Hemostasis and Blood Coagulation

The term hemostasis means prevention of blood loss. This achieved by several mechanisms, including:

1. **Vascular spasm.**
2. **Formation of a platelets plug.**
3. **Formation of blood clot.**
4. **Growth of fibrous tissue into the blood clot to close the whole vessel permanently.**

Vascular Spasm

The most immediate protection against blood loss is vascular spasm, a prompt constriction of the broken vessel. Several things trigger this reaction. An injury stimulates with pain receptors, some of which directly innervate nearby blood vessels and cause them to constrict. Immediately after a blood vessel is cut or ruptured, the stimulus of the trauma to the vessel causes the wall of the vessel to contract due to nervous reflexes, local myogenic spasm and local humoral factors from blood platelets.

Formation of a Platelet Plug.

Platelets are not cells, but small fragments of megakaryote cytoplasm. Although they were once called thrombocytes. Platelets are small round or oval discs 2-4 µm in diameter.

They are formed in the bone marrow from megakaryocytes which are extremely large cells of the hemopoietic series in the bone marrow that fragment into platelets. The normal concentration of platelets in the blood is between 150,000 and 400,000 per µL.

Platelets have many functional, even through these do not have nuclei and can not reproduce. In their cytoplasm are such active factor as:

1. **They secrete growth factors that stimulate mitosis in fibroblasts and smooth muscle and help to maintain the linings of blood vessels.**

2. **They secrete vasoconstrictors that cause vascular spasm in broken vessels.**

3. **They form temporary platelet plugs to stop bleeding.**

4. **They phagocytize and destroy bacteria.**

5. **They secrete chemicals that attract neutrophils and monocytes to sites of inflammation.**

6. **They dissolve blood clots that have outlasted their usefulness.**

The cell membrane of the platelets is also important, on its surface is a coat of glycoproteins that causes it to avoid adherence to normal endothelium and yet to adhere to injured areas of the vessel wall.

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 or damaged endothelial cells, they immediately change their characteristics. They begin to swell, they assume irregular forms and become sticky so that they stick to the collagen fibers, they secrete large quantities of ADP and their enzymes form thromboxane A2 in turn act on nearby platelets to activate them as well forming a platelet plug.

Formation of Blood Clot

The clot begins to develop in 15 seconds, if trauma of the vascular wall has been severe, and in 1-2 minutes if it is minor.

Mechanism of Blood Coagulation

The clotting takes place in three steps:

1. **In response to rupture of the vessel or damage to the blood, the complex of activated substances collectively called prothrombin activator.**
2. **The prothrombin activator catalyzes the conversion of prothrombin into thrombin.**
3. **The thrombin acts an enzyme to convert fibrinogen into fibrin fibers, that enmesh platelets, blood cells and plasma to form the clot.**

Conversion of Prothrombin to Thrombin :

Prothrombin is a plasma protein, an alpha 2- globulin, having a molecular weight of 68,700. it is present in normal plasma in a concentration 15 mg/dl. It is unstable protein that can easily split into thrombin which has a molecular weight 33,700 in presences of prothrombin activator and calcium ions.

Prothrombin is formed by the liver, vitamin K is required by the liver for normal formation of prothrombin.

Conversion of Fibrinogen to Fibrin

Fibrinogen is a high-molecular weight protein (340,000) that occurs in the plasma in quantities of 100-700 mg/dl. It's formed in the liver.
Thrombin is a protein enzyme with proteolytic capabilities, it act on fibrinogen to remove four low-molecular weight peptides from each

molecule of fibrinogen, forming a molecule of fibrin monomer that has the automatic capability of polymerizing with other fibrin molecule forming long fibrin fibers that form the reticulum of clot. There are two reaction pathways to coagulation, one of them, extrinsic mechanism, is initiated by clotting factors released by the damaged blood vessel and perivascular tissues. The reaction pathway it use only clotting factors found in the blood itself called intrinsic mechanim.

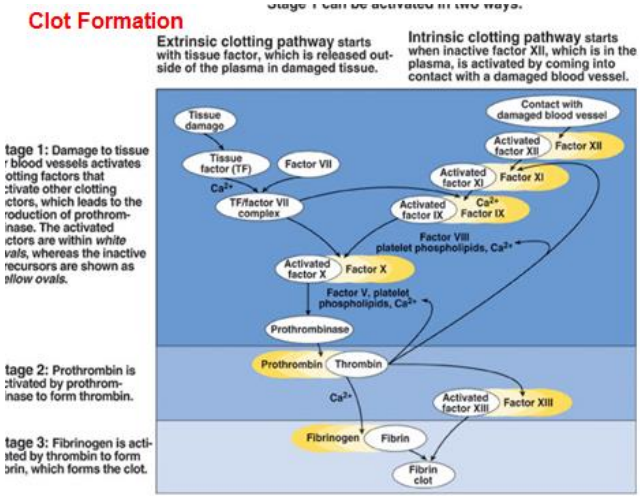
The extrinsic mechanism is the damage of blood vessel release lipoprotein mixture called thromboplastin (factor III) in the presences of Ca , thromboplatin activates factor VII, which then activates factor X. the extrinsic and intrinsic pathways differ only in how they arrive at active factor X.

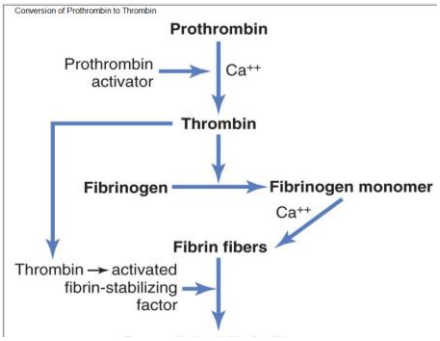
The intrinsic mechanism, when platelets degranulate, they release factor XII (Hageman factor) and then this leads to activated factors XI, IX and VIII, in that order, each serving as an enzyme that catalyzes the next step and finally to factor X. This pathway also requires calcium ions and platelet thomboplastic factor (PF3).

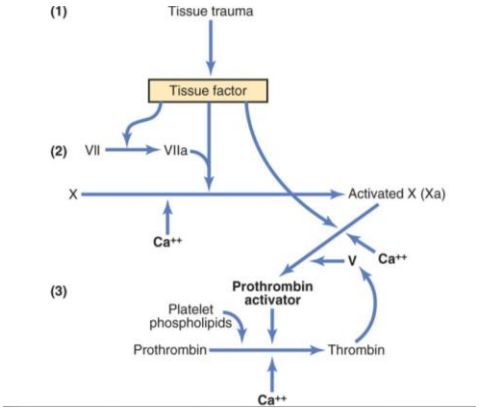
Once factor X is activated, the remaining events are identical in the intrinsic and extrinsic mechanisms. Factor X combines with factors III and V in the presence of (Ca and PF3) to produce an enzyme, prothombin activator, this enzyme acts on a globulin called prothrombin (factor II) , converting it to enzyme thrombin. Thrombin then converts fibrinogen to fibrin. Fibrin forms a loose mesh at first, but factor VIII causes the formation of covalent cross-links that convert this to fibrin polymer – a dense aggregation of fibers that forms the structural basis of the clot.

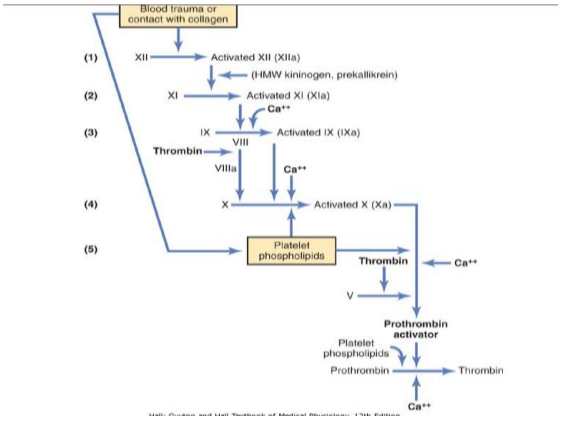
The especially important difference between extrinsic and intrinsic pathway is the extrinsic can explosive nature, once initiated, its speed of occurrence is limited only by the amount of tissue factor released from the traumatized tissues and by the quantities of factor X, VII and V in the blood. With severe trauma, clotting can occur in 15 seconds. While intrinsic usually 1-6 minutes to cause clotting.

Clot Formation









Prevention of Clotting in the Normal Vascular System

The intravascular anticoagulants

1. **<u>Endothelial surface factor:</u>**

    a. **The smoothness of endothelium, which prevents contact activation of the intrinsic clotting system.**
    b. **Layer of glycocalyx, a mucopolysaccharides adsorbed to the inner surface of the endothelium, which repels the clotting factor and platelets.**
    c. **A protein bound with endothelial membrane, thrombin which bind thrombomodulin, this dulin-thrombin not only slows the clotting process, but also activates a plasma protein, protein C, that acts as an anticoagulant by inactivating activated factors V and VIII.**

2. **<u>Antithrombin factor:</u> the most important anticoagulants in the blood itself that remove thrombin from blood, the most powerful**

    1. **The fibrin fibers that themselves are formed during the process of clotting and**
    2. **an alpha- globulin called antithrombin III or antithrombin – heparin co factor, about 85-90% of thrombin formed adsorbed to the fibrin fibers as they develop. The thrombin that does not adsorb to fibrin fibers, soon combines with antithrombin III, which block the effect of the thrombin on the fibrinogen and inactivates it within 12-20 minutes.**

3. **<u>Heparin:</u> is a conjugated polysaccharide, formed by the basophilic mast cells located in the pericapillary connective tissue throughout the body. It prevents blood coagulation by combining with antithrombin-heparin co factor which makes this factor combine with thrombin. The antithrombin heparin complex removes several other activated coagulation factors in addition to thrombin from circulating blood, the others include factors XII, XI, IX and X.**

Prevention of Blood Coagulation outside the Body:

1. **Heparin: it prevents the blood coagulation when added to the sample of blood outside the body as well as in the body.**

2. **Calcium-deionizing agent used for preventing coagulation is sodium, ammonium, or potassium citrate. The citrate ion combines with Ca in the blood to cause an un-ionized Ca compound, and lack of Ca prevents coagulation.**

3. **Collecting of the blood in siliconized containers, which prevents contact activation of platelets and factor XII, which are effects that initiate the intrinsic clotting mechanism.**

4. **Coumarine derivates: these are used internally to prolong the coagulation time from the normal range of about 2-3 minutes to 10 minutes. Vitamin K is essential for the formation of prothrombin by the liver, these substances when given they interfere with action of Vit. K and this cause a decrease in the formation of prothrombin by the liver and this causes prolongation of coagulation time, and this prevents the occur of blood clots.**

Blood Disease

1. **Decreased prothrombin, factor VII, IX and X caused by Vitamin K.**

Hepatitis , cirrhosis (replacement of liver cells by fibrous tissue), acute yellow atrophy and the presence of a stone in the common bile duct (in which bile does not reach the duodenum) and this effect on the absorption of vit. K . all these factors cause a severe tendency to bleed.
These liver diseases often cause decreased production of prothrombin and the other factor both because of poor vitamin K absorption and because of the diseased liver cells.

2. ***Hemophilia:*** **it is a hereditary disease which affects the male only, the female is not affected by the disease, 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.**

3.

There are three types of Hemophilia:

1. **Classical hemophilia (hemophilia A):**

This is caused by the deficiency of factor VIII.

2. **Hemophilia B: this caused by deficiency of factor IX.**
3. **Hemophilia C: this caused by the deficiency of factor XI.**

The treatment by giving the patient deficient factor.

3. **<u>Thrombocytopenia:</u> this means the presence of a very low quantity of platelets in the circulating system, this caused by drugs, chemicals and sometimes due to unknown reason, in this case it's called idiopathic thrombocytopenia.**

The treatment by giving the patient blood containing fresh blood platelets. (ordinary, bleeding does not occur until the number of platelets in the blood below 50,000 µl rather than normal 150,000-300,000 levels as low as 10,000 µl are frequently lethal.