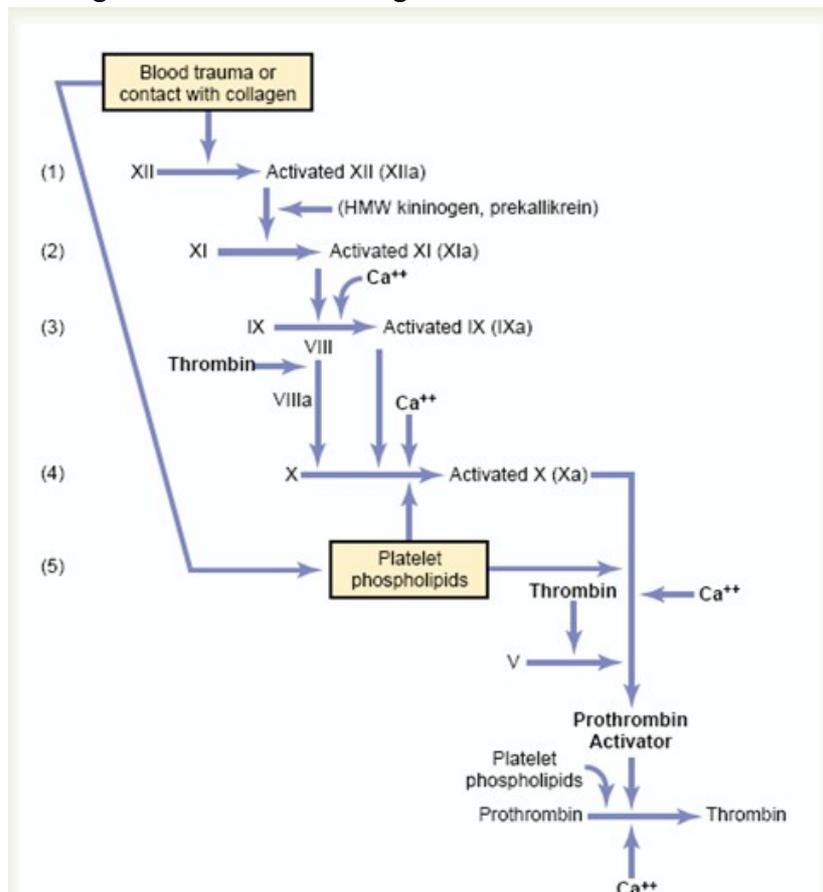
Figure 4 Intrinsic pathway for initiating clotting

1. Blood trauma causes (1) activation of Factor XII and (2) release of platelet phospholipids. Blood trauma or contact with collagen wall collagen alters two important clotting factors in the blood: Factor XII and the platelets. When Factor XII is disturbed, such as by coming into contact with collagen or with a wettable surface such as glass, it takes on a new molecular configuration that converts it into a proteolytic enzyme called "activated Factor XII." Simultaneously, the blood trauma also damages the platelets because of adherence to either collagen or a wettable surface (or by damage in other ways), and this releases platelet phospholipids that contain the lipoprotein called platelet factor 3, which also plays a role in subsequent clotting reactions.

2. Activation of factor XI. The activated Factor XII acts enzymatically on factor XI to activate this factor as well, which is the second step in the intrinsic pathway. This reaction also requires HMW (high-molecular-weight) kininogen and is accelerated by prekallikrein.

3. Activation of factor IX by activated factor XI. The activated factor XI then acts enzymatically on factor IX to activate this factor also.

4. Activation of factor X—role of factor VIII. The activated factor IX, acting in concert with activated factor VIII and with the platelet phospholipids and factor 3 from the traumatized platelets, activates factor X. It is clear that when either factor VIII or platelets are in short supply, this step is deficient. Factor VIII is the factor that is missing in a person who has classic hemophilia, for which reason it is called antihemophilic factor. Platelets are the clotting factor that is lacking in the bleeding disease called thrombocytopenia.

5. Action of activated factor X to form prothrombin activator—role of factor V. This step in the intrinsic pathway is the same as the last step in the extrinsic pathway. That is, activated factor X combines with factor V and platelet or tissue phospholipids to form the complex called prothrombin activator. The prothrombin activator in turn initiates within seconds the cleavage of prothrombin to form thrombin, thereby setting into motion the final clotting process, as described earlier.

Except for the first two steps in the intrinsic pathway, calcium ions are required for promotion or acceleration of all the blood-clotting reactions. Therefore, in the absence of calcium ions, blood clotting by either pathway does not occur. In the living body, the calcium ion concentration seldom falls low enough to significantly affect the kinetics of blood clotting. But, when blood is removed from a person, it can be prevented from clotting by reducing the calcium ion concentration below the threshold level for clotting, either by deionizing the calcium by causing it to react with substances such as citrate ion or by precipitating the calcium with substances such as oxalate ion.

It is clear from the schemas of the intrinsic and extrinsic systems that after blood vessels rupture, clotting occurs by both pathways simultaneously.Tissue factor initiates the extrinsic pathway, whereas contact of factor XII and platelets with collagen in the vascular wall initiates the intrinsic pathway. An especially important difference between the extrinsic and intrinsic pathways is that the extrinsic pathway can be explosive; once initiated, its speed of completion to the final clot is limited only by the amount of tissue factor released from the traumatized tissues and by the quantities of factors X, VII, and V in the blood. With severe tissue trauma, clotting can occur in as little as 15 seconds. The intrinsic pathway is much slower to proceed, usually requiring 1 to 6 minutes to cause clotting.

Prevention of blood clotting in the normal vascular system

Probably the most important factors for preventing clotting in the normal vascular system are (1) the smoothness of the endothelial cell surface,which prevents contact activation of the intrinsic clotting system; (2) a layer of glycocalyx on the endothelium (glycocalyx is a mucopolysaccharide adsorbed to the surfaces of the endothelial cells), which repels clotting factors and platelets, thereby preventing activation of clotting; and (3) a protein bound with the endothelial membrane, thrombomodulin, which binds thrombin. Not only does the binding of thrombin with thrombomodulin slow the clotting process by removing thrombin, but the thrombomodulin-thrombin complex also activates a plasma protein, protein C, that acts as an anticoagulant by inactivating activated factors V and VIII. When the endothelial wall is damaged, its smoothness and its glycocalyx-thrombomodulin layer are lost, which activates both factor XII and the platelets, thus setting off the intrinsic pathway of clotting. If factor XII and platelets come in contact with the subendothelial collagen, the activation is even more powerful.

Among the most important anticoagulants in the blood itself are those that remove thrombin from the blood. The most powerful of these are (1) the fibrin fibers that themselves are formed during the process of clotting and (2) an alpha-globulin called antithrombin III or antithrombin-heparin cofactor. While a clot is forming, about 85 to 90 per cent of the thrombin formed from the prothrombin becomes adsorbed to the fibrin fibers as they develop. This helps prevent the spread of thrombin into the remaining blood and, therefore, prevents excessive spread of the clot. The thrombin that does not adsorb to the fibrin fibers soon combines with antithrombin III, which further blocks the effect of the thrombin on the fibrinogen and then also inactivates the thrombin itself during the next 12 to 20 minutes.

Heparin is another powerful anticoagulant, but its concentration in the blood is normally low, so that only under special physiologic conditions does it have significant anticoagulant effects. However, heparin is used widely as a pharmacological agent in medical practice in much higher concentrations to prevent intravascular clotting. The heparin molecule is a highly negatively charged conjugated polysaccharide. By itself, it has little or no anticoagulant properties, but when it combines with antithrombin III, the effectiveness of antithrombin III for removing thrombin increases by a hundredfold to a thousandfold, and thus it acts as an anticoagulant. Therefore, in the presence of excess heparin, removal of free thrombin from the circulating blood by antithrombin III is almost instantaneous. The complex of heparin and antithrombin III removes several other activated coagulation factors in addition to thrombin, further enhancing the effective- ness of anticoagulation. The others include activated Factors XII, XI, X, and IX. Heparin is produced by many different cells of the body, but especially large quantities are formed by the basophilic mast cells located in the pericapillary connective tissue throughout the body.These cells continually secrete small quantities of heparin that diffuse into the circulatory system. The basophil cells of the blood, which are functionally almost identical to the mast cells, release small quantities of heparin into the plasma. Mast cells are abundant in tissue surrounding the capillaries of the lungs and to a lesser extent capillaries of the liver.It is easy to understand why large quantities of

heparin might be needed in these areas because the capillaries of the lungs and liver receive many embolic clots formed in slowly flowing venous blood; sufficient formation of heparin prevents further growth of the clots.

Lysis of blood clots—plasmin

The plasma proteins contain a euglobulin called plasminogen (or profibrinolysin) that, when activated, becomes a substance called plasmin (or fibrinolysin). Plasmin is a proteolytic enzyme that resembles trypsin, the most important proteolytic digestive enzyme of pancreatic secretion. Plasmin digests fibrin fibers and some other protein coagulants such as fibrinogen, factor V, factor VIII, prothrombin, and factor XII. Therefore, whenever plasmin is formed, it can cause lysis of a clot by destroying many of the clotting factors, thereby sometimes even causing hypocoagulability of the blood.

When a clot is formed, a large amount of plasminogen is trapped in the clot along with other plasma proteins. This will not become plasmin or cause lysis of the clot until it is activated. The injured tissues and vascular endothelium very slowly release a powerful activator called tissue plasminogen activator (t-PA) that a few days later, after the clot has stopped the bleeding, eventually converts plasminogen to plasmin, which in turn removes the remaining unnecessary blood clot. In fact, many small blood vessels in which blood flow has been blocked by clots are reopened by this mechanism. Thus, an especially important function of the plasmin system is to remove minute clots from millions of tiny peripheral vessels that eventually would become occluded were there no way to clear them.

Conditions that cause excessive bleeding in human beings

Excessive bleeding can result from deficiency of any one of the many blood-clotting factors. Three particular types of bleeding tendencies that have been studied to the greatest extent are discussed here: bleeding caused by (1) vitamin K deficiency,(2) hemophilia,and (3) thrombocytopenia (platelet deficiency).

With few exceptions, almost all the blood-clotting factors are formed by the liver. Therefore, diseases of the liver such as hepatitis, cirrhosis, and acute yellow atrophy can sometimes depress the clotting system so greatly that the patient develops a severe tendency to bleed. Another cause of depressed formation of clotting factors by the liver is vitamin K deficiency.Vitamin K is necessary for liver formation of five of the important clotting factors: prothrombin, Factor VII, Factor IX, Factor X, and protein C. In the absence of vitamin K, subsequent insufficiency of these coagulation factors in the blood can lead to serious bleeding tendencies. Vitamin K is continually synthesized in the intes- tinal tract by bacteria, so that vitamin K deficiency seldom occurs in the normal person as a result of vitamin K absence from the diet (except in neonates before they establish their intestinal bacterial flora). However, in gastrointestinal disease, vitamin K deficiency often occurs as a result of poor absorption of fats from the gastrointestinal tract. The reason is that vitamin K is fat-soluble and ordinarily is absorbed into the blood along with the fats. One of the most prevalent causes of vitamin K deficiency is failure of the liver to secrete bile into the gastrointestinal tract (which occurs either as a result of obstruction of the bile ducts or as a result of liver disease). Lack of bile prevents adequate fat digestion and absorption and, therefore, depresses vitamin K absorption as well. Thus, liver disease often causes decreased production of

prothrombin and some other clotting factors both because of poor vitamin K absorption and because of the diseased liver cells. Because of this, vitamin K is injected into all surgical patients with liver disease or with obstructed bile ducts before performing the surgical procedure. Ordinarily, if vitamin K is given to a deficient patient 4 to 8 hours before the operation and the liver parenchymal cells are at least one-half normal in function, sufficient clotting factors will be produced to prevent excessive bleeding during the operation.

Hemophilia is a bleeding disease that occurs almost exclusively in males.In 85 per cent of cases, it is caused by an abnormality or deficiency of factor VIII; this type of hemophilia is called hemophilia A or classic hemophilia. About 1 of every 10,000 males in the United States has classic hemophilia. In the other 15 per cent of hemophilia patients, the bleeding tendency is caused by deficiency of factor IX. Both of these factors are transmitted genetically by way of the female chromosome. Therefore, almost never will a woman have hemophilia because at least one of her two X chromosomes will have the appropriate genes. If one of her X chromosomes is deficient, she will be a hemophilia carrier,transmitting the disease to half of her male offspring and transmitting the carrier state to half of her female offspring. The bleeding trait in hemophilia can have various degrees of severity, depending on the character of the genetic deficiency. Bleeding usually does not occur except after trauma, but in some patients, the degree of trauma required to cause severe and prolonged bleeding may be so mild that it is hardly noticeable. For instance, bleeding can often last for days after extraction of a tooth. Factor VIII has two active components,a large component with a molecular weight in the millions and a smaller component with a molecular weight of about 230,000. The smaller component is most important in the intrinsic pathway for clotting, and it is deficiency of this part of factor VIII that causes classic hemophilia. Another bleeding disease with somewhat different characteristics, called von Willebrand's disease, results from loss of the large component. When a person with classic hemophilia experiences severe prolonged bleeding, almost the only therapy that is truly effective is injection of purified factor VIII. The cost of Factor VIII is high, and its availability is limited because it can be gathered only from human blood and only in extremely small quantities.

Thrombocytopenia means the presence of very low numbers of platelets in the circulating blood. People with thrombocytopenia have a tendency to bleed, as do hemophiliacs, except that the bleeding is usually from many small venules or capillaries, rather than from larger vessels as in hemophilia. As a result, small punctate hemorrhages occur throughout all the body tissues.The skin of such a person displays many small, purplish blotches, giving the disease the name thrombocytopenic purpura. As stated earlier, platelets are especially important for repair of minute breaks in capillaries and other small vessels. Ordinarily, bleeding will not occur until the number of platelets in the blood falls below 50,000/ml, rather than the normal 150,000 to 300,000. Levels as low as 10,000/ml are frequently lethal. Even without making specific platelet counts in the blood, sometimes one can suspect the existence of thrombocytopenia if the person's blood fails to retract, because, as pointed out earlier, clot retraction is normally dependent on release of multiple coagulation factors from the large numbers of platelets entrapped in the fibrin mesh of the clot. Most people with thrombocytopenia have the disease known as idiopathic thrombocytopenia, which means thrombocytopenia of unknown cause. In most of these people, it has been discovered that for unknown reasons,specific antibodies have formed and react against the

platelets themselves to destroy them. Relief from bleeding for 1 to 4 days can often be effected in a patient with thrombocytopenia by giving fresh whole blood transfusions that contain large numbers of platelets. Also, splenectomy is often helpful, sometimes effecting almost complete cure because the spleen normally removes large numbers of platelets from the blood.

Thromboembolic conditions in the human being

An abnormal clot that develops in a blood vessel is called a thrombus. Once a clot has developed, continued flow of blood past the clot is likely to break it away from its attachment and cause the clot to flow with the blood; such freely flowing clots are known as emboli. Also, emboli that originate in large arteries or in the left side of the heart can flow peripherally and plug arteries or arterioles in the brain, kidneys, or elsewhere. Emboli that originate in the venous system or in the right side of the heart generally flow into the lungs to cause pulmonary arterial embolism.

The causes of thromboembolic conditions in the human being are usually twofold:

(1) Any roughened endothelial surface of a vessel—as may be caused by arteriosclerosis, infection, or trauma—is likely to initiate the clotting process.

(2) Blood often clots when it flows very slowly through blood vessels, where small quantities of thrombin and other procoagulants are always being formed.

Genetically engineered t-PA (tissue plasminogen activator) is available. When delivered directly to a thrombosed area through a catheter, it is effective in activating plasminogen to plasmin, which in turn can dissolve some intravascular clots. For instance, if used within the first hour or so after thrombotic occlusion of a coronary artery, the heart is often spared serious damage.

Because clotting almost always occurs when blood flow is blocked for many hours in any vessel of the body, the immobility of patients confined to bed plus the practice of propping the knees with pillows often causes intravascular clotting because of blood stasis in one or more of the leg veins for hours at a time.Then the clot grows, mainly in the direction of the slowly moving venous blood, sometimes growing the entire length of the leg veins and occasionally even up into the common iliac vein and inferior vena cava. Then, about 1 time out of every 10, a large part of the clot disengages from its attachments to the vessel wall and flows freely with the venous blood through the right side of the heart and into the pulmonary arteries to cause massive blockage of the pulmonary arteries, called massive pulmonary embolism.If the clot is large enough to occlude both of the pulmonary arteries at the same time, immediate death ensues. If only one pulmonary artery is blocked, death may not occur, or the embolism may lead to death a few hours to several days later because of further growth of the clot within the pulmonary vessels.

Disseminated Intravascular Coagulation

Occasionally the clotting mechanism becomes activated in widespread areas of the circulation, giving rise to the condition called disseminated intravascular coagulation. This often results from the presence of large amounts of traumatized or dying tissue in the body that releases great quantities of tissue factor into the blood. Frequently, the clots are small but numerous, and they plug a large share of the small peripheral blood vessels. This occurs

especially in patients with widespread septicemia, in which either circulating bacteria or bacterial toxins—especially endotoxins—activate the clotting mechanisms. Plugging of small peripheral vessels greatly diminishes delivery of oxygen and other nutrients to the tissues—a situation that leads to or exacerbates circulatory shock. It is partly for this reason that septicemic shock is lethal in 85 per cent or more of patients. A peculiar effect of disseminated intravascular coagulation is that the patient on occasion begins to bleed. The reason for this is that so many of the clotting factors are removed by the widespread clotting that too few procoagulants remain to allow normal hemostasis of the remaining blood.

In some thromboembolic conditions, it is desirable to delay the coagulation process. Various anticoagulants have been developed for this purpose. The ones most useful clinically are heparin and the coumarins.

Prevention of blood coagulation outside the body

Although blood removed from the body and held in a glass test tube normally clots in about 6 minutes, blood collected in siliconized containers often does not clot for 1 hour or more. The reason for this delay is that preparing the surfaces of the containers with silicone prevents contact activation of platelets and Factor XII, the two principal factors that initiate the intrinsic clotting mechanism. Conversely, untreated glass containers allow contact activation of the platelets and Factor XII, with rapid development of clots. Heparin can be used for preventing coagulation of blood outside the body as well as in the body. Heparin is especially used in surgical procedures in which the blood must be passed through a heart-lung machine or artificial kidney machine and then back into the person. Various substances that decrease the concentration of calcium ions in the blood can also be used for preventing blood coagulation outside the body. For instance, a soluble oxalate compound mixed in a very small quantity with a sample of blood causes precipitation of calcium oxalate from the plasma and thereby decreases the ionic calcium level so much that blood coagulation is blocked. Any substance that deionizes the blood calcium will prevent coagulation.The negatively charged citrate ion is especially valuable for this purpose, mixed with blood usually in the form of sodium, ammonium, or potassium citrate. The citrate ion combines with calcium in the blood to cause an unionized calcium compound, and the lack of ionic calcium prevents coagulation. Citrate anticoagulants have an important advantage over the oxalate anticoagulants because oxalate is toxic to the body, whereas moderate quantities of citrate can be injected intravenously. After injection, the citrate ion is removed from the blood within a few minutes by the liver and is polymerized into glucose or metabolized directly for energy. Consequently, 500 milliliters of blood that has been rendered incoagulable by citrate can ordinarily be transfused into a recipient within a few minutes without dire consequences. But if the liver is damaged or if large quantities of citrated blood or plasma are given too rapidly (within fractions of a minute), the citrate ion may not be removed quickly enough, and the citrate can, under these conditions, greatly depress the level of calcium ion in the blood, which can result in tetany and convulsive death.