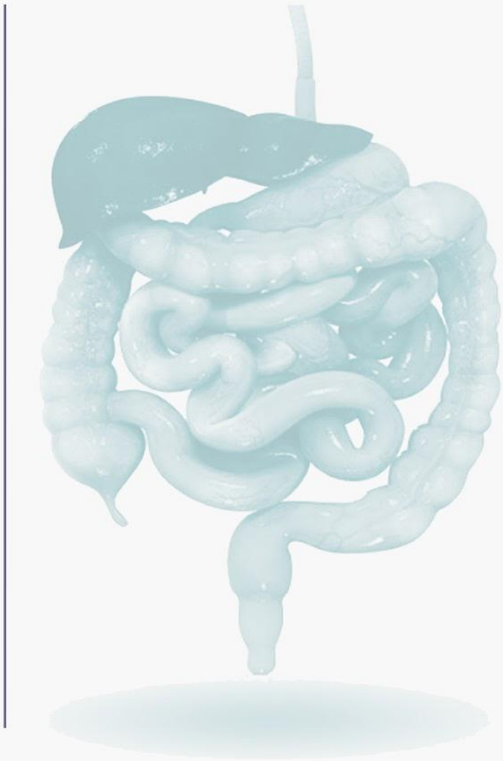
#10 Platelet Structure and Function



This lecture is only 11 slides, the rest are EXTRA for better understanding + summaries.

objectives :

- Understand platelet normal ultrastructure
- Understand the functions of different platelets
- organelles and surface receptors
- Understand the mechanisms of platelet functions
- Relate membrane receptors and granule content to normal function in hemostasis and bleeding (platelet) disorders
- recognize different clotting factors & cascade of clotting.
- Describe the intrinsic, extrinsic and common pathway.
- Recognize the role of thrombin in coagulation
- Explain process of fibrinolysis and function of plasmin.

Doctors' notes

Extra

Important

Revised by
خولة العماري & هشام الغفيلي

Resources: 435 Boys' & Girls' slides | Guyton and Hall 12th & 13th edition

Editing file

Physiology435@gmail.com

Let's start the journey with our tiny/superhero cells :)

Thrombocytes

Anuclear and discoid cell → <u>spherical</u> when activated

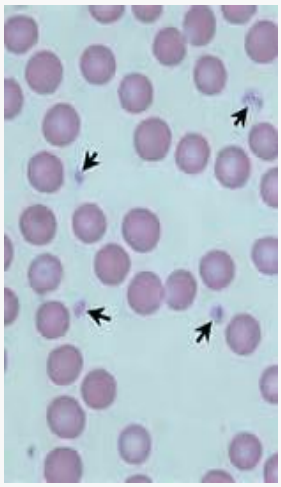
Platelet count = $150x10^3$ - $300x10^3$\ml (RBCs > Platelets > WBCs) because we need them in specific times(injuries) not like RBC we need them all the time.

Size: 1.5-3.0µm \ Lifespan: 7-10 days

Sequestrated in the spleen (hypersplenism may lead to low platelet count)

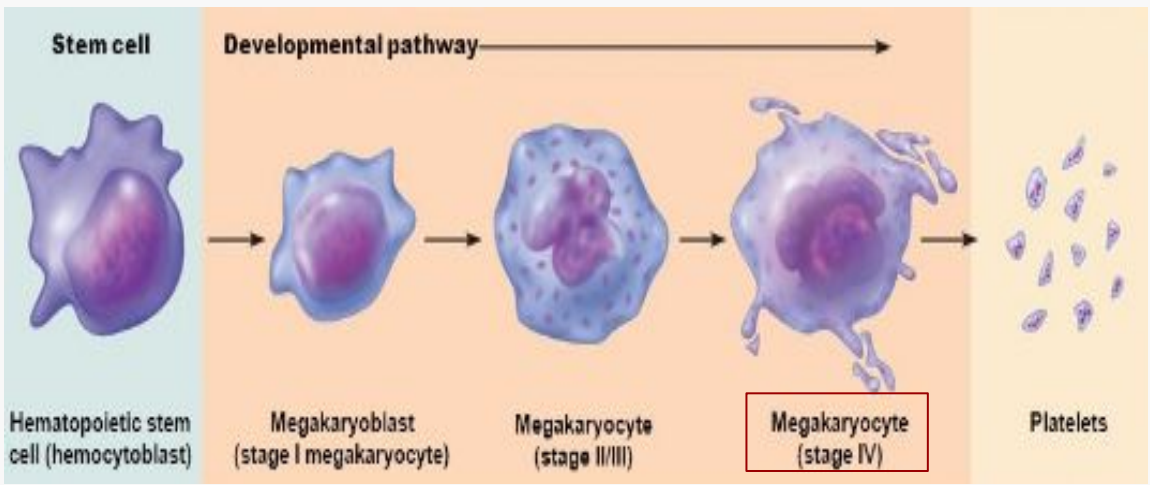
Hypersplenism is a condition in which the spleen becomes increasingly active and then rapidly removes the blood cells. It can result from any splenomegaly. It is most common with splenomegaly secondary to portal hypertension and haematological disorders.

They are formed in the bone marrow from megakaryocyte



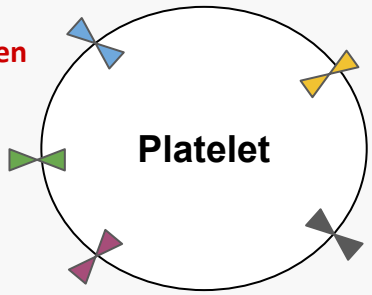
synthesis of platelet
start from undifferentiated stem cell in the bone marrow it'll be converted to megakaryoblast, then megakaryoblast will be converted to megakaryocyte (megakaryocyte known as big cell located in the bone marrow), her there's the difference between platelet and red blood cell, RBC is cell turn to another cell, platelet is not, here the megakaryocyte will divided to many small cells (break down to megakaryocyte) those small cells are the platelet in ratio 1 megakaryocyte will give me **1000** platelet.

regulation of platelet
it's regulate by thrombopoietin(from liver) what the function of thrombopoietin? it's stimulate platelet (increase the number of megakaryocyte and increase the platelet produce from each megakaryocyte) in ratio of 1 megakaryocyte will give me **1500** platelet
While the RBC regulate by erythropoietin (from kidneys).



Platelet Receptors :

GP: glycoprotein
vWf: Von Willebrand factor
- These receptors are important for the platelet to perform its function , also we use them to inhibit the platelet to treat some diseases.



(GP Ia, GP VI): will bind with collagen

(GP Ib-IX-V) : vW Factor

(TPα) : TXA2 (thromboxane a2)

(P2Y12) : ADP

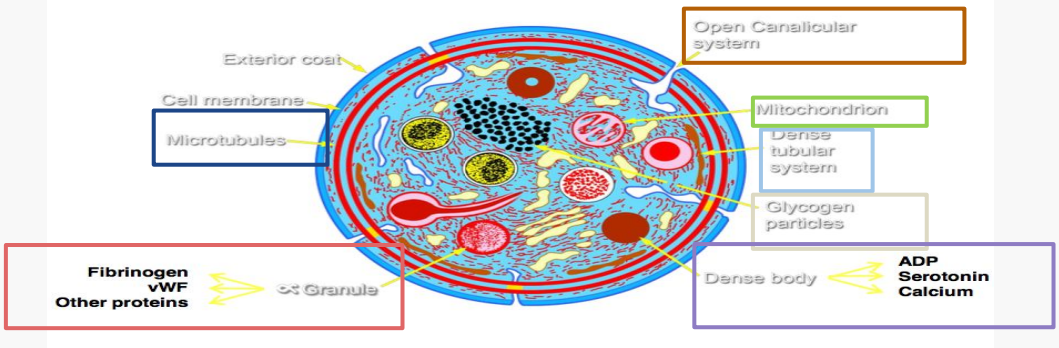
(GP IIb-IIIa): will bind with Fibrinogen & vW factor

The binding of von Willebrand factor (vWF) results in conformational changes within the GPIb-V-IX complex. In consequence, this complex activates GPIIb / IIIa membrane glycoproteins allowing them to bind fibrinogen. Fibrinogen molecules then interconnect the platelets serving as the basis for platelet aggregation. In the absence of fibrinogen, the platelets are joined by vWF due to its ability to bind the activated GPIIb / IIIa complex.

Ultrastructure of Platelet :

- **Ultrastructure of Platelet**
  - **Dens body** (delta granules)
    - Calcium
    - Serotonin
    - ADP\ATP
  - **Alpha granules**
    - Von Willebrand factor (vWF)
    - Thrombospondin
    - P-selectin
    - fibrinogen
    - Chemokines (PF4)
  - **Mitocondria**
  - **Dens tubular system**
  - **Glycogen particles**
  - **Microtubules**
  - **Open canalicular system (OCS)**

- Microtubules: give the platelet the disk shape (support the platelet).
- No nucleus.
-OCS : the stimulus will pass through it to activate the platelet and cause release of the granules content. Also the OCS is connected to the other side of the platelet.(look like amsterdam canals)



Overview from Guyton (you can skip it)

❖ Vascular Constriction :

Immediately after a blood vessel has been cut or ruptured, the trauma to the vessel wall 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 **platelet**s, 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 **platelet**s are responsible for much of the vasoconstriction by releasing a vasoconstrictor substance, *thromboxane* A_2.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. To understand this, it is important that we first discuss the nature of **platelet**s themselves.

❖ Physical and Chemical Characteristics of Platelets :

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 megakaryocytes fragment into the minute **platelet**s either in the bone marrow or soon after entering the blood, especially as they squeeze through capillaries. The normal concentration of **platelet**s 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 **platelet**s 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,* which we discuss later in relation to blood coagulation; 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 **platelet**s 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 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 **platelet**s are removed by macrophages in the spleen, where the blood passes through a latticework of tight trabeculae.

❖ Mechanism of the Platelet Plug :

Platelet repair of vascular openings is based on several important functions of the **platelet**. When **platelet**s come in contact with a damaged vascular surface, especially with collagen fibers in the vascular wall, the **platelet**s 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* A_2. The ADP and thromboxane in turn act on nearby **platelet**s to activate them as well, and the stickiness of these additional **platelet**s causes them to adhere to the original activated **platelet**s.

Therefore, at the site of any opening in a blood vessel wall, the damaged vascular wall activates successively increasing numbers of **platelet**s that themselves attract more and more additional **platelet**s, 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 **platelet**s, thus constructing an unyielding plug.

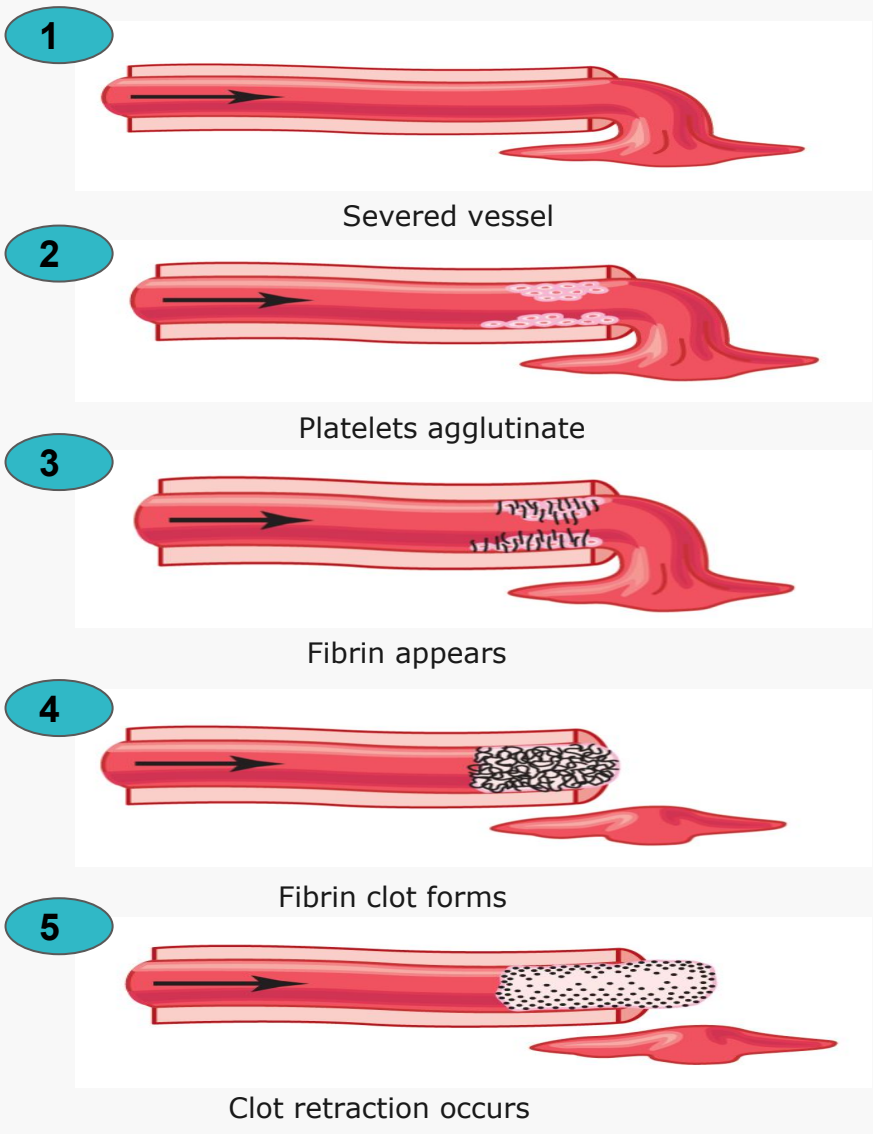
Overview from Guyton (you can skip it)

❖ Blood Coagulation in the Ruptured Vessel :

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 **platelet**s, and from blood proteins adhering to the traumatized vascular wall initiate the clotting process. 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. **Platelet**s also play an important role in this clot retraction.

❖ Fibrous Organization or Dissolution of the Blood Clot :

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 **platelet**s). This continues to complete organization of the clot into fibrous tissue within about 1 to 2 weeks.



General functions of the platelets:

1. HEMOSTASIS MECHANISM:

1. VASCULAR PHASE

vasoconstriction probably results from local myogenic contraction of the blood vessels initiated by direct damage to the vascular wall

2. PLATELET PHASE

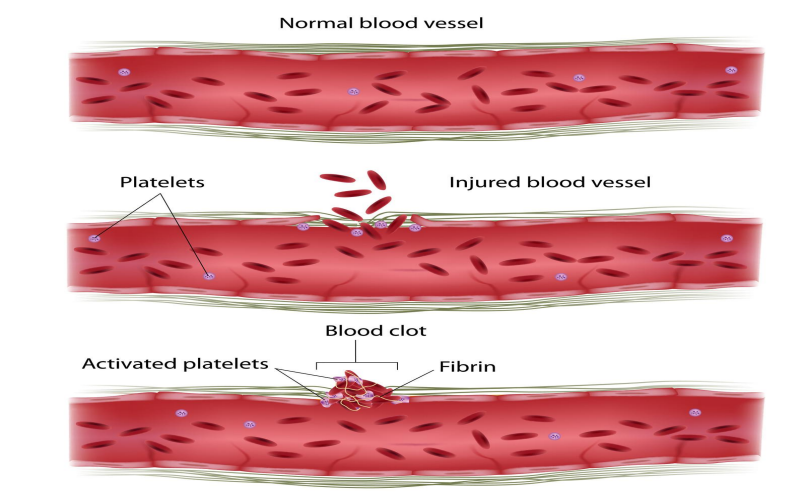
platelet responsible for much of vasoconstriction by releasing vasoconstrictor substance thromboxane A2 also it migrate to the site of endothelial wall rupture forming **platelet plug**

3. COAGULATION PHASE

the clot begin to develop in 15 to 20 seconds if the trauma to the vascular wall has been severe. Activator substance from traumatized vascular wall, from platelets, and from blood proteins adhering to the traumatized vascular wall initiate the clotting process.

4. FIBRINOLYTIC PHASE

once the 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 fibrous tissue formation is partially promoted by growth factors secreted by platelet .



hemostasis = stop of blood loss.
homeostasis = balance

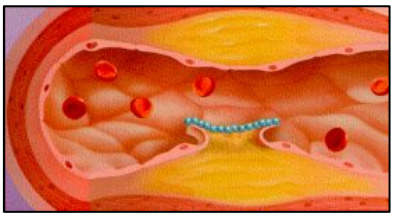
- 1st function of platelet is initial arrest of bleeding by platelet plug formation.

- platelet function work everywhere and everytime in our body not only if we injured in the outside (skin), but we can't notice that because we're normal, diseased people with low count of platelet or dysfunction are more likely to notable symptoms, could be as **microhemorrhage** under the skin or in the internal organs

❖ Platelet Activation:

1. Adhesion: (Platelets + Endothelial tissue)

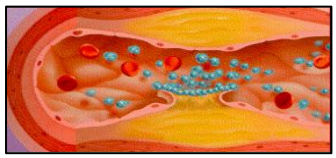
- **Exposed** collagen attracts platelets.
- Platelets stick to exposed collagen underlying damaged endothelial cells in vessel wall.
- Platelets are activated by adhesion: extend projections to make contact with each other.



- platelet is a quiet cell they call it quiescent cell, but don't touch her it will turn to dangerous cell وظيفتها زي شرطي المرور مسالم ويمشي في حاله بس لو شاف حادث(نزيف) بيوقف وينادي بقية الشرطة
- adhesion (interaction between platelet and subendothelial tissue)
  * direct way: when there's injury, the collagen explode (there's strong attraction between platelet and collagen, so as long as the collagen covered the platelet won't adhere endothelial cells, and when there's explosion there will be uncover to the collagen and the attraction will happen (binding by coreceptor))
  * indirect way: the Von Willebrand factor will stick to the collagen when there's injury and help the platelet to bind toit.

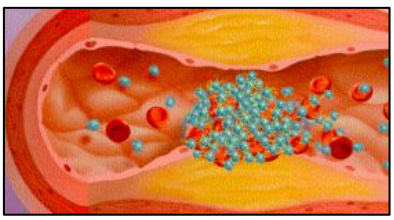
2. Shape change:

- Platelet Activation means changing in platelet shape to form the plug.
- When platelets come in contact with damaged vascular surface, especially collagen fibers, they immediately change their shapes into globular disc, begin to swell and form irregular shape with protruding from their pores.



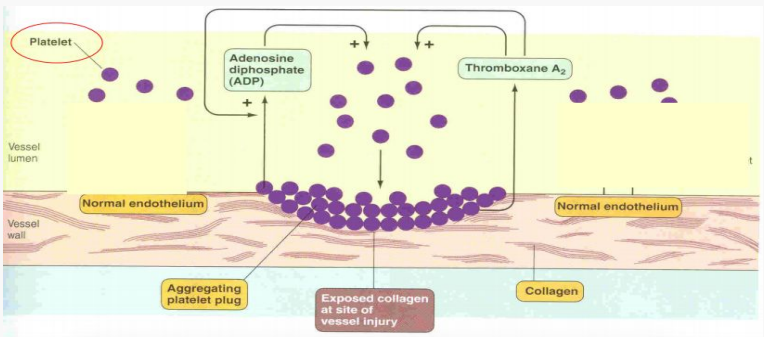
3. Aggregation: (Platelets + Platelets)

- adhering one platelet with other one.
- Activated platelets stick together and activate platelets to form a mass called a platelet plug.
- Plug reinforced by fibrin threads formed during clotting process.
- **Fibrinogen** is needed to join platelets to each other via platelet fibrinogen receptors.



- how does the aggregation happen?

the receptors on the platelet are silent normally, once it's activate the receptor will change in shape to give the ability to bind to fibrinogen. the fibrinogen after binding will link two platelet together(aggregation)

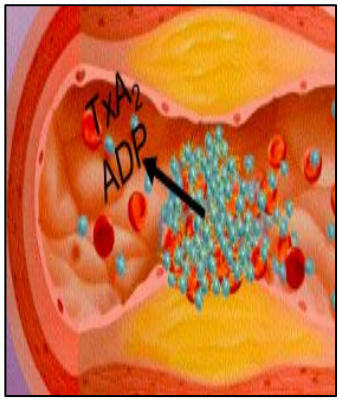


4. Platelet haemostatic plug formation: "secretion":

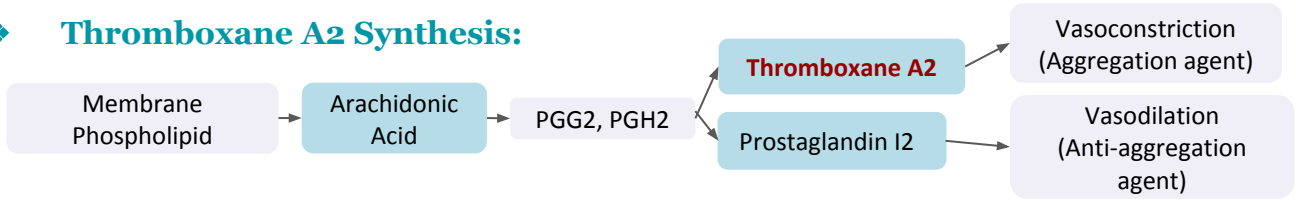
Activated Platelets Secrete the component inside dense body(ADP,ATP,CA+) released:

1. **ADP \ ATP:** causes stickiness and enhances aggregation. ATP released by activated platelet will travel to another silent platelet and turn it to active
2. **5HT:** causes **vasoconstriction** (decreasing blood flow through the injured vessel) and activating other platelets.
3. **Platelet phospholipid (PF3):** causes clot formation.
4. **Thromboxane A2 (TXA2):** is a prostaglandin formed from arachidonic acid. Its Function:
   - **vasoconstriction** (decreasing blood flow through the injured vessel).
   - **Platelet aggregation**. Very strong aggregator.

(TXA2 inhibited by aspirin). Aspirin will inhibit cyclooxygenase enzyme.



❖ Thromboxane A2 Synthesis:



- why thromboxane A2 and prostacyclin are together even when they're opposite in action? to maintain balance.
- platelet plug fast to form but weak and easy to break down, what's make it strong? when phospholipide released to the surface of the cell and reaction of coagulation and formation of fibrin will happen

5. Clot Retraction:

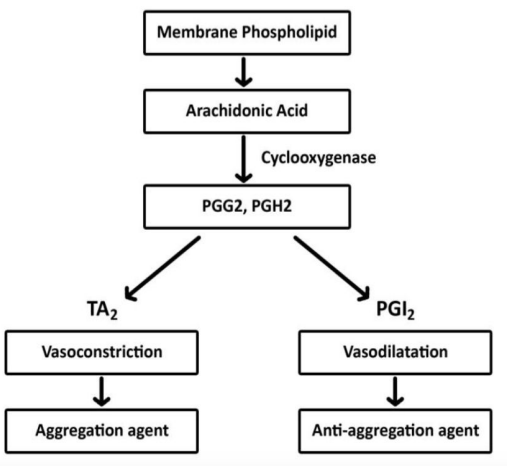
Myosin and actin filaments in platelets are stimulated to contract during aggregation further reinforcing the plug and help release of granule contents.

- clot retraction is a result of actin and myosin, so they're stimulated to contract during aggregation, why? inforce further platelet plug and help healing.
- after sealing the platelet release growth factor those proteins act as healing factor to repair blood vessels, stimulation for smooth muscle cell synthesis and fibroblast. نفس فكرة حقن نضارة الوجه

Guyton corner :

-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, 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.

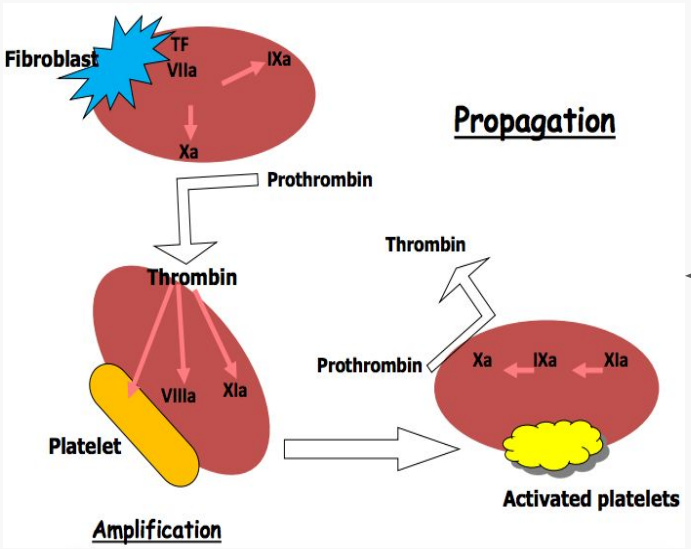
-Blood Clot: The clot is composed of a meshwork of fibrin fibers running in all directions and entrapping blood cells, platelets, and plasma. The fibrin fibers also adhere to damaged surfaces of blood vessels; therefore, the blood clot becomes adherent to any vascular opening and thereby prevents further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



General functions of the platelets(cont..):

2. Role of platelet in blood coagulation

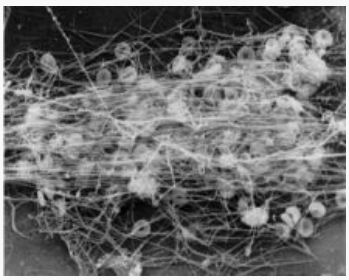
(The cell based model of blood coagulation):



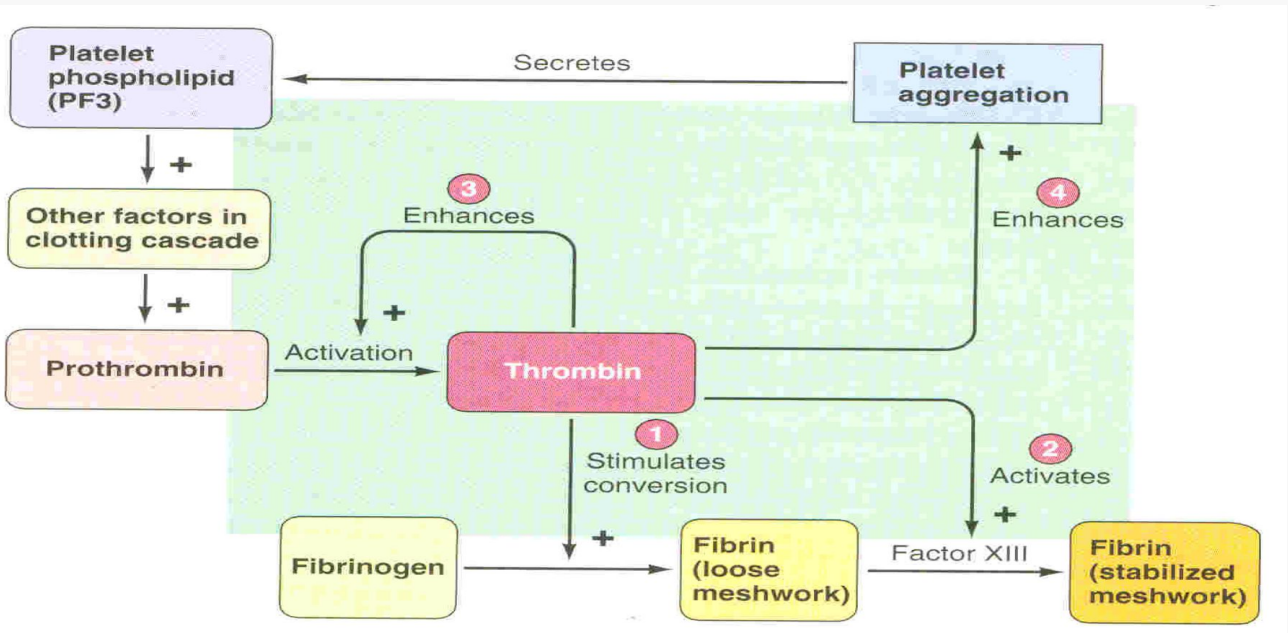
سألنا د.عبير إذا مطالبين فيها وقالت إنها للاستزادة فقط

- It is happened in the platelet's surface (phospholipids).
- If there is not platelet -> no coagulation + no fibrin clot

3. Maintenance of vascular integrity.



- Initial arrest of bleeding by **platelet plug formation**.
- **Stabilization** because the clot is weak need something to stabilize it of hemostatic plug by contributing to **fibrin formation.**
- Adequate number and function of platelet is essential to participate optimally in haemostasis.



Mechanism of Blood Coagulation (GUYTON)

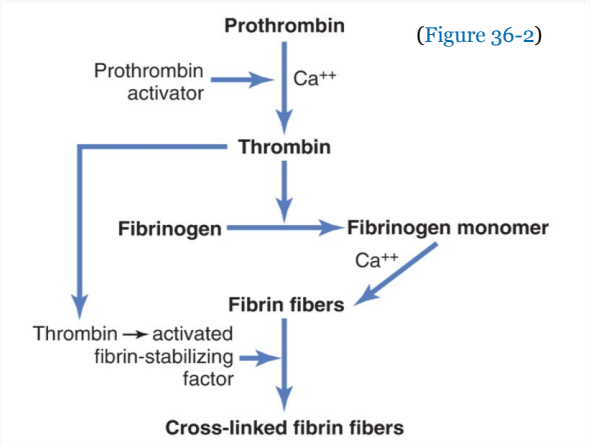
General Mechanism

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 **platelet**s, blood cells, and plasma to form the clot.

Conversion of Prothrombin to Thrombin

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 36-2). 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.**Platelet**s also play an important role in the conversion of prothrombin to thrombin because much of the prothrombin first attaches to prothrombin receptors on the **platelet**s already bound to the damaged tissue.

Prothrombin and Thrombin.



(Figure 36-2)

It is an unstable protein that can split easily into smaller compounds, one of which is *thrombin,* which has a molecular weight 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 activation of prothrombin, as well as 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.

Action of Thrombin on Fibrinogen to Form Fibrin.

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 earlier. 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.

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 normal plasma but is also released from **platelet**s entrapped in the clot. It must 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 cross-linkages between adjacent fibrin fibers.

Blood Clot.

The clot is composed of a meshwork of fibrin fibers , blood cells, **platelet**s, and plasma.

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. **Platelet**s are necessary for clot retraction to occur. Therefore, failure of clot retraction is an indication that the number of **platelet**s in the circulating blood might be low. Furthermore, **platelet**s entrapped in the clot continue to release procoagulant substances, one of the most important of which is *fibrin-stabilizing factor*.In addition, the **platelet**s themselves contribute directly to clot contraction by activating **platelet** thrombosthenin, actin, and myosin molecules, which are all contractile proteins in the **platelet**s and cause strong contraction of the **platelet** spicules attached to the fibrin. This also helps compress the fibrin meshwork into a smaller mass.

As the clot retracts, the edges of the broken blood vessel are pulled together, thus contributing still further to hemostasis.

Mechanism of Blood Coagulation (GUYTON)

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 36-3:

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 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 **platelet**s, 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.

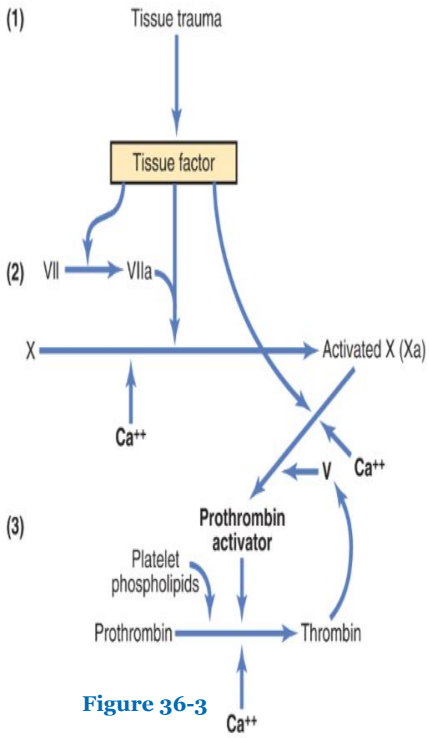


Figure 36-3

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 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 36-4

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 **platelet**s. 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 **platelet**s 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 as well.
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 **platelet**s, activates Factor X. It is clear that when either Factor VIII or **platelet**s 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*.**Platelet**s 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

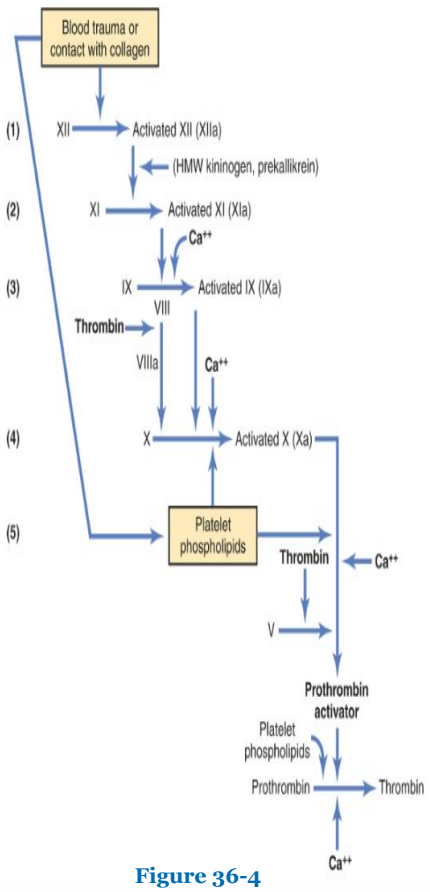
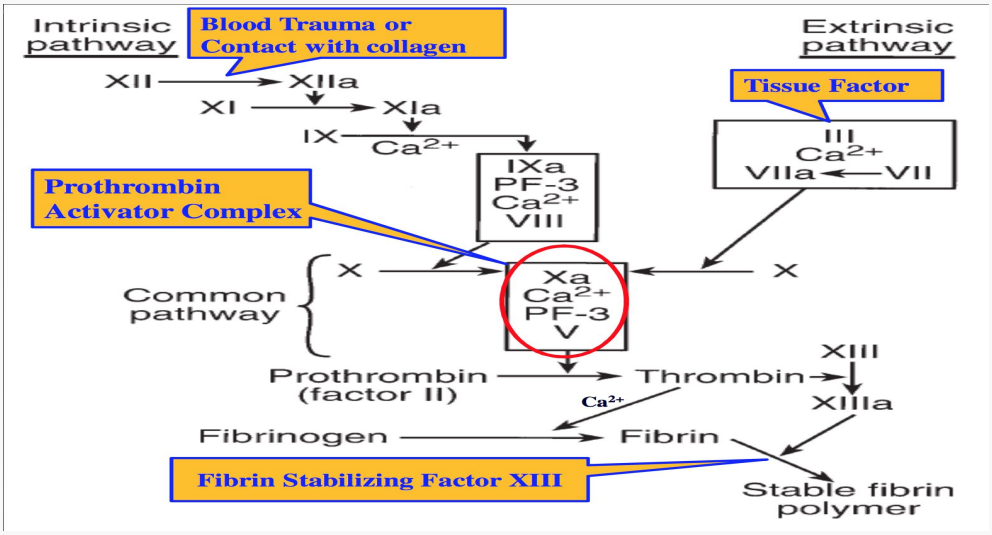


Figure 36-4

Coagulation pathway (Boys' slides) :



Intrinsic pathway	Extrinsic pathway
Contact with injured blood vessel activate 1- XII(surface of injured blood vessel or glass) INTO the active form XIIa, and this will activate: 2- XI INTO the active form XIa, and this will activate: 3-IX INTO the active form IXa with the presence of Ca And this will activate: 4-VIII with the presence of platelet phospholipids factor(PF3) + Ca 5- X is activated by VIII ➔ **The common pathway will start (12+11+9+4+8+10)**	Triggered by tissue factor III (thromboplastin) activate 1- VII INTO VIIa with Ca and this activate 2- X is activated by VII ➔ **The common pathway will start (3+4+7+10)**

Common pathway

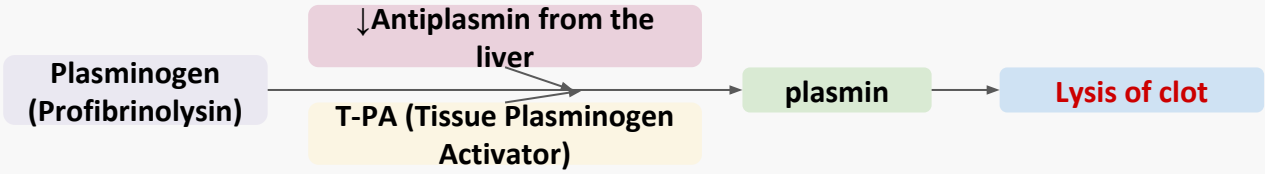
1-Xa activate V with Ca & PF3
2- V activate prothrombin(II) to thrombin
3- thrombin activate fibrinogen(I) to Fibrin with Ca and also thrombin will activate XIII to XIIIa(fibrin stabilizer)
4- Xiiia stabilize the fibrin (10+5+2+4+1+13)
*Ca is factor IV

Interaction Between the Extrinsic and Intrinsic Pathways—Summary of Blood-Clotting Initiation (GUYTON)

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.

LYSIS OF BLOOD CLOTS BY PLASMIN

- Formed blood clot can either become fibrous or dissolve.
- Fibrinolysis (dissolving) = Break down of fibrin by naturally occurring enzyme plasmin therefore prevent intravascular blocking.



➔ Tissue Plasminogen Activator (TPA) used to activate plasminogen to dissolve coronary and cerebral clots.

Lysis of Blood Clots - Plasmin: (GUYTON)

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.

Activation of Plasminogen to Form Plasmin, Then Lysis of Clots.

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.

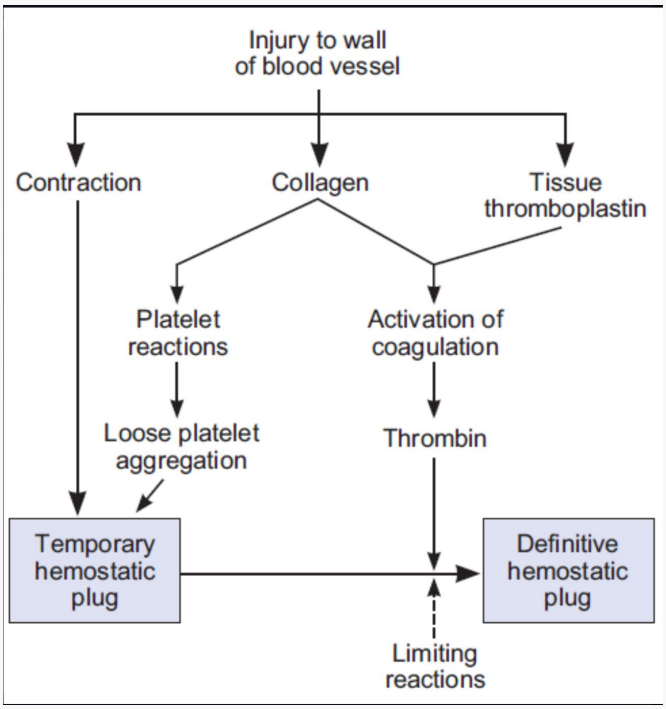
❖ Read the table below:

TABLE 31–5 System for naming blood-clotting factors.

Factor[a]	Names
I	Fibrinogen
II	Prothrombin
III	Thromboplastin
IV	Calcium
V	Proaccelerin, labile factor, accelerator globulin
VII	Proconvertin, SPCA, stable factor
VIII	Antihemophilic factor (AHF), antihemophilic factor A, antihemophilic globulin (AHG)
IX	Plasma thromboplastic component (PTC), Christmas factor, antihemophilic factor B
X	Stuart–Prower factor
XI	Plasma thromboplastin antecedent (PTA), antihemophilic factor C
XII	Hageman factor, glass factor
XIII	Fibrin-stabilizing factor, Laki–Lorand factor
HMW-K	High-molecular-weight kininogen, Fitzgerald factor
Pre-Ka	Prekallikrein, Fletcher factor
Ka	Kallikrein
PL	Platelet phospholipid

[a]Factor VI is not a separate entity and has been dropped.

❖ Summary of reactions involved in hemostasis :



Bleeding Disorders: Pts will present with prolong bleeding.

Bleeding can result from Platelet defects:

- Deficiency in **number** (thrombocytopenia).
- Defect in **function**. May be acquired or congenital.

❖ Thrombocytopenia:

The causes of **decreased platelet counts** are:

Increased destruction	Decreased Production
• Autoimmune diseases: Idiopathic (immune) thrombocytopenic purpura Medications: quinine, antibiotics containing sulfa, Dilantin, vancomycin, rifampin, heparin-induced thrombocytopenia • Surgery: man-made heart valves, blood vessel grafts, bypass machines • Infection: septicemia • Pregnancy: about 5% of pregnant women develop mild decrease Thrombotic thrombocytopenic purpura • Disseminated intravascular coagulation	• Leukemia or lymphoma • Cancer treatments such as radiation or chemotherapy • Various anemias • Toxic chemicals • Medications: diuretics, chloramphenicol • Viruses: chickenpox, mumps, Epstein-Barr, parvovirus, AIDS • Alcohol in excess • Genetic conditions: Wiskott-Aldrich, May-Hegglin,
Abnormal distribution	**Pseudothrombocytopenia**
• Splenomegaly with sequestration in the spleen	• Partial clotting of specimen EDTA-platelet clumping Platelet satellitism around WBCs Cold agglutinins Giant platelets. ثرمبوسايتوبينيا كاذبة! ليش كاذبة لان المشكله هنا مو بعدد البليتليت حيث ان عددها طبيعي, المشكله بتأديتها لوظيفتها فتسوي لنا زي اعراض الثرمبوسايتوبينيا.

Platelets & medications (EXTRA)

- **Clopidogrel (Antiplatelet) :** works by blocking platelets from sticking together and prevents them from forming harmful clots.used to reduce the risk of heart disease and stroke in those at high risk.
- **Aspirin (NSAID) :** Inhibition of cyclooxygenase > inhibition of ThxA2 > prevention of clotting mechanism > high tendency of bleeding.

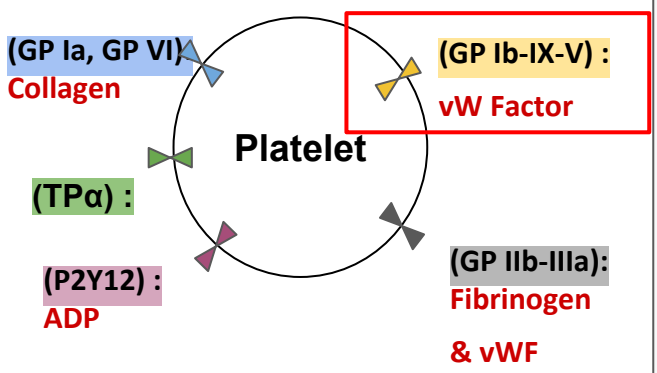
Bleeding Disorders

❖ Congenital Platelet Disorders: Defect in **platelet Function**, caused by :

Disorders of Adhesion	**Bernard-Soulier**
Disorder of Aggregation	**Glanzmann thrombasthenia**
Disorders of Granules	• Grey Platelet Syndrome . • Storage Pool deficiency . • Hermansky-Pudlak syndrome . • Chediak-Higashi syndrome
Disorders of Cytoskeleton	Wiskott-Aldrich syndrome
Disorders of Primary Secretion	Receptor defects (TXA2, collagen ADP, epinephrine)
Disorders of Production	• Congenital amegakaryocytic thrombocytopenia . • MYH9 related disorders . • Thrombocytopenia with absent radii (TAR) . • Paris-Trousseau/Jacobsen

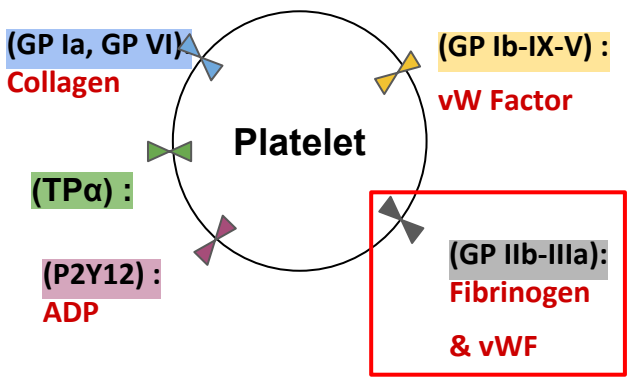
Bernard-Soulier syndrome:
Disorder of Adhesion

- Called hemorrhagic parous thrombocytic dystrophy.
- Rare autosomal recessive coagulopathy (bleeding disorder).
- Deficiency of glycoprotein Ib (Gp Ib), the receptor for von Willebrand factor.
- BSS is a giant platelet disorder, meaning that it is characterized by abnormally large platelets.



Glanzmann Thrombasthenia:
Disorder of Aggregation

- Is an abnormality of the platelets. It is an extremely rare coagulopathy
- Deficiency or low levels of glycoprotein IIb/IIIa (Gp IIb/IIIa), which is a receptor for fibrinogen. As a result --> no fibrinogen bridging of platelets to other platelets can occur, and the bleeding time is significantly prolonged (Aggregation).



Laboratory investigations of Platelet Functions

- **Electron-microscopy** → to see the shape and granules
- **Bleeding time** → a sharp pointed used to pierce the tip of finger or lobe of ear normally the bleeding last for 1-6 min if it is prolonged that's mean lack of platelet
- **Platelet count and shape**
- **Platelet Function Analyzer**
- **Flow-cytometry**
- **Platelet Aggregation** → A platelet aggregation test requires a blood sample. The sample will be examined to see how the platelets are distributed through the plasma. Plasma is the liquid part of the blood. The lab technician will also add certain chemicals to your blood sample to test how quickly your platelets form a clot. also called aggregometry.
  (PRP) Platelet rich plasma: provide information on time course of platelet activation. Agonists : ADP Arachidonic acid Collagen Adrenaline Ristocetin Thrombin
- **Granule release products**

Lab tests in bleeding and clotting

Test	Normal	Importance
Platelet count	100,000-400,000	**Thrombocytopenia**
Platelet function	Normal Aggregation	**Thrombocytopathy** (abnormal function normal count)
Bleeding time	2-8 min	**Bleeding disorder**
Prothrombin time (PT)	10-15 sec	**Measure the effectiveness of the extrinsic factor**
Partial thrombin time (PTT)	25-40 sec	**Measure the effectiveness of the intrinsic factor**

Factors affecting blood platelet count

INCREASE	DECREASE
Injury - Adrenaline - Hypoxia - After the Menstrual cycle	**Age - pregnancy - Smoking Before the Menstrual cycle Nutritional deficiency**

PBL Case (Vomited dark blood)

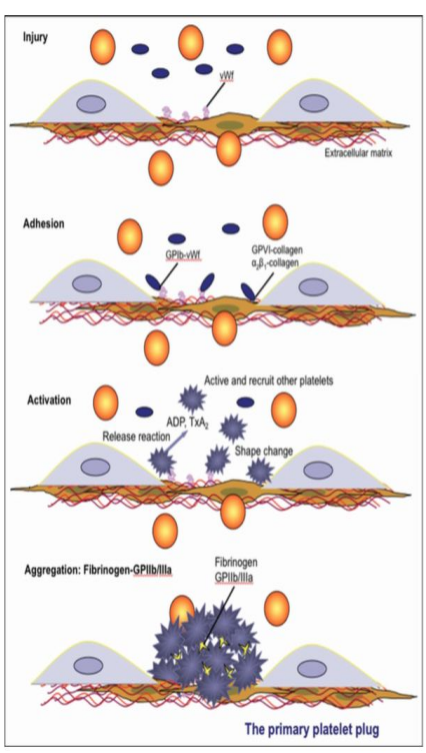
In the last PBL case Saif abdullah was suffering from liver cirrhosis. After investigating his blood (CBC) the results revealed that he has very few platelet count which is known as (Thrombocytopenia.

so what is the relation between liver cirrhosis and Thrombocytopenia?

In liver cirrhosis patients, Thrombocytopenia is a common finding in advanced liver disease. It is predominantly a result of portal hypertension and platelet sequestration in the enlarged spleen.

SUMMARY

❖ Platelet Activation: (READ IT)



1) Platelets are activated when brought into contact with collagen exposed when the endothelial blood vessel lining is damaged.
2) Activated platelets release a number of different coagulation and platelet activating factors.
3) Transport of negatively charged phospholipids to the platelet surface; provide a catalytic surface for coagulation cascade to occur.
4) Platelets adhesion receptors (integrins): Platelets adhere to each other via adhesion receptors forming a hemostatic plug with fibrin.
5) Myosin and actin filaments in platelets are stimulated to contract during aggregation further reinforcing the plug and help release of granule contents.
6) GPIIb/IIIa: the most common platelet adhesion receptor for
7) fibrinogen and von Willebrand factor (vWF) Bleeding

❖ In general :

- Platelets are cell fragments derived from megakaryocyte in the bone marrow.
- Platelets play a pivotal role in haemostasis by arresting bleeding from an injured blood vessels
- Bleeding can result from: Platelet defects acquired or congenital
- Platelet function tests are used to detect abnormal platelet function.

Thrombocytes:

Anuclear and discoid cell → spherical when activated

Platelet count = 150-300x10^3\ml **Size: 1.5-3.0µm** **Lifespan: 7-10 days**

- Sequestrated in the spleen

- They are formed in the bone marrow from megakaryocyte

Platelet Receptors

GP Ia & GP VI Collagen	GP Ib-IX-V vW factor	P2Y12 ADP	TPα TXA2	GP IIb-IIIa Fibrinogen ,vWF

SUMMARY

Ultrastructure of Platelet :

Mitocondria	**Dens tubular system**	**Glycogen particles**
Alpha granules Von Willebrand factor (vWF) Thrombospondin - P-selectin fibrinogen - Chemokines (PF4)	**Dens body** Calcium Serotonin ADP\ATP	**Microtubules** **Open canalicular system**

General functions of the platelets

Hemostasis mechanism 1. VASCULAR PHASE 2. PLATELET PHASE 3. COAGULATION PHASE 4. FIBRINOLYTIC PHASE	**Role of platelet in blood coagulation**	**Maintenance of vascular integrity.**

❖ Platelet Activation:

1. Adhesion:

2. Shape change: (Platelets + Endothelial tissue)

3. Aggregation: (Platelets + Platelets) Fibrinogen is needed to join platelets to each other via platelet fibrinogen receptors.

4. Release reaction "secretion":

Activated Platelets Secrete:

1. ADP :2. 5HT: 3. Platelet phospholipid (PF3) 4. Thromboxane A2 (TXA2)

5. Clot Retraction:

SUMMARY

★ Bleeding Disorders

Bleeding can result from Platelet defects:

- Deficiency in **number** (thrombocytopenia).
- Defect in **function**.

❖ Thrombocytopenia: The causes of decreased platelet counts are:

Increased destruction	**Decreased Production**
Abnormal distribution	**Pseudothrombocytopenia**

❖ Congenital Platelet Disorders: Defect in platelet Function, caused by :

Disorders of Adhesion	**Bernard-Soulier**
Disorder of Aggregation	**Glanzmann thrombasthenia**
Disorders of Granules	Grey Platelet Syndrome .
Disorders of Cytoskeleton	Wiskott-Aldrich syndrome
Disorders of Primary Secretion	Receptor defects (TXA2, collagen ADP, epinephrine)
Disorders of Production	Congenital amegakaryocytic thrombocytopenia .

Laboratory investigations of Platelet Functions

- Electron-microscopy
- Bleeding time
- Platelet count and shape
- Platelet Function Analyzer
- Flow-cytometry
- Platelet Aggregation
- Granule release products

Factors affecting blood platelet count

INCREASE	DECREASE
Injury - Adrenaline - Hypoxia - After the Menstrual cycle	Age - pregnancy - Smoking Before the Menstrual cycle Nutritional deficiency

MCQs

1-Which condition of the following most likely can cause low platelets count:

A- Splenomegaly

B- Hepatomegaly

C- Hypersplenism

D- A&C

2-Dense Granule contain:

A- ADP/ATP
B- Calcium
C- Serotonin
D- All of them

3-von Will brand Factors found in which of the following structure:

A- Alpha granule
B- Microtubule
C- Dense body
D- open canaliculi system

4-the platelet get activated directly after adhesion on endothelial damged by:

A- GP IA/ GP VI
B- GP IIb/ IIIa
C- GP Ib
D- VW factor

5-what are the receptors for Fibrinogen in aggregation:

A- GP IB-IX-V

B- GP IIB/IIIA

C- TP alpha

6-Myosin and actin FUNCTIONS:

A- reinforcing the plug

B- activate other platelets
C- help release of granule contents

D- A&C

7-TXA2 & serotonin FUNCTIONS:

A- Enhance platelet aggregation
B- Decrease blood flow
C- Vasodilation
D- A&B

8-Normal Platelets Count:

A- (100-200) x103/ml

B- (200-400)) x103/ml

C- (15-30)) x103/ml

D- (150-300) x103/ml

9-Thrombocytopenia due to increased destruction:

A- HIV
B- Pregnancy
C- Chemotherapy
D- leukemia

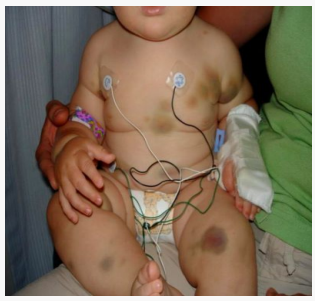
10-Platelet contribute in fibrin formation:

A- True
B- false

❖ **Case study : A 7 years old girl complaining of:**
severe bruising since birth and if she had injury she would bleed for days.She had epistaxis which lasted for days.Her mother said "she just bruise more easily than her older sister"

- Investigation: ماقدرنا نتوصل للتشخيص إلا عن طريق الجهاز

CBC	RBC, WBC and Platelet morphology: normal
Aggregometry	absent platelet aggregation in response to ADP, collagen, thrombin, & epinephrine,



➔ What is your diagnosi ? **Glanzmann's Thrombasthenia** for further reading

answer key: 1:D , 2:D , 3:A , 4:A , 5:B , 6:D , 7:D , 8:D , 9:B . 10:A.

خولة العمَّاري
نجود الحيدري
نورة الطويل
لولوة الصغير
لجين السواط
رزان السبتي
ربى السليمي
ديما الفارس
خولة العريني
ملاك الشريف
منيرة الحسيني
مروج الحربي
أفنان المالكي
دلال الحزيمي
رناد القحطاني
سارة الخليفة
فرح مندوزا
مي العقيل
نورة الخراز
سارة الخليفة
نورة الخيال
رغد النفيسة
منيرة السلولي
نوف العبدالكريم
سها العنزي
نورة القحطاني

عمر آل سليمان
عبدالعزيز الحماد
عبدالرحمن السياري
محمد أبونيان
عبدالرحمن البركه
إبراهيم النفيسه
محمد البشر
عمر العتيبي
حمزة الفعر
عبدالله الجعفر
عبدالله الضحيان
حسن البلادي
حسن الشماسي
محمد الفواز
محمد السحيباني
وائل العود
رواف الرواف
عمر الشهري