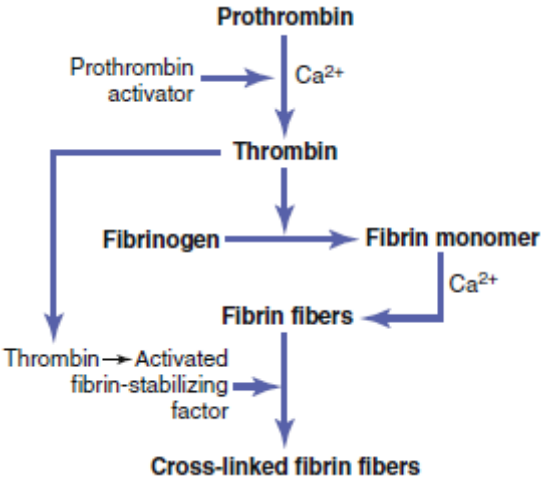
Blood Coagulation: also known as clotting, is the process by which blood loses its fluidity and sets into a semisolid jelly. Its purpose is to stop further hemorrhage.

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 12 blood coagulation factors. The net result is the formation of a complex of activated substances collectively called *prothrombin activator*.
2. The prothrombin activator in the presence of sufficient amounts of ionic calcium (Ca^{2+}),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.



Prothrombin activator is generally considered to be formed in two interacting ways:
(1) by the *extrinsic pathway* & (2) by the *intrinsic pathway.*

Extrinsic Pathway:

- The extrinsic pathway is activated by external trauma that causes blood to escape from the vascular system.
- This pathway is quicker than the intrinsic pathway.
- It involves factor VII.

Intrinsic Pathway:

- The intrinsic pathway is activated by trauma inside the vascular system, and is activated by platelets, exposed endothelium, chemicals, or collagen.
- This pathway is slower than the extrinsic pathway, but more important.
- It involves factors XII, XI, IX, VIII.

Note:

Prothrombin and Thrombin: Prothrombin is a plasma protein, which is an unstable protein that can split easily into smaller compounds, one of which is thrombin. 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 activation of prothrombin, as well as a few other clotting factors. Therefore, lack of vitamin K or the presence of liver disease that prevents normal prothrombin formation can decrease the prothrombin to such a low level that a bleeding tendency results.

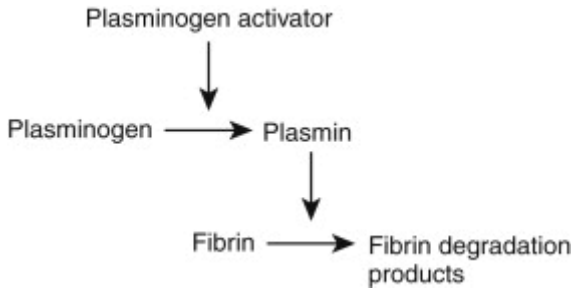
Blood-clotting factors: are inactive forms of proteolytic enzymes. When converted to the active forms, their enzymatic actions cause the successive, cascading reactions of the clotting process.

Prothrombin activator: activated factor X combines with factor V and platelet or tissue phospholipids in the presence of calcium ions to form the complex called *prothrombin activator.*

Clot Retraction: Usually blood clot retracts to about half its initial volume within 20 to 24 hours. The clot retraction prevents thrombolysis, it blocks or seals the damaged injured blood vessel and also facilitates wound healing.

Fibrinolysis: is the breakdown of fibrin in the clot. It is brought about by a proteolytic enzyme in the plasma known as plasmin or fibrinolysin.

There are two types of fibrinolysis: primary and secondary fibrinolysis. Primary fibrinolysis occurs naturally and secondary fibrinolysis occurs due to an external cause such as medicine or a medical disorder.



Plasminogen: produced by the liver.

Plasminogen activators: convert plasminogen into plasmin

Plasmin: acts as scissors specifically to cut up fibrin clots.

Intravascular Anticoagulants

1. **Endothelial Cells Factors:**

2. **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: 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.

(2) *antithrombin III:* 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.

3. Heparin:

- Heparin is a powerful anticoagulant.
- It has significant anticoagulant effects only under special physiological conditions because its concentration in the blood is normally low.
- Heparin is used widely as a pharmacological agent in medical practice in much higher concentrations to prevent intravascular clotting.
- The heparin by itself 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 thousand fold and thus acts as an anticoagulant.
  The complex of heparin and antithrombin III removes several other activated coagulation factors in addition to thrombin, further enhancing the effectiveness of anticoagulation.
- The largest quantities of heparin in the body 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 because large quantities of heparin might be needed in these capillaries to prevent further growth of the embolic clots that have formed in slowly flowing venous blood.

Coagulation Disorders:

1. Decreased Prothrombin (factor II), Factor VII, Factor IX, and Factor X Caused By Vitamin K Deficiency:

The patient develops a severe tendency to bleed. This is due to diseases of the liver such as *hepatitis*, *cirrhosis*, and *acute yellow atrophy* (degeneration of the liver caused by toxins, infections, or other agents) or due to vitamin K deficiency.

Vitamin K is continually synthesized in the intestinal tract by bacteria, so vitamin K deficiency seldom occurs in healthy persons as a result of the absence of vitamin K from the diet (except in neonates, before they establish their intestinal bacterial flora). However, in persons with gastrointestinal disease, vitamin K deficiency often occurs as a result of poor absorption of fats from the GIT because vitamin K is fat-soluble and is absorbed into the blood along with the fats.

Vitamin K deficiency may occur due to failure of the liver to secrete bile into the GIT, which occurs as a result of obstruction of the bile ducts or 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 because of poor vitamin K absorption and because of the diseased liver cells. As a result, vitamin K is injected into surgical patients with liver disease or with obstructed bile ducts before the surgical procedure is performed.

2. Hemophilia:

- Is a bleeding disease that occurs almost exclusively in males but is transmitted through females.
- In 85% of cases, it is caused by an *abnormality or deficiency of factor VIII*; this type of hemophilia is called *hemophilia A* or *classic hemophilia*.
- In the other 15% of patients with *hemophilia B*, the bleeding tendency is caused by deficiency of factor IX (Christmas factor).
- Both *factor VIII* and *factor IX* are transmitted genetically by way of the female (X) chromosome and are recessive in their inheritance.
- 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 for example, bleeding can often last for days after extraction of a tooth.
- Therapy is by injection of purified factor VIII or factor IX. Recombinant factor VIII and recombinant factor IX made by genetic engineering are immensely useful in management of hemophilia.

3. von Willebrand disease:

- Caused by the deficiency in the formation of quality or quantity of von Willebrand factor (vWF) which is required for platelet adhesion.
- The characteristic features of this disease are varying degrees of bleeding tendency, such as easy bruising, bleeding gums and nosebleeds.
- Desmopressin is used in management of this disease as it stimulates the release of vWF from the endothelial cells, and increases levels of vWF nearly up to five-fold.

4. Thrombocytopenia:

- It 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. The skin of such a person displays many small *petechiae*, red or purplish blotches, giving the disease the name *thrombocytopenic purpura*.
- The normal platelet count is 150,000 to 450,000 platelets per microliter of blood. The risk for serious bleeding occurs when platelet count becomes low as 10,000 or 20,000 platelets per microliter. Mild bleeding sometimes occurs when the platelet count is less than 50,000 platelets per microliter.
- Relief from bleeding for 1 to 4 days in a patient with thrombocytopenia by giving *fresh whole blood transfusions* that contain large numbers of platelets. Also, *splenectomy* may be helpful, sometimes resulting in an almost complete cure because the spleen normally removes large numbers of platelets from the blood.