Case 2: “This Oozing Makes Me Woozy”

MECHANISMS INVOLVED IN HEMOSTASIS

VASCULAR CONSTRICTION

- Immediately after a blood vessel has been cut or ruptured, the trauma to the vessel wall itself causes the vessel to contract; this instantaneously reduces the flow of blood from the vessel rupture.
- The contraction results from nervous reflexes, local myogenic spasm, and local humoral factors (e.g. endothelin - a potent endothelium-derived vasoconstrictor) from the traumatized tissues and blood platelets.
- The nervous reflexes are initiated by pain nerve impulses or other impulses that originate from traumatized vessel or from nearby tissues.
- However, most of the vasoconstriction probably results from local direct damage to the vascular wall. For the smaller vessels, the platelets are responsible for much of the vasoconstriction by releasing the vasoconstrictor substance thromboxane A2.
- The more a vessel is traumatized, the greater the degree of spasm; this means that a sharply cut blood vessel usually bleeds much more than does a vessel ruptured by crushing. The local vascular spasm can last for many minutes or even hours, during which time the processes of platelet plugging and blood coagulation can take place.

PLATELET PLUG FORMATION

- If the rent in the blood vessel is very small — and many very small vascular holes do develop throughout the body each day — it is often sealed by a platelet plug, rather than by a blood clot. To understand this, it is important that we first discuss the nature of platelets themselves.
- **Physical and Chemical Characteristics of Platelets**
  - Platelets (also called thrombocytes) are minute round or oval 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 bone marrow; the megakaryocytes fragment into the minute platelets either in the bone marrow or soon after entering the blood, especially as they try to squeeze through the pulmonary capillaries.
  - Platelets have many functional characteristics of whole cells, even though they do not have nuclei and cannot reproduce. In their cytoplasm are active factors such as:
    - (1) actin and myosin molecules, similar to those found in muscle cells, as well as 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 and adenosine diphosphate (ADP);
    - (4) enzyme systems that synthesize prostaglandins, which are local hormones that cause many types of vascular and other local tissue reactions;
    - (5) an important protein called fibrin-stabilizing factor;
    - (6) a growth factor that causes vascular endothelial cells, vascular smooth muscle cells, and fibroblasts to multiply and grow, thus causing cellular growth that 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 in the vessel wall. In addition, the platelet membrane contains large amounts of phospholipids that play several activating roles at multiple points 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.
- **Mechanism of the Platelet Plug**
  - 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, such as the collagen fibers in the vascular wall, the platelets themselves immediately change their 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 spreads throughout 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 originally activated platelets. Therefore, at the site of any rent in a blood vessel wall, the damaged vascular wall or extravascular tissues elicit activation of successively increasing numbers of platelets that themselves attract more and more additional platelets, thus forming a platelet plug. This is the process of primary hemostasis. This is at first a loose plug, but it is usually successful in blocking the 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. This sequence, secondary hemostasis, takes longer than the initial platelet plug.
  - If the rent in a vessel wall is small, the platelet plug by itself can stop blood loss, but if there is a large hole, a blood clot in addition to the platelet plug is required to stop the bleeding.
  - The platelet-plugging mechanism is extremely important for closing the 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 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.

FORMATION OF BLOOD CLOT

- 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.
- Withing 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 play an important role in this clot retraction.

COAGULATION FACTORS

- The coagulation factors may be divided into 3 groups based on their properties.
- The thrombin sensitive group consists of fibrinogen and factors V, VIII and XIII.
    - They are consumed during the process of coagulation and are absent in serum and present in plasma.
- The vitamin K dependent group includes prothrombin and factors VII, IX and X.
    - Vitamin K is necessary for their synthesis which takes place in the liver.
- The contact group is composed of factors XI and XII, prekallikrein and HMWK.
    - They are not consumed during coagulation.

FIBRINOGEN

- Fibrinogen is synthesized in the liver
- It is made up of 3 pairs of peptide chains named a, β and δ.
- When acted on by thrombin, the alpha chain yields fibrinopeptide A and the beta chain yields fibrinopeptide B.
- The normal plasma concentration of fibrinogen is approximately 200 to 400 mg/dL.

PROTHROMBIN

- Prothrombin is synthesized in the liver and is almost entirely consumed in the coagulation process so that little remains in the serum.
- It is an alpha-2 globulin and is heat stable.

TISSUE FACTOR (FACTOR III)

- Tissue factor (factor III) is a lipoprotein found in most of the body tissues, with increased concentrations in the lungs and brain.
- It has no enzymatic activity and acts as a cofactor in activating extrinsic coagulation.

CALCIUM (FACTOR IV)

- Calcium (Factor IV), in the ionized state is necessary for coagulation.
- The fact that it is essential for coagulation makes possible the use of anticoagulants, which bind the calcium and, therefore, inhibit coagulation

PROACCELERIN (FACTOR V)

- Factor V (proaccelerin) is synthesized in the liver but does not need for its production.
- It is the most unstable of the vitamin coagulation factors.

PROCONVERTIN (FACTOR VII)

- Factor VII (proconvertin) is synthesized in the liver and requires vitamin K for its production.
- It is a beta globulin and although it is stable at 4°C for 2 or more weeks.
- It is slightly heat labile.

FACTOR VIII

- Factor VIIII circulates in the blood bound to von Willebrand factor.
- This unit is called the factor VIII complex. It was originally thought that factor VIII and vWf were the same molecule. This, however, has been found not to be the case.
- The site of synthesis for factor VIII is not completely understood and it may be produced in multiple sites, including the liver.
- Factor VIII is a single chain glycoprotein.
- It is heat labile and is unstable in citrated plasma.
- During coagulation, it functions as a cofactor to enhance the activation of factor X by IXa with phospholipid and calcium ions.
- Based on its characteristics, factor VIII may be symbolized as follows:
    - (1) factor VIII, factor VIIIC, and factor VIII:C stands for the coagulant property of the factor, that portion of the molecule that is measured by standard factor VIII assays, and it is markedly decreased in classic hemophilia;
    - (2) factor VIII antigen (factor VIII:Ag) represents the antigenic properties of factor VIII measured by immunoassays.
- Von Willebrand factor functions in primary hemostasis, acts as a carrier for the coagulant portion of the factor VIII complex, and constitutes greater than 90% of this complex. It is synthesized in the megakaryocytes and is also present in the alpha granules of platelets.

ANTIHEMOPHILIC B (FACTOR IX)

- Factor IX (antihemophilic B factor) is a single chain glycoprotein synthesized in the live, and requires vitamin K for its production.
- It is decreased in the plasma of patients with Christmas disease.

STUART FACTOR (FACTOR X)

- Factor X (Stuart factor) is a glycoprotein. liver and requires vitamin K for its production.
- It is relatively heat stable and may be stored up to 2 months at 4°C.
- It may be activated by both intrinsic and extrinsic coagulation systems.

PLASMA THROMBOPLASTIN ANTECEDENT (FACTOR XI)

- Factor XI (plasma thromboplastin antecedent) is a beta-2 globulin that is thought to circulate in the plasma in a complex with HMWK.
- It is probably synthesized in the liver and is relatively stable at room temperature.

HAGEMAN FACTOR (FACTOR XII)

- Factor XII (Hageman factor) is a single chain polypeptide.
- The actual site of production is not known.
- It is stable in that it can be stored at 4°C for almost 3 months. It is relatively heat stable.

FIBRIN STABILIZING FACTOR (FACTOR XIII)

- Factor XIII (fibrin stabilizing factor) is heat stable. Although its site of production is not known, it is thought that the liver may play a role.

PREKALLIKREIN (FLETCHER FACTOR)

- Prekallikrein (Fletcher factor) is a single chain y globulin.
- It is produced in the liver but is not dependent on Vitamin k for its production.
- This factor is present in serum.

HIGH MOLECULAR WEIGHT KININOGEN (FITZGERALD FACTOR)

- High molecular weight kininogen (Fitzgerald factor) is a single chain glycoprotein and is present in serum. It is produced in the liver and is not vitamin K-dependent.

BLOOD COAGULATION CASCADE

- More than 50 important substances that 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 in the area tissue damage become "activated" and override 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 complex of activated substances collectively called prothrombin activator.
    - (2) The prothrombin activator catalyzes the 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.
- Initiation of Coagulation: Formation of Prothrombin Activator

- Prothrombin activator is generally considered to be formed in two ways, although, in reality, the two ways inter act with each other.
  - (1) by the extrinsic pathway that begins with trauma to the vascular wall and surrounding tissues
  - (2) by the intrinsic pathway that begins in the blood itself

EXTRINSIC PATHWAY

- The extrinsic pathway for initializing the formation of prothrombin activator begins with a traumatized vascular wall or extravascular tissues that come in contact with the blood. This leads to the following steps as shown in the figure below.

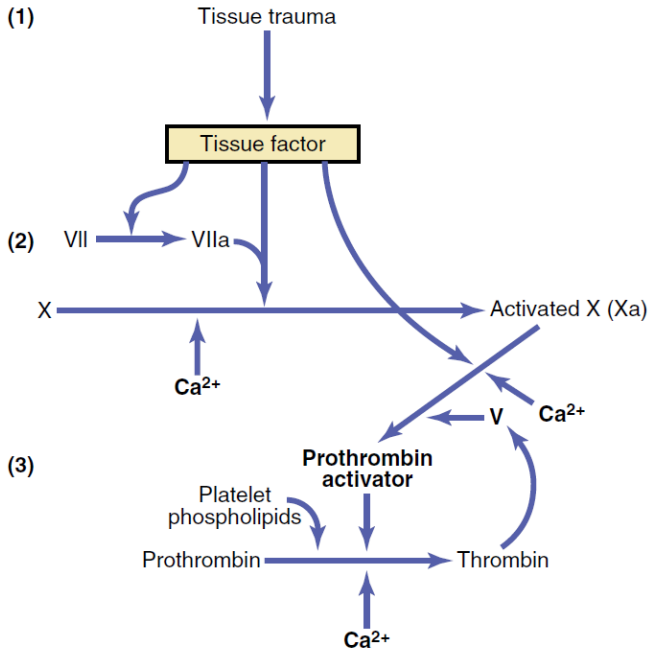


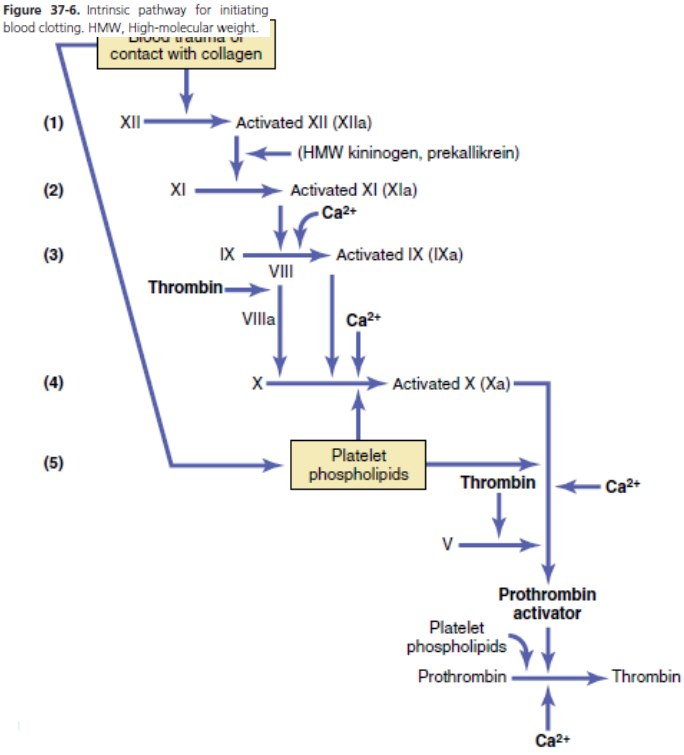
Figure 37-5. Extrinsic pathway for initiating blood clotting.

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.
3. **Effect of Xa to form prothrombin activator—role of factor V.** The activated factor X combines immediately with tissue phospholipids that are part of tissue factors 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 Ca2+, prothrombin is split 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 activation 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

- The second mechanism for initiating formation of prothrombin activator, and therefore for initiating clotting, begins with trauma to the blood 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.

Figure 37-6. Intrinsic pathway for initiating blood clotting. HMW, High-molecular weight.



1. **Blood trauma causes (1) activation of factor XII and (2) release of platelet phospholipids.** Trauma to the blood or exposure of the blood to vascular 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 collagen or to a wettable surface (or by damage in other ways); 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 also acts enzymatically on factor XI to activate this factor, which is the second step in the intrinsic path way. This reaction also requires 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 as well.
4. **Activation of factor X**—role of factor VIII. The activated factor IX, acting in concert with activated factor VIII and the platelet phospholipids and factor III 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, so 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 the cleavage of prothrombin to form thrombin within seconds, thereby setting into motion the final clotting process, as described earlier.

CONVERSION OF PROTHROMBIN TO THROMBIN

1. 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.
2. Prothrombin activator, in the presence of sufficient amounts of ionic calcium (Ca2+), causes conversion of prothrombin to thrombin (Figure 37-3 and 37-4).
3. Thrombin causes polymerization of fibrinogen molecules into fibrin fibers within another 10 to 15 seconds.

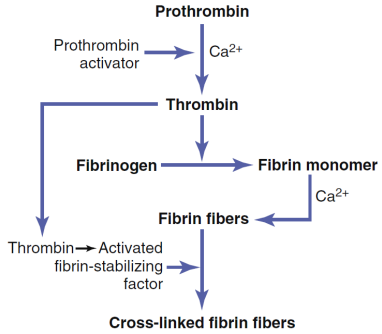


Figure 37-3 Schema for conversion of prothrombin to thrombin and polymerization of fibrinogen to form fibrin fibers.

- 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.
- Platelets also play an important role in the conversion of prothrombin to thrombin because much of the prothrombin first attaches to prothrombin receptors on the platelets that are already bound to the damaged tissue.

ACTION OF THROMBIN ON FIBRINOGEN TO FORM FIBRIN

- 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 non covalent 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. However, another process occurs during the next few minutes that greatly strengthens the fibrin reticulum. This process 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 be activated. The same thrombin that causes fibrin formation also activates the fibrin stabilizing factor. This activated substance then operates as an enzyme to form covalent bonds between more and more of the fibrin monomer molecules, as well as multiple cross-linkages between adjacent fibrin fibers, thus adding tremendously to the three-dimensional strength of the fibrin meshwork.

BLOOD CLOT

- The clot is composed of a meshwork of fibrin fibers running in all directions and entrapping blood cells, platelets, and plasma (see Figure 37-4).
- 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.

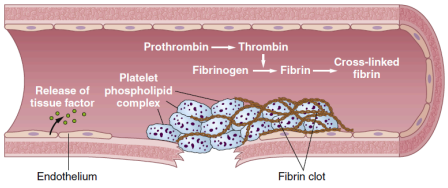


Figure 37-4. Coagulation cascade after vascular injury. Exposure of blood to the vascular wall causes release of tissue factor (also called factor III or thromboplastin) from endothelial cells, phospholipid expression, activation of thrombin, which then acts on fibrinogen to form fibrin, and fibrin polymerization to form a meshwork that stabilizes the platelet plug.

CLOT RETRACTION AND EXPRESSION OF 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 and 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 contribute directly to clot contraction by activating platelet thrombosthenin, actin, and myosin molecules, which are all contractile proteins in the platelets; they cause strong contraction of the platelet spicules attached to the fibrin. This action also helps compress the fibrin meshwork into a smaller mass. The contraction is activated and accelerated by thrombin and 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 hemostasis.

INTRAVASCULAR ANTICOAGULANTS THAT PREVENT BLOOD CLOTTING IN THE NORMAL VASCULAR SYSTEM

ENDOTHELIAL SURFACE FACTORS

- Probably the most important factors for preventing clotting in the normal vascular system are the following:
  - (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 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 into contact with the subendothelial collagen, the activation is even more powerful.
- Intact endothelial cells also produce other substances such a prostacyclin and nitric oxide (NO) that inhibit platelet aggregation and initiation of blood clotting. Prostacyclin, also called prostaglandin I2 (PGI2), is a member of the eicosanoid family of lipids and is a vasodilator, as well as an inhibitor of platelet aggregation. NO is a powerful vasodilator released from healthy vascular endothelial cells throughout the body, and it is an important inhibitor of platelet aggregation. When endothelial cells are damaged, their production of prostacyclin and NO is greatly diminished.

ANTITHROMBIN ACTION OF FIBRIN AND ANTITHROMBIN III

- Among the most important anticoagulants in the blood are those that remove thrombin from the blood. The most powerful of these are the following:
  - (1) the fibrin fibers that are formed during the process of clotting; and
  - (2) an α globulin called antithrombin III or antithrombin-heparin cofactor.
- While a clot is forming, about 85% to 90% of the thrombin formed from the prothrombin becomes adsorbed to the fibrin fibers as they develop. This adsorption 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. This further blocks the effect of thrombin on the fibrinogen and then also inactivates thrombin itself during the next 12 to 20 minutes.

HEPARIN

- Heparin is another powerful anticoagulant but, because its concentration in the blood is normally low, it has significant anticoagulant effects only under special physiological conditions. 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 acts as an anticoagulant. Therefore, in the presence of excess heparin, the 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 effectiveness of anticoagulation. The others include activated factors IX through XII.
- Heparin is produced by many different cells of the body, but the largest 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 that have formed in slowly flowing venous blood; sufficient production of heparin prevents further growth of the clots.

MECHANISMS AND FACTORS BEHIND FIBRINOLYSIS

- The plasma proteins contain a euglobulin called plasminogen (profibrinolysin) that when activated, becomes a substance called plasmin (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.

Activation of Plasminogen to Form Plasmin, Then Clot Lysis

- 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); a few days later, after the clot has stopped the bleeding, t-PA 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.

TESTS TO ASSESS DIFFERENT SYSTEMS INVOLVED IN HEMOSTASIS

TOURNIQUET TEST (CAPILLARY FRAGILITY TEST)

- This test measures the resistance of the capillaries to the increased intraluminal pressure and partial anoxia caused by a carefully controlled tourniquet on the proximal aspect of the upper extremity. It is a crude measure of capillary fragility. Because platelets function to maintain capillary integrity, the degree of thrombocytopenia will correlate with the tourniquet test, as will the bleeding time. In normal patients, none to very few petechiae are formed during the test.
- A positive tourniquet test (presence of numerous petechiae) will be found in thrombocytopenia, decreased fibrinogen and in vascular purpura.

BLEEDING TIME

- This test provides an estimate of the integrity of the primary hemostatic plug and thus measures the interaction between the microvasculature (capillaries) and platelets. Hence it is abnormal in a variety of quantitative and qualitative defects and occasionally in vascular disorders.
- The test requires that an atraumatic subcutaneous incision be made without transecting vessels larger than subcutaneous capillaries. depth and length of the incision requires careful control, as does the removal of blood welling from the incision. It is vital to remove all blood from the incision, otherwise fibrin formation may produce a spuriously low bleeding time.
- The position of the extremity on which the incision is made will interfere with the intracapillary pressure; therefore, most methods now recommend that this be stabilized using an exterior pressure cuff (sphygmomanometer) cuff and constant pressure of 40 mmHg if an upper extremity is used.
- The end point of the test is reached when all bleeding ceases, and this is most conveniently detected for routine purposes using a filter paper to blot away the surplus blood. When the filter paper remains clean, the end point is reached.
- Normal range: Depends on location and orientation of cut and on particular device used, typically 2 to 8 minutes.

CLOTTING TIME

- Whole blood is delivered using a carefully controlled venipuncture and collection process into standardized glass tubes.
- The clotting time of the blood is timed and expressed in minutes.
- It is prolonged in defects of intrinsic and extrinsic coagulation and in the presence of certain pathological anticoagulants and heparin.
- Normal Range (Lee and White method): 4 to 10 minutes

PROTHROMBIN TIME

- Blood removed from the patient is immediately oxalated so that none of the prothrombin can change into thrombin.
- Later, a large excess of calcium ion and tissue factor is suddenly mixed with the oxalated blood.
- The calcium nullifies the effect of the oxalate, and the tissue factor activates the prothrombin to thrombin reaction by means of the extrinsic clotting pathway.
- The time required for coagulation to take place is known as prothrombin time (PT).
- The prothrombin time is a useful screening procedure for the extrinsic coagulation mechanism including the common pathway (dejects deficiencies in factors II, V, VII, and X).
- The PT will also be prolonged when the fibrinogen concentration is less than 80 mg/dL and in cases of dysfibrinogenemia. The test is frequently used to follow the course of oral anticoagulant therapy.
- Normal Range: 10 - 12 seconds

ACTIVATED PARTIAL THROMBOPLASTIN TIME

- The APTT is a most useful procedure for routine screeing of coagulation disorders in the intrinsic system, for detecting the presence of circulating anticoagulants (inhibitors), and for monitoring heparin therapy.
- It measures those factors present in the intrinsic coagulation mechanism except for platelets and factor XIII.
- Normal Range: 25 - 35 seconds

CLOT RETRACTION

- When blood coagulation is complete, the clot normally undergoes retraction (serum is expressed from the clot, and the clot becomes denser).
- In the past, this procedure has been used as a screening test for platelet function. With the advent of more sophisticated tests for platelet function, however, this test is used infrequently. Normal clot retraction requires a normal number of functioning platelets, calcium, ATP, and a normal interaction of platelets with fibrinogen and fibrin.
- Normally, clot retraction begins within 30 seconds after the blood has clotted.
- At the end of 1 hour, there should be appreciable clot retraction with most retraction occurring within the first 4 hours. Clot retraction should be complete within 24 hours.