Hematology

Problem Based Learning

☑ Sheet ☐ Slide ☐ Handout

Number: 2

Subject: Hemostasis

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Price:

بسم الله الرحمن الرحيم

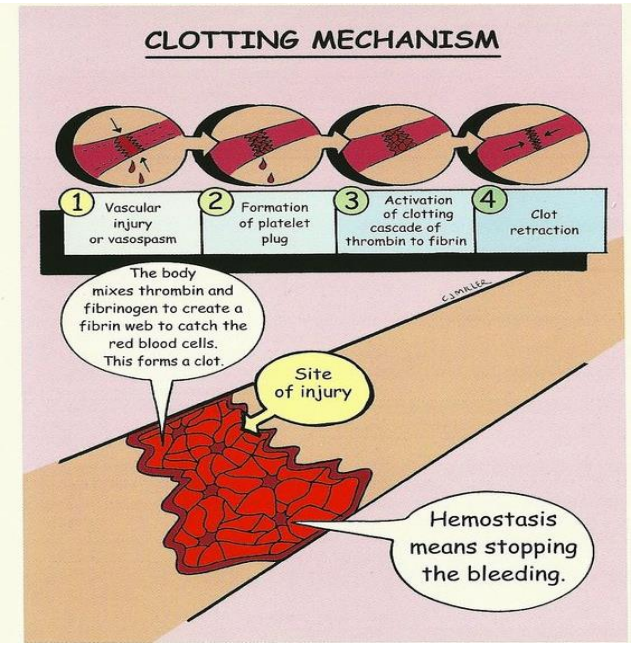
❀ This sheet was written according to section 2 recording.

This lecture will be about:

1. Hemostasis which we already have taken before in physiology in details, so most of the information here were mentioned before.
2. Lab tests for Bleeding Abnormalities

"باختصار محاضرة معظم محتوياتها معادة ومابيها شي جديد الا كم شغلة بسيطة"

☆ Hemostasis:



Definition: Arrest of bleeding

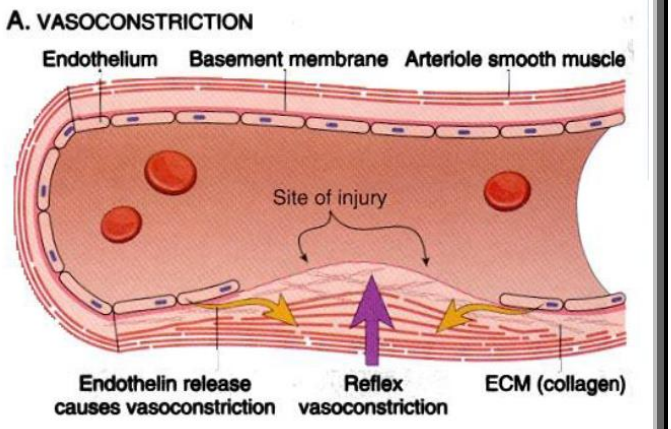
There are **4** major players of hemostasis:

- **Blood vessels**
- **Platelets**
- **Coagulation factors**
- **Anticoagulation factors (fibrinolytic system)**

The hemostasis occurs in steps which are:

A. **Vasoconstriction**, which happens by two methods:
   1. Production of a substance called **Endothelin** from endothelial cells
   2. Neural reflex which causes smooth muscles to contract

- This process will not be enough to cause significant arrest of bleeding,,



B. Formation of primary **Platelet plug** (primary hemostasis)

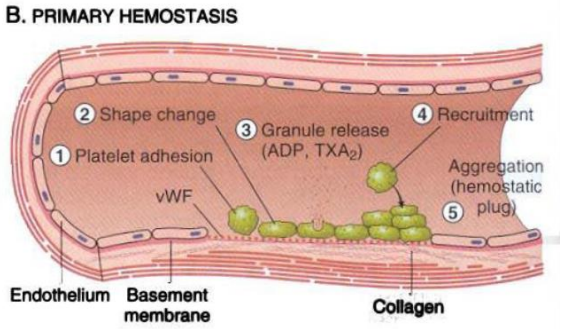
- Happens due to the adhesion of platelets to collagen and traces of thrombin.
- This adherence is usually weak and might not be able to stop significant bleeding!

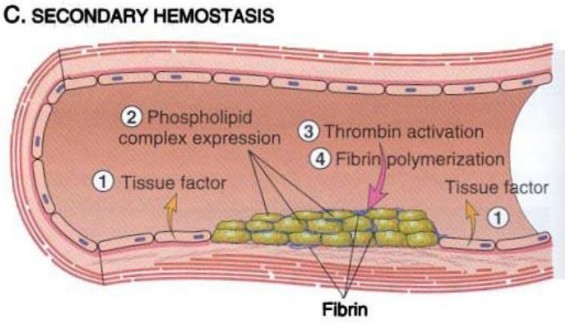
C. **Secondary Hemostasis**: Conversion of the platelet plug into permanent plug supported by **fibrin clot**,

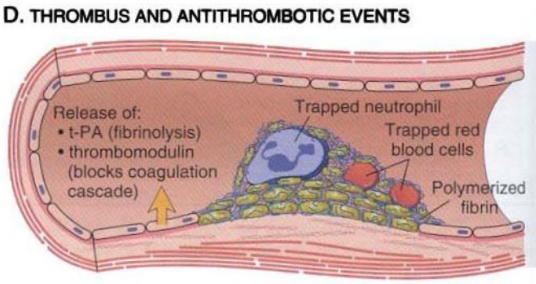
- Which is done by coagulation factors, "most of them are proteins synthesized in the liver primarily and present in the blood"
- They will produce fibrin meshwork which acts on stabilizing the clot "as we have learned before"

D. **Lysis of fibrin** and confinement of clot to the site of injury,

- Stopping the process from spreading to other site and limit it to the site of injury, and with time when healing takes place fibrinolysis starts and digest the fibrin clot







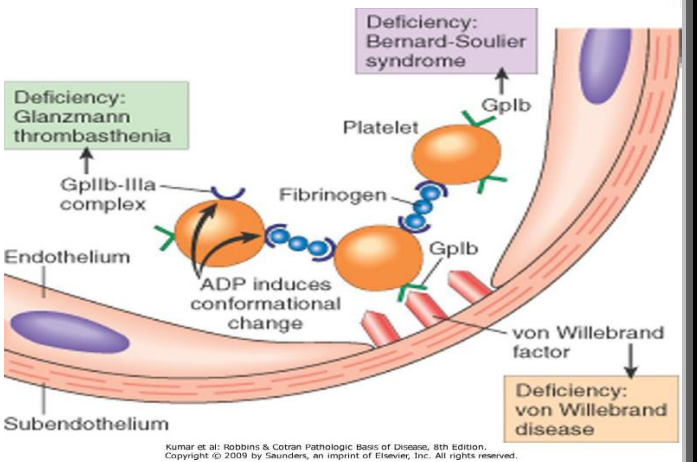
Now we will learn about the platelets "Once Again!",,,

☆ The Platelets:

i. ADHERENCE:

When there is injury, the endothelial cells are damaged and therefore subendothelial substances will be exposed "collagen fibers", and platlets will adhere to them by certain receptors, (GpIb adhere to collagen and this adherence is falicitated by von Wilbrand factor)

"platelets without vWF will not be able to adhere to the collagen fibers"



ii. AGGREGATION:

Facilitated by fibrinogen which binds on platelets surface receptor GpIIb-IIIa

Remember:	
GpIb Is for vWF and adhere to collagen fiber	GpIIb-IIIa Is for fibrinogen binding and platelet aggregation

❖ **Platelet number**:

Normal number is 140,000-400,000/µl.

•this number is "Redundant", which means a person don't need 200,000 to stop bleeding, only 100,00 or even 80,000 is enough to stop bleeding, in the next lecture the other doctor said even platelet count as low as 5,000 maybe enough to stop bleeding!?

•*Life span: 8-10 days, Volume: 6-12 fL, Diameter: 2-4 µm.*

❖ The platelets have a set of canals called "Open Canalicular system"

❖ There are also microtubules, glycogen , granules (**dense** and **alpha** granules)

a) α granules content: Fibrinogen, PDGF, vWF, Thromboglobulin, PF4 (heparin neutralizing), Factor V, P selectin.

b) δ granules (dense) content: ADP, ATP, Ca++, 5 hydroxytryptamine(serotonin).

😄 They are called dense granules cause they appear as dense black spots in the electron microscope.

❖ **Membrane lipids**:

The important thing about them is that normally the phospholipids on the outer surface of the platelet are neutral in charge but when the platelets gets activated to form the plug, these PL flip and the anionic (-ve charged) part switch to the outer surface which promotes coagulation.

❖ **Platelet Response to Stimuli:**

Once platelet are activated they change their shape from spherical to an irregular shape with spikes on the surface to promote adhesion, and start secreting granules content.

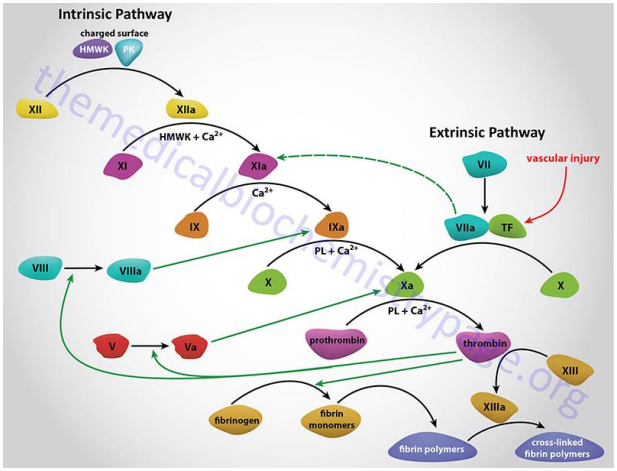
❖ **Production of Thromboxane A2:**

Produced through the enzyme phospholipase A2 which works on the cell wall of the platelets releasing Arachidonic acid, then cyclooxygenase enzyme will work on it and produce prostaglandins, and at the end thromboxane A2 is produced.

(TxA2 is a very powerful inducer of coagulation and platelet activation)

Aspirin
Aspirin blocks cyclooxygenase enzyme which leads to inhibition of TxA2 production, so it will prevent platelet adherence and activation, thus clotting will be inhibited

☆ Coagulation Cascade:



We have two cascades, Physiologic and Lab cascade which are a bit different from each other:

In the lab we have two pathways that we already know from physiology lectures:

A- Intrinsic pathway:

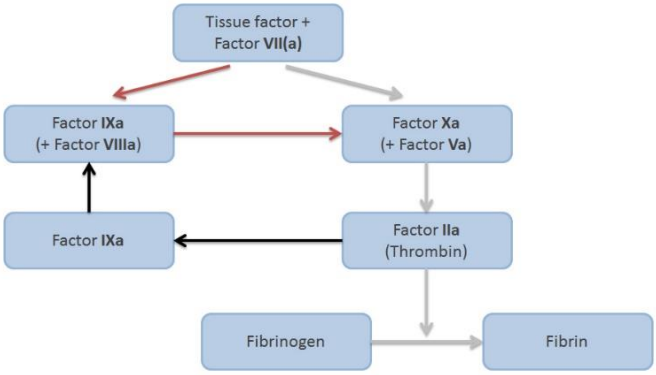
XII activates XI which activates IX, IXa with the help of VIIIa activates X.

Xa will work on Prothrombin to form thrombin, thrombin will activate fibrinogen to become fibrin which will form the clot

B- Extrinsic pathway:

Tissue factor (thromboplastin) activates factor VII, VIIa with TF activates X and Xa activates prothrombin to thrombin etc...

Physiologic cascade:



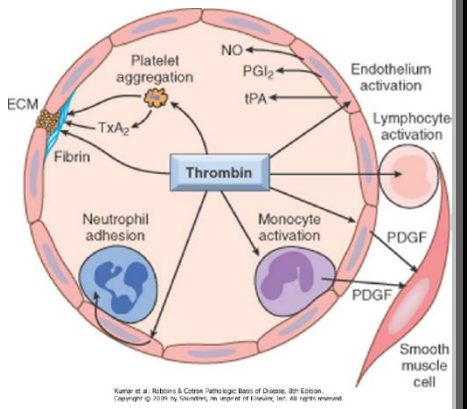
The physiologic cascade begins with activation of factor VII not XII!

Once VII is activated with the help of TF (tissue factor), it activates factor IX and X at the same time, and then Xa will activate prothrombin to thrombin (with the help of Va), and thrombin will turn fibrinogen to fibrin.

(note: in the physiologic cascade factor XII and all the intrinsic pathway are not important)

What the doctor meant by lab and physioloc pathway is that in our body only the latter occurs to some extent…

- Functions of **Thrombin:**
  - Thrombin activates V, VIII, XI, XIII and protein C



*(Notes: a) V, VIII called **cofactors** because they are not part of the coagulation cascade, they only help the process of activation of factor X and Thrombin. b) factor XIII is responsible for cross-linking of fibrin to become more powerful and resistant to fibrinolyisis. c) protein C is an anticoagulant protein that counteratcs the coagulation factors)*

  - Thrombin also activates platelets, endothelial cells, inflammatory cells *(thrombin is a link between the coagulation cascade and the inflammatory process)*

Note: thrombin is called a multifaceted molecule due to its multiple functions

  - *Thrombin converts fibrinogen to fibrin*

Note: Vit K is important to produce factors II, VII, IX and X in the liver, there are some anti-coagulant drugs (Coumadin "Warfarin") that inhibit Vit K so these factors won't be produced.

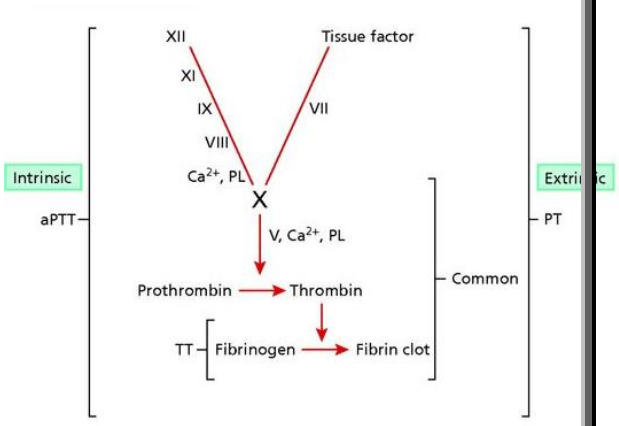
☆ Lab Tests of Coagulation Cascade:

We have three main tests:

1. Prothrombin Time (PT)
2. Partial Thromboplastin Time (PTT)
3. Thrombin Time (TT)

Other tests are:

4. Platelet count (most common)
5. Bleeding time



1. Prothrombin Time (PT):

- Essentially measures the **Extrinsic** and common pathways!
- Test result comes in seconds usually 13-14s
- If it is let's say 20s or 30s (prolonged) means there's abnormality in the extrinsic and common pathway.
- And that means the factor VIII, IX, XI, XII are not related to this so you should only think about **factor VII, X, I** (fibrinogen) **and II** (prothrombin), the one in the extrinsic and common pathway

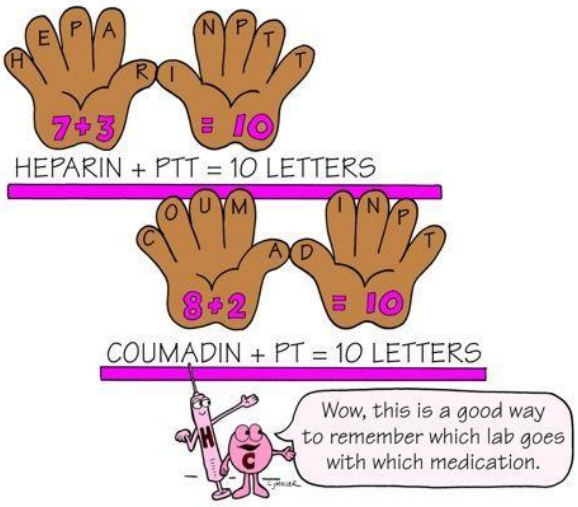
- Patients receiving **oral anti-coagulants** (Vit K inhibitors, **Coumadin "warfarin")** usually take PT test for follow up

2. Partial Thromboplastin Time (PTT):

- This test measures the **Intrinsic** and common Pathways!
- Test results comes in seconds too, usually 25s

- If a patient for example has a PTT of 55s (prolonged), this means that any of the intrinsic and common pathways could be abnormal(**all factors** except VII & XIII), but not factor VII and XIII (extrinsic pathway factor)

- Patients who takes **Heparin** as an anti-coagulant especially in hospitals take PTT test to measure the response to the drug (monitoring), cause it interferes with the intrinsic and common pathway.



Role of PT, PTT:
Warfarin, Heparin Monitoring

Anticoagulant	PT	aPTT
Heparin	Normal	Prolonged
Warfarin (Coumadin)	Prolonged	Normal

3. Thrombin Time (TT):

This test measures the **Common** pathway only!

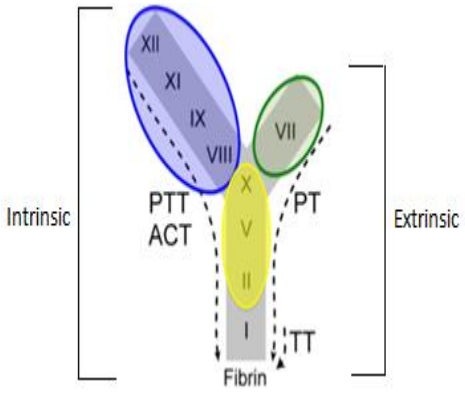
So it measures the conversion of fibrinogen to fibrin

A colleague asked the doc about Vit K and that it produces factors II, VII, IX and X but in PT we measure only II, VII(and X) ?

Ans: factors II and VII are more sensitive to Vit K, therefore the effect on Vit K will be more important on these two factors, while the effect on factor IX is less important

Another question is that if there is a relation between PT and TT?

Ans: PT measures factor VII, X, II (prothrombin) and I (fibrinogen), so if a patient has a low fibrinogen, prothrombin or factor VII the PT will be prolonged, and we can't know which one of them is low or abnormal, but if we did a PT and TT at the same time , TT measures essentially fibrinogen so if it comes normal we rule out fibrinogen problems!



(so it could be that the TT is normal and the PT is abnormal)

But if we did a PT and a PTT test to see which one is abnormal and which is normal we can have a good idea about what pathway is abnormal, if both of them were abnormal means that the problem is in the common factors between them

4. Platelet count: is the most common test

5. Bleeding time: a test that is "dying", basically we make a standardized skin wound and measure the duration until bleeding is stopped, this process is dependent on the platelet count and function only.

❖ INR "International Randomized Ratio":

$$INR = \left(\frac{PT_{Patient}}{PT_{mean-normal}} \right)^{ISI}$$

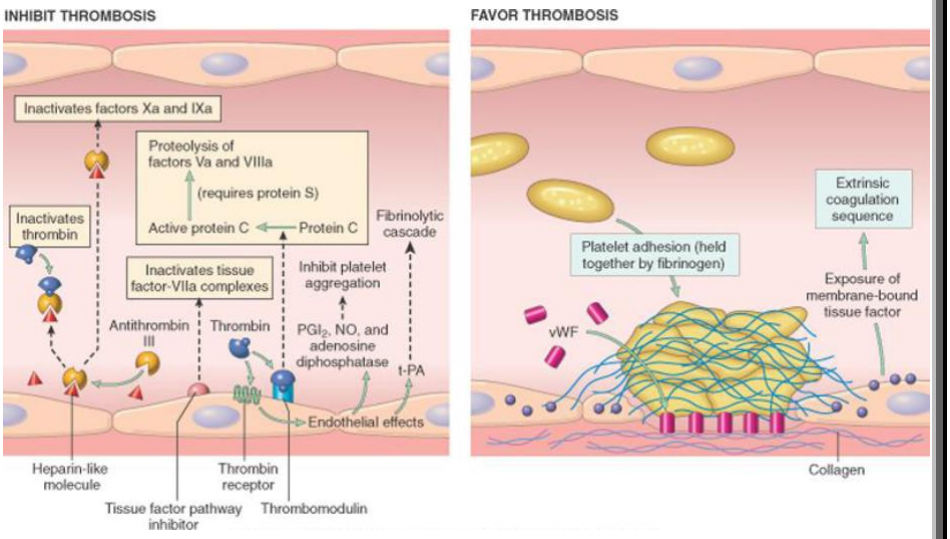
ISI: international standardized index

Basically when we do **PT** in a certain lab it would get us a slightly different results from another lab due the different chemicals used in each one of them, so to **standardize** these results we take the INR ratio

INR is similar to PT but it's given as a ratio, normal value is 1 and below, more than 2 means PT is prolonged. *(patient is taking warfarin for example)*

Finally we will talk a little bit about the endothelial cells

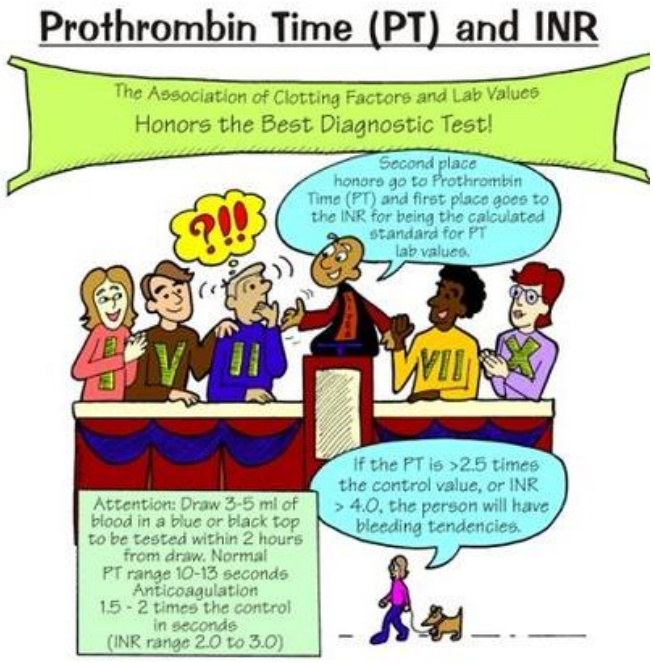
❖ Endothelial Cells:



Endothelial cells have two major roles in coagulation:

a) Induce thrombosis at one site
b) Inhibit thrombosis at the other site

- In a normal condition they work as anti-coagulant, once there is an injury then the process is reversed and this will induce thrombosis and coagulation at the injury site



Number and/or name	Function
I (fibrinogen)	Forms clot (fibrin)
II (prothrombin)	Its active form (IIa) activates I, V, VIII, XI, XIII, protein C, platelets
III (Tissue factor or thromboplastin	Co-factor of VIIa
IV (Calcium)	Required for coagulation factors to bind to phospholipid
V (proaccelerin, labile factor)	Co-factor of X with which it forms the prothrombinase complex
VI	Unassigned – old name of Factor Va
VII (stable factor)	Activates IX, X
VIII (antihemophilic factor)	Co-factor of IX with which it forms the tenase complex
IX (Christmas factor)	Activates X: forms tenase complex with factor VIII
X (Stuart-Prower factor)	Activates II: forms prothrombinase complex with factor V
XI (plasma thromboplastin antecedent)	Activates IX
XII (Hageman factor)	Activates factor XI and prekallikrein
XIII (fibrin-stabilizing factor)	Crosslinks fibrin
von Willebrand factor	Binds to VIII, mediates platelet adhesion

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"Factors names are not so important yet it's nice to know them as the doc said" ☺

Le Fin.