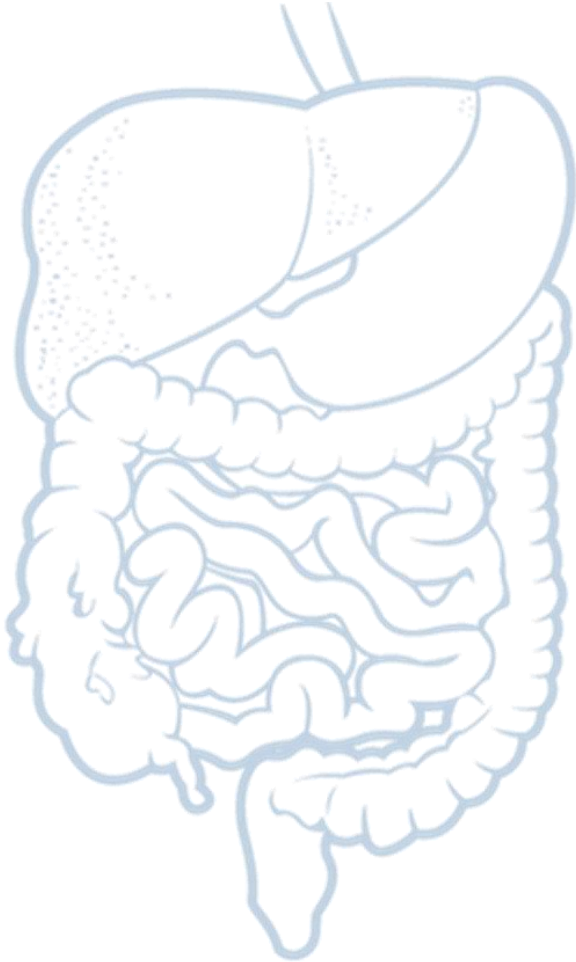
MEDICINE
KING SAUD UNIVERSITY

تمت المراجعة
شوق الأحمري & عبدالعزيز العنقري



Physiology Team 436

- Text
- Only in Females' slide
- Only in Males' slides
- Important
- Numbers
- Doctor notes
- Notes and explanation

GIT PHYSIOLOGY

Lecture No.8

الأفضل تدرسون محاضرة الPlatelets أول، لو درستوا هذه أول بعد ما تخلصون دراستها، ادرسوا جزئية الThrombin & tests من محاضرة الPlatelets.. مشروحة بالتفصيل هناك منعا للتكرار

(إذا مات ابن ادم انقطع عمله إلا من ثلاث إلا من صدقة جاريه أو **علم ينتفع به** أو ولد صالح يدعوا له)..

To prevent excessive bleeding of marks, please study this lecture Very Well!! This lecture is very important.

Coagulation mechanism and hypercoagulability

Objectives:

1- Recognize the different clotting factors.

2- Understand the role of calcium ions during clotting cascades.

3- Describe the cascades of intrinsic and extrinsic pathways for clotting.

4- Recognize process of fibrinolysis and function of plasmin.

5- Recognize some conditions causing excessive bleeding.

6- Understand some important anticoagulants and their mechanism of action.

7- Normal Hemostasi: Coagulation cascade, Fibrinolysis, Natural anti-coagulants, Hemostatic balance.

8- Hypercoagulability: Definition, Types, Causes, Laboratory testing.

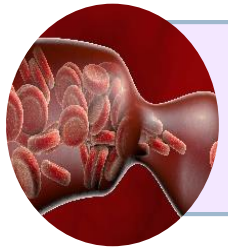
الفيديو راح يساعدكم على فهم المحاضرة كاملة

Hemostasis

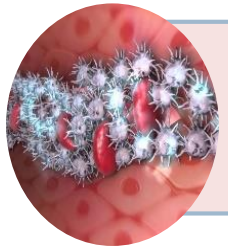
Hemostasis
9:59

- Hemostasis: the spontaneous arrest (Prevention or stoppage) of bleeding from ruptured blood vessels.

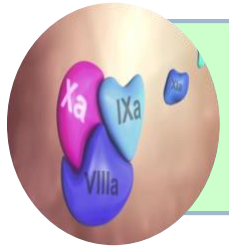
- Stages of Hemostasis:



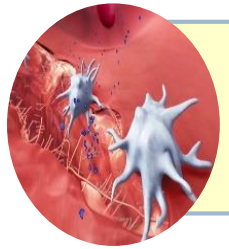
1. Vascular phase:
Vascular spasm (vasoconstriction)



2. Platelet phase:
Production, activation and
Formation of platelet plug



3. Coagulation phase:
Blood coagulation & clot retraction



4. Fibrinolytic phase:
fibrinolysis

- Coagulation: formation of fibrin meshwork (threads) to form a clot.

الفيديو هذا للناس البصريّة!
3:27

1. Vascular phase:

Immediately After injury there is localized Vasoconstriction (Vascular spasm).

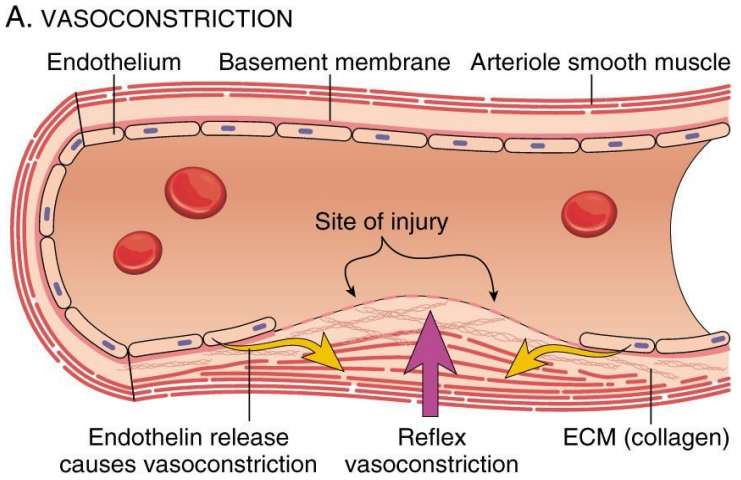
Causative Factors

1. Nervous reflexes.
2. Local myogenic spasm.
3. Local humoral factor → Platelets Thromboxane A2 [TXA2] (Vasoconstrictor).
4. TXA2 (Thromboxane A2) is inhibited by aspirin.

Importance

Crushing injuries → Intense spasm → No lethal loss of blood.

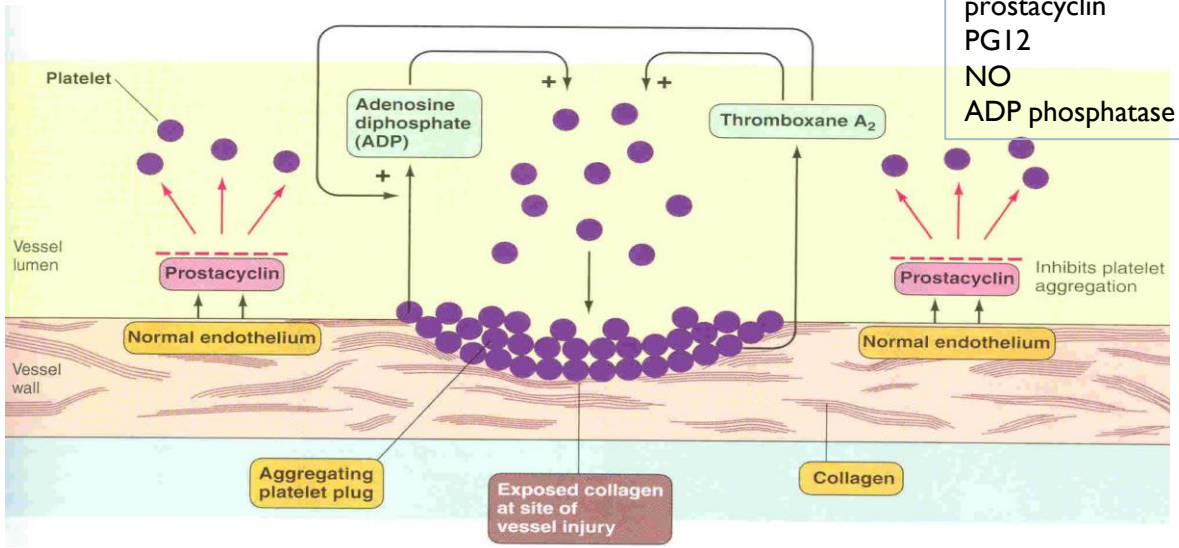
Picture



2. Platelet phase:

formation of platelet plug (primary hemostasis).

Will Secret (very important)

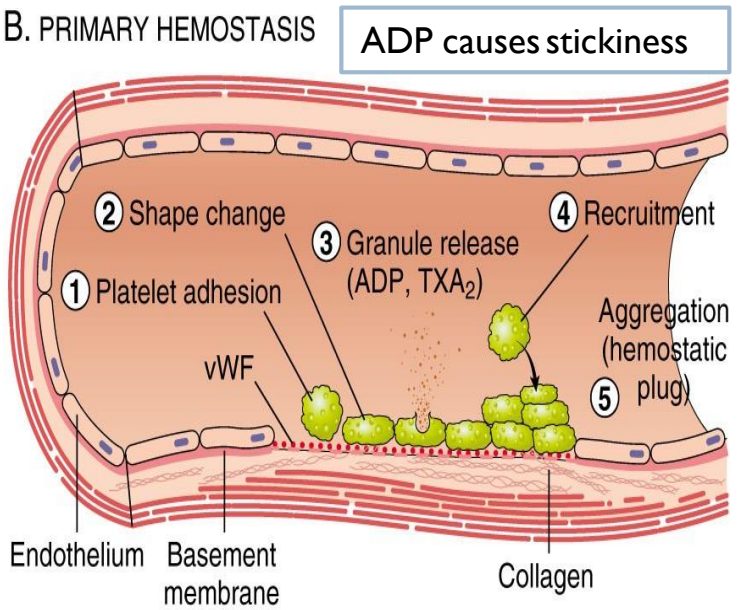


Secret:
prostacyclin
PG12
NO
ADP phosphatase

Importance

Enough to stop bleeding from small vascular damage.

Picture



Serotonin & thromboxane A2 are vasoconstrictors

Mechanism Hemostasis

The Mechanism of clotting is very important

3- blood coagulation

(formation of clot or thrombus)

{secondary hemostasis}

Only in Males' Slides

Blood clotting is the transformation of blood (soluble fibrinogen) from a liquid into a solid gel form (insoluble fibrin strands).

Pathways:

- ✓ Intrinsic
- ✓ Extrinsic

Blood clotting is considered a positive feedback mechanism

Begins to develop in:

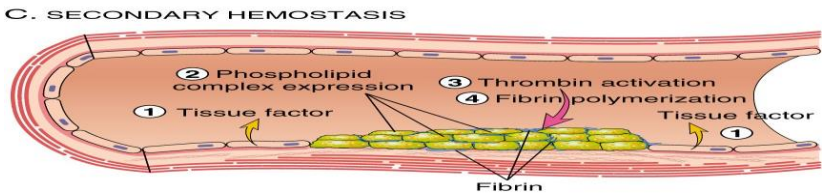
- ✓ 1-2 min → Minor trauma.
- ✓ 15-20 sec → Severe trauma.

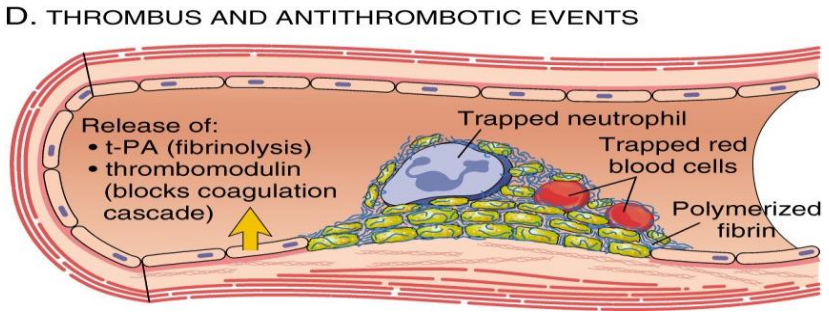
Clot is a meshwork of fibrin fibers running in all directions entrapping blood cells, platelets and plasma.

Mechanism of clotting – STEPS:

Formation of Prothrombin activator complex (Xa + Ca + PF-3 +V) by Extrinsic & Intrinsic Pathways leading to Common Pathway → Conversion of prothrombin into thrombin → Conversion of fibrinogen into fibrin → Fibrin converts to stable fibrin polymer

Picture





4- fibrinolysis

(lysis of blood clot by plasmin)

Thrombin and plasmin both circulate in inactive form

Fibrous clots tend to form in people of old age.

Formed blood clot can either become fibrous or dissolve.

Fibrinolysis (dissolving):

Break down of fibrin by naturally occurring enzyme plasmin therefore prevent intravascular blocking.

There is a balance between cloting and fibrolysis:

- ✓ Excess clotting → blocking of Blood Vessels.
- ✓ Excess fibrinolysis → tendency for bleeding.

Only in Males' Slides

Plasminogen (Profibrinolysin)

T-PA (Tissue Plasminogen Activator)

it can only be given within 3 hours only
if it was given after 3 hours the patient will die

↓ Antiplasmin from the liver

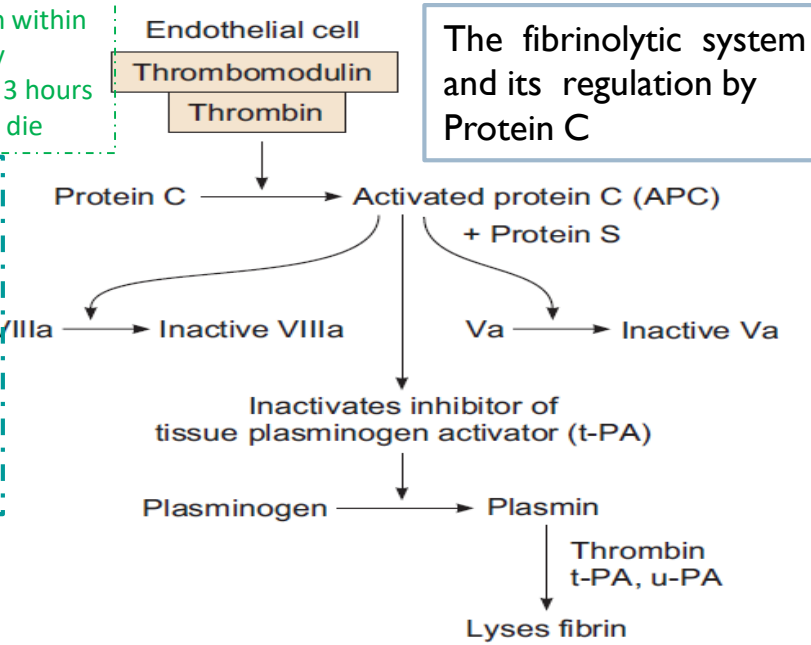
Plasmin (Fibrinolysis)

Lysis of clot

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

Only in Males' Slides

The fibrinolytic system and its regulation by Protein C



Clotting factors

بعض الFactors لهم أكثر من اسم، لازم ينحفظون كلهم ☹

Blood clot: is composed of a meshwork of fibrin fibers running in all directions and entrapping blood cells, platelets, plasma.

Name	Factor
Fibrinogen	I
Prothrombin	II
Tissue factor or thromboplastin	III
Calcium	IV
Proaccelerin (Labile factor) accelerator	V
Proconvertin (Stable factor)	VII NOT VI انتبهوا أن مافي 6
Antihaemophilic factor A Antihaemophilic globulin	VIII
Antihaemophilic factor B Plasma thromboplastin component Christmas factor	IX
Stuart-Prower factor	X
Plasma thromboplastin antecedent (PTA) Antihaemophilic factor C Rosenthal syndrome	XI
Hageman factor	XII
Fibrin stabilising factor Laki-Lorand factor	XIII

Clotting factors mnemonic

- ✓ *Person Told Cancer Leads Sickness, Another Chap Said Protein High Fat.*
- ✓ *Fresher's Party Tonight, Come Let's Sing And Call Seniors, Please Have Fun.*

Clotting factors mnemonic

1:00

Cont.	
Fibrinogen (I)	✓ High-molecular-weight plasma protein. ✓ Mol. W_t. – 340,000 ✓ It is continually formed by the liver. ✓ Little or no fibrinogen leak from blood vessels. ✓ Plasma conc. – 100 – 700 mg/dl
Prothrombin (II)	✓ Is a plasma protein, α2-globulin. ✓ Mol. W_t. - 68,700 ✓ present in normal plasma in a concentration of 15 mg/dl. ✓ It is unstable protein that can be split easily into thrombin. ✓ It is continually formed by the liver. ✓ Vitamin K is important for normal production of prothrombin by the liver. ✓ Lack of Vit-K or liver disease can decrease the of prothrombin formation to a very low level → bleeding.
Fibrin stabilising factor (XIII) Laki-Lorand factor	✓ Is a plasma protein. ✓ It is also released from platelets that is entrapped in the clot. ✓ It must be activated before it affects the fibrin fibres. ✓ Activated XIII factor operates as an enzyme causing additional strength of fibrin meshwork.

Thrombin (key enzyme)

This slide is very important INCLUDE the PICTURES

Thrombin: is a protein enzyme with weak proteolytic capabilities.

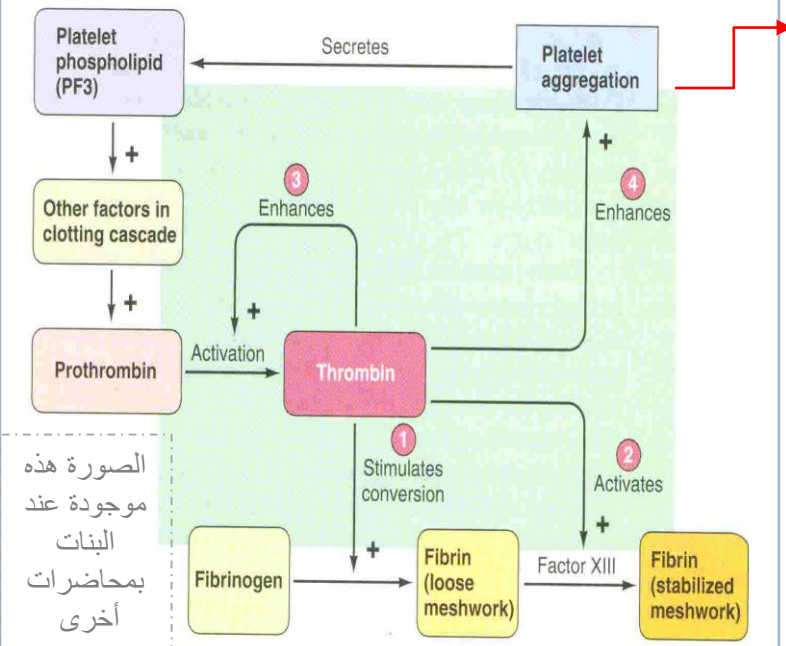
- ✓ It acts on fibrinogen to form one molecule of fibrin monomer.
- ✓ Fibrin monomers polymerize with one another to form fibrin fibres.
- ✓ It activates factor XIII.
- ✓ Thrombin is essential in platelet morphological changes to form primary plug.
- ✓ Thrombin stimulates platelets to release ADP & thromboxane A2; both stimulate further platelets aggregation.

Role of thrombin in hemostasis

- ✓ Thrombin is a serine protease that converts fibrinogen into fibrin and plays a crucial role in haemostasis and thrombosis.
- ✓ During coagulation, factor Xa/Va complex formed on phospholipid or platelet membrane converts prothrombin to thrombin in the presence of Ca^{2+}

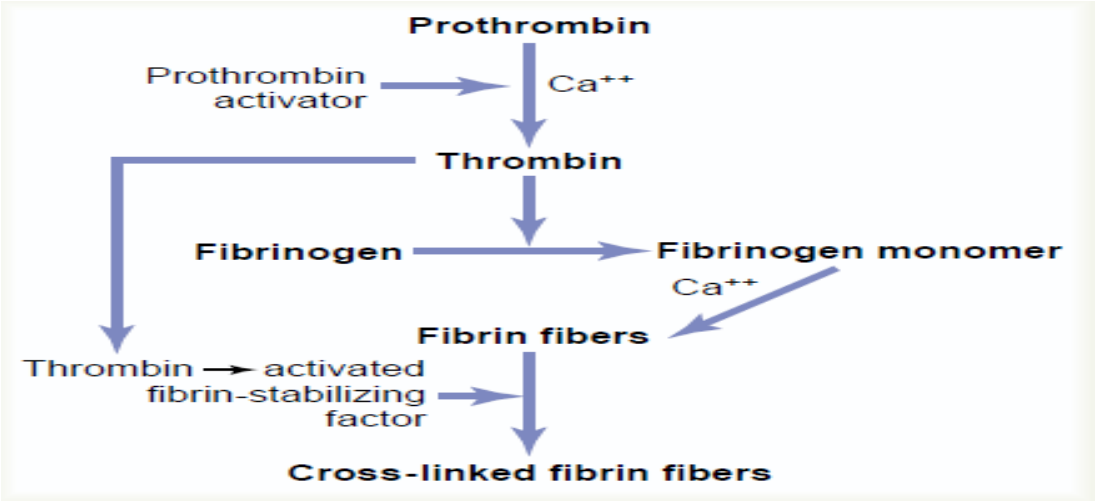
- ✓ Important to know what normal endothelium secretes & remember to write ADP Phosphatase not just ADP alone!

Secret:
prostacyclin
PG12
NO
ADP phosphatase



الصورة هذه موجودة عند البنات بمحاضرات أخرى

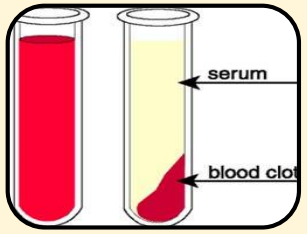
Role of thrombin in fibrinolysis (Action of thrombin on fibrinogen to form fibrin)



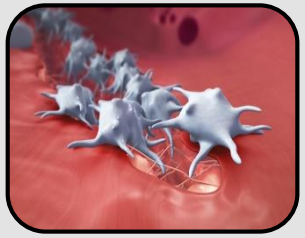
- ✓ Fibrinogen is formed in the liver, and liver disease can decrease the concentration of circulating fibrinogen, as it does the concentration of prothrombin, pointed out earlier. Because of its large molecular size, little fibrinogen normally leaks from the blood vessels into the interstitial fluids, 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 platelets 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.

Clot retraction

When clot retracts (contracts), it expresses most of the fluid from the clot within 20-60 min called → Serum



Serum cannot clot



Role of platelets in clot formation&
Retraction → they are contractile.

The Notes here is very Important

- افهموا هذه السلايد كويس، لو ما فهمتوا بسطناها لكم بالسلايد الجاية، ولو لسا ما فهمتوا اقرؤوا شرح قايتون بسلايد 12 و13 ☺

- بعد ما تفهمون الباثواي كويس، اختاروا واحد من الـ diagram الأنسب لكم من اللي بسلايد 14 و15 وطبقوا الكلام عليه !

Extrinsic & intrinsic mechanism

Intrinsic mechanism	Extrinsic mechanism
✓ Trauma to the blood itself or exposure of the blood to collagen (from a traumatized blood vessel wall), foreign surface/glass. ✓ All clotting factors present in the blood. 1. The trigger is the activation of factor XII by contact with foreign surface, injured blood vessel, and glass. 2. Activated factor XII will activate factor XI. 3. Activated factor XI will activate IX. 4. Activated factor IX + factor VIII + platelet phospholipid factor (PF3)+ Ca activate factor X. Blood coagulates in a plain glass tube by the intrinsic pathway	✓ TF (tissue thromboplastin) includes phospholipids from the membranes of the tissue plus a lipoprotein complex that functions mainly as a proteolytic enzyme. ✓ Triggered by material released from damaged tissues (tissue thromboplastin). ✓ Tissue thromboplastin + VII + Ca → activate X. Coagulation Cascade 5:22

Common pathway

- ✓ Activated factor X + factor V +PF3 + Ca activate prothrombin activator; a proteolytic enzyme which activates prothrombin.
- ✓ Activated prothrombin activates thrombin.
- ✓ Thrombin acts on fibrinogen and change it into insoluble thread like fibrin.
- ✓ Factor XIII + Calcium → strong fibrin (strong clot).

الفيديو رهيب خاصة للناس البصريّة! 1:53

PTT[1] is for the intrinsic pathway while PT[2] is for the extrinsic pathway

[1] PPT= Partial Thromboplastin Time
[2] PT= prothrombin time

Simple way to memorize the coagulation cascade (Extra)

- لو ما فهمتوا السلايد السابق، بسطناها لكم هنا، ولو لسا ما فهمتوا اقرؤوا شرح قايتون بالسلايدتين الجاية ☺

- بعد ما تفهمون الباثواي كويس، اختاروا واحد من الـ diagram الأنسب لكم من اللي بسلايد 14 و15 وطبقوا الكلام عليه !

Intrinsic mechanism	Extrinsic mechanism
12 → 11 → 9 → 10. The pattern? 1. Split 12 into two numbers; 1 and 2 2. First, minus 1 to get from 12 to 11 3. Then, minus 2 to get from 11 to 9 In order for factor 9 to activate factor 10, there needs to be factor 8 present. The pattern? 1. Count 8, 9, 10 2. You need 8 to get 9 to activate 10	3 → 7 → 10. The pattern? 1. Split the 12 from the intrinsic pathway again into two numbers; 1 and 2 2. Add them together so that 1 + 2 = 3 3. In order to get to 10, you need 7 more
Thrombin comes before fibrin Back at the start when we talked about how factor 3 is generally the "spark" that starts it all? Which is known as tissue factor 3 (TF). TF. : thrombin –> fibrin	

- لو فهمتوا اللي قبل Skip

- بعد ما تفهمون الباثواي كويس، اختاروا واحد من الـ diagram الأنسب لكم من اللي بسلايد 14 و15 وطبقوا الكلام عليه !

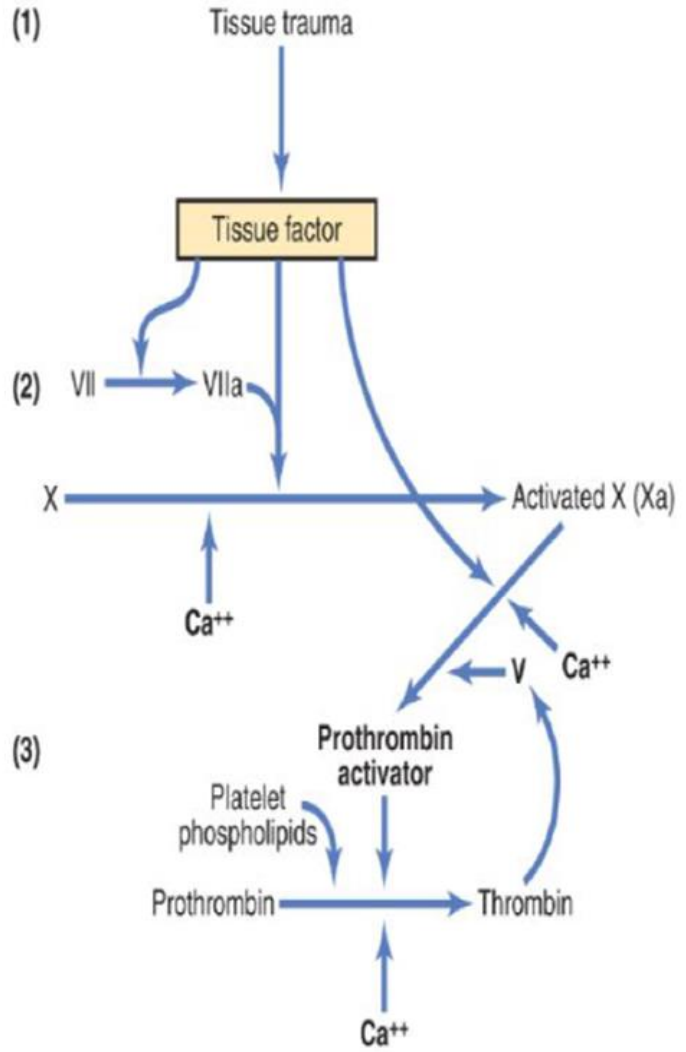
Extrinsic pathway for initiating clotting (Guyton)

- 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 the picture.

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 platelets, 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.



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Intrinsic pathway for initiating clotting (Guyton)

- 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 the picture.

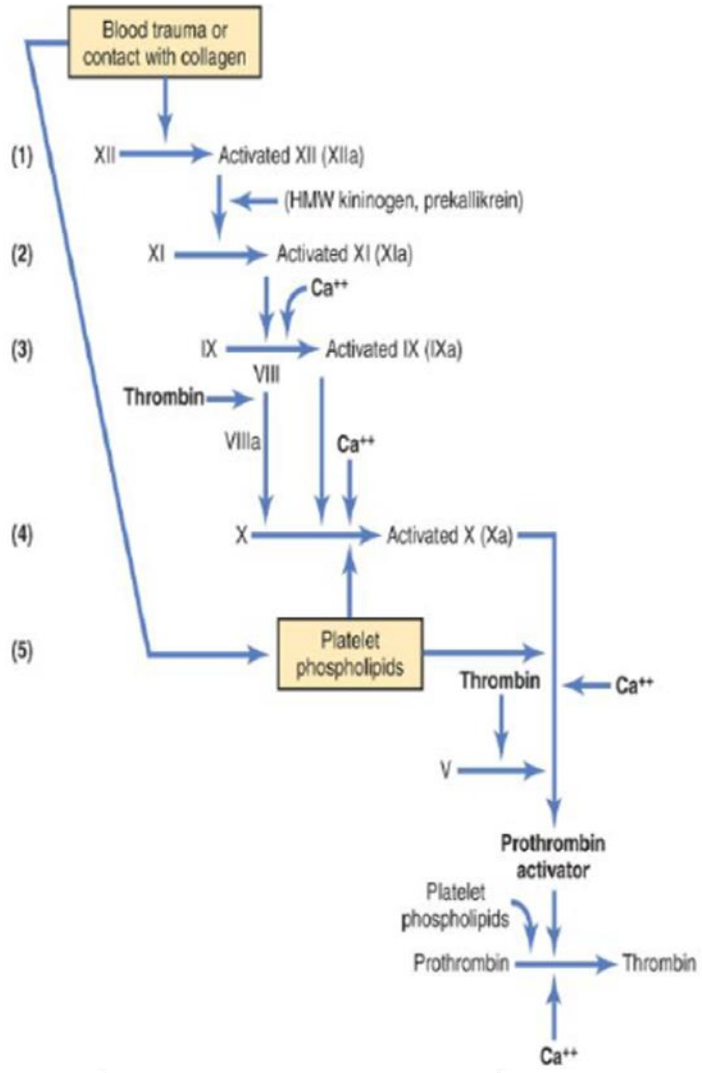
1. Blood trauma causes (1) activation of Factor XII and (2) release of platelet phospholipids.Trauma to the blood or exposure of the blood to vascular wall collagen alters two important clotting factors in the blood: Factor XII and the platelets. When Factor XII is disturbed, such as by coming into contact 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 either collagen or a wettable surface (or by damage in other ways), and this releases platelet phospholipids that contain the lipoprotein called plateletfactor 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 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, for which reason 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 within seconds the cleavage of prothrombin to form thrombin, thereby setting into motion the final clotting process



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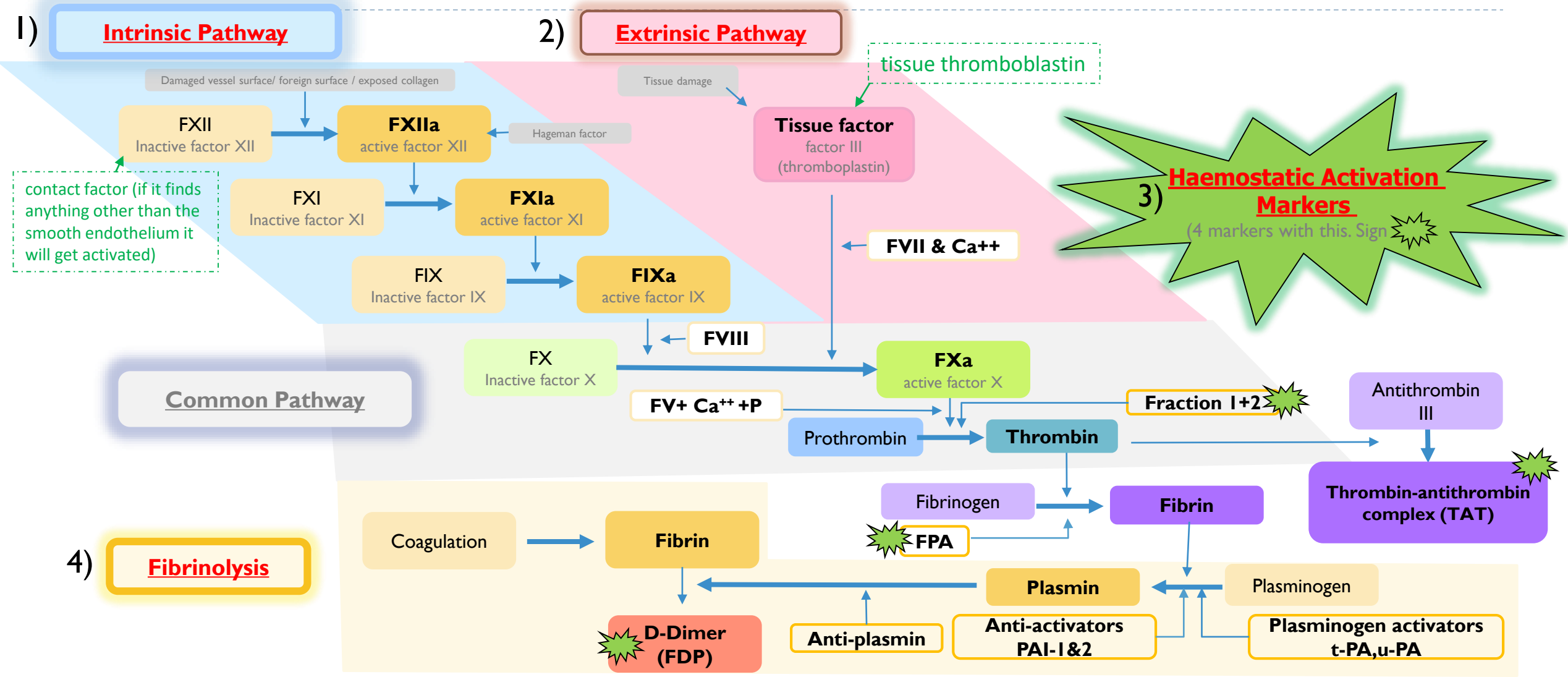
The Coagulation Cascade



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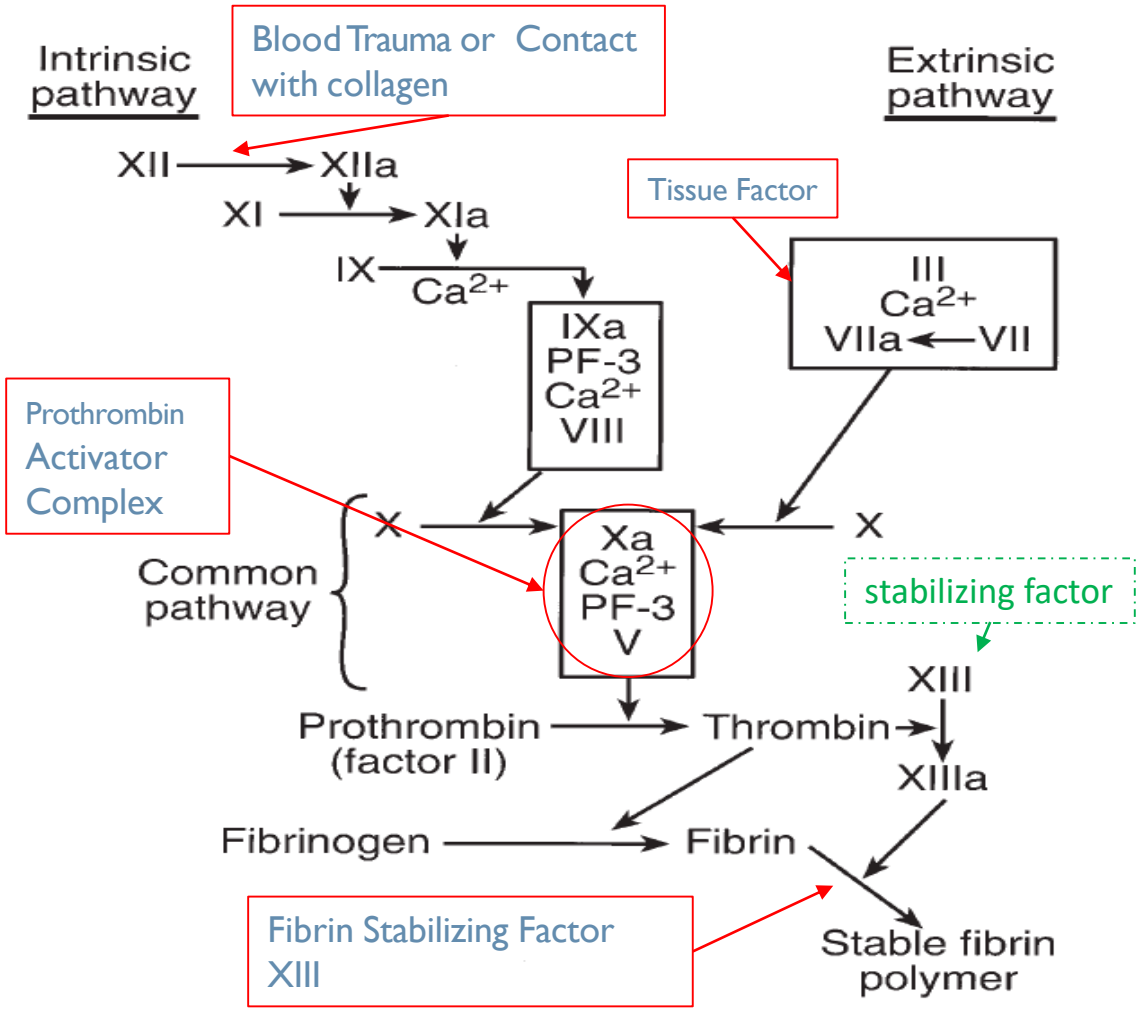
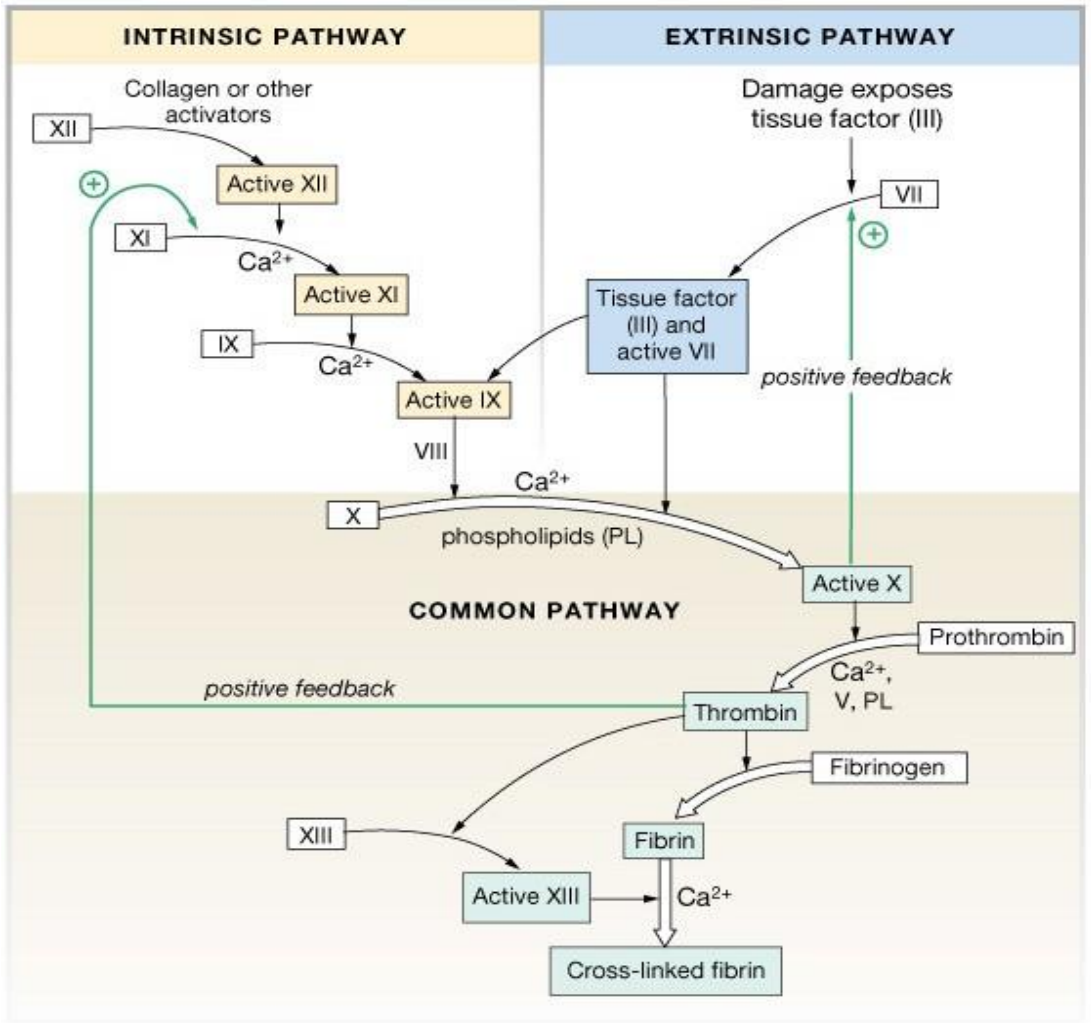
Extrinsic & intrinsic mechanism

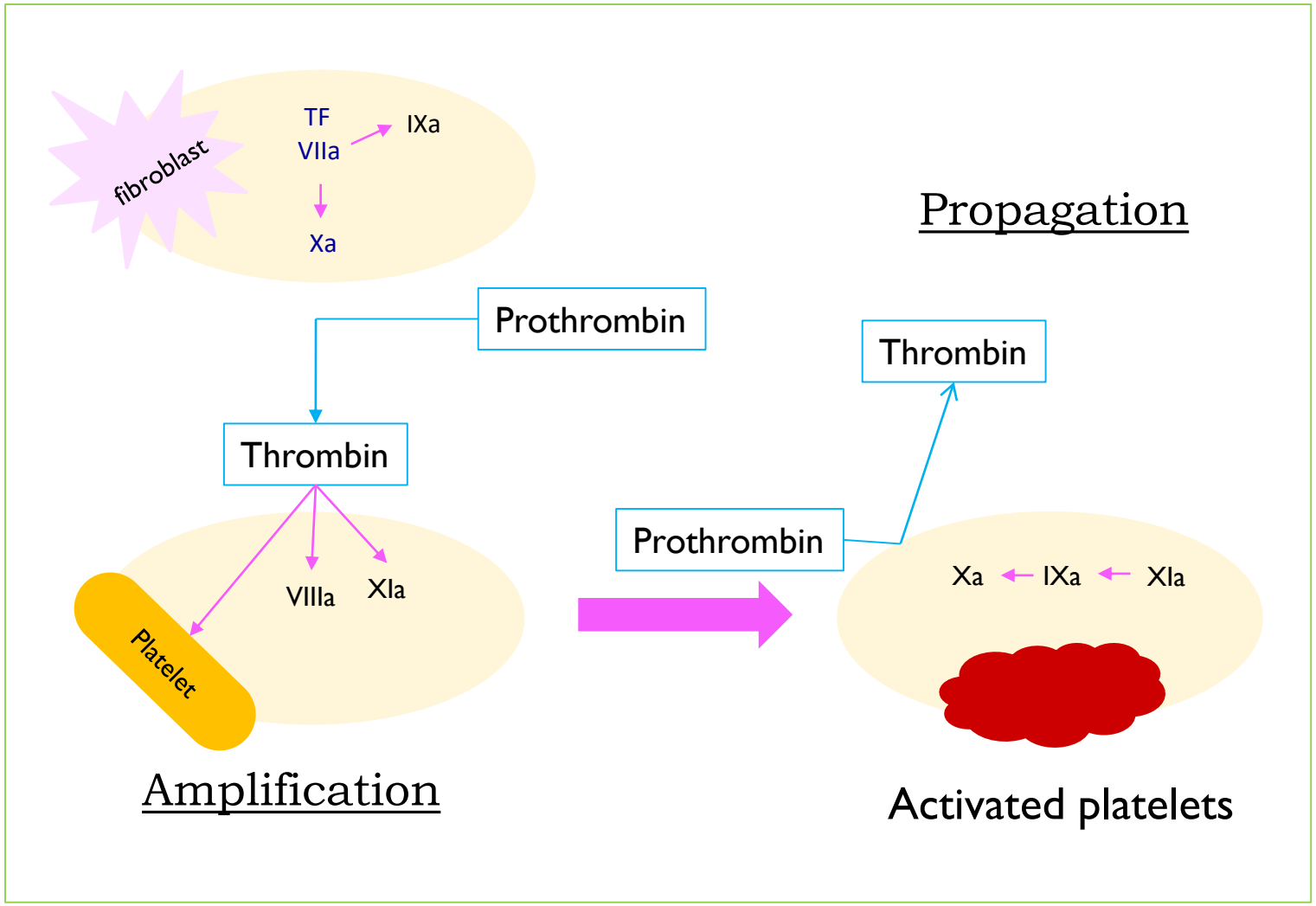




Activation & Inactivation of coagulation

Activation and Inactivation of coagulation	
Activation of coagulation	Inactivation of coagulation
Are not coded for by specific genes, and their concentrations reflect the overall activation of the coagulation and fibrinolytic systems.	By natural anticoagulants
Enzymatic activation products of coagulation and fibrinolytic mechanisms such as : o prothombin 1+2 (F1+2) o thrombin-antithrombin complex (TAT) o FPA o D-dimer	Natural anticoagulants : i. Anti-thrombin III (AT-III) ii. Protein C (inhibits Va & VIIIa) iii. Protein S (cofactor for protein C)

Cell based model



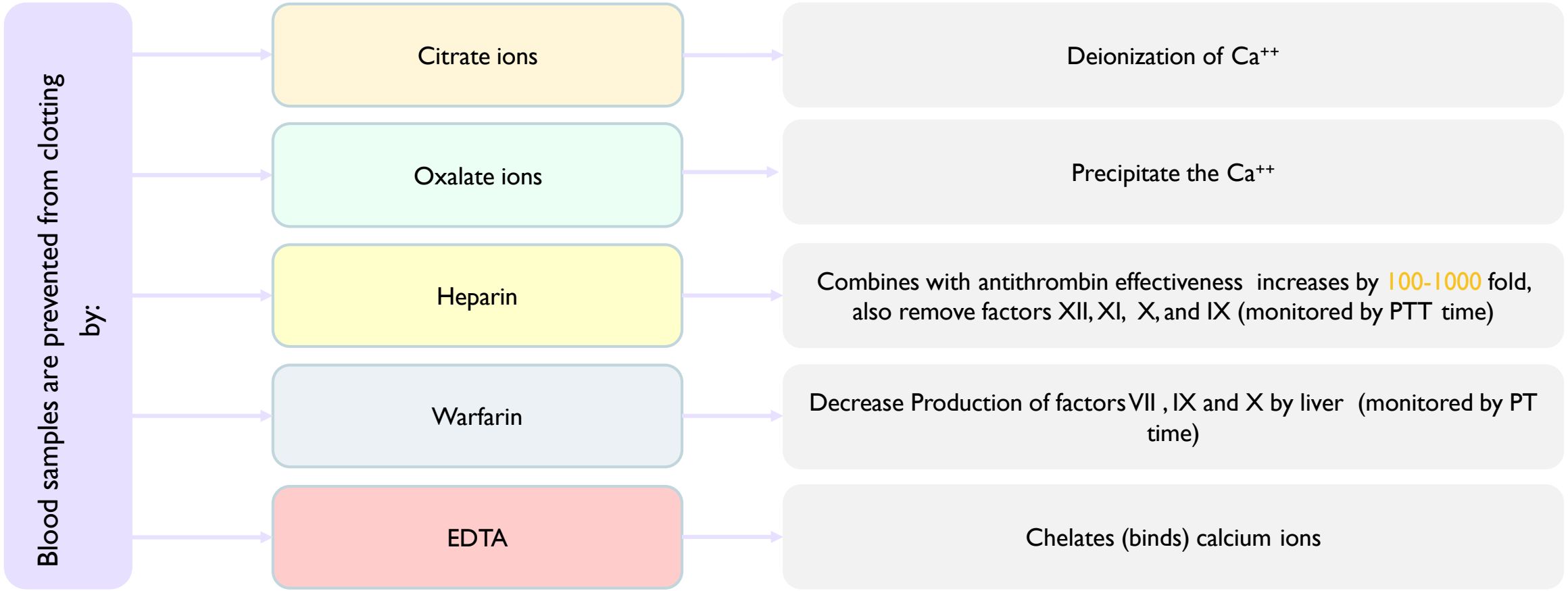
This is ONLY FOR YOUR INFORMATION.

بس المطلوب تعرفون من هذه الصورة أن ال

Cell based model means the Extrinsic & intrinsic pathway occur in the surface of the platelets & endothelium.

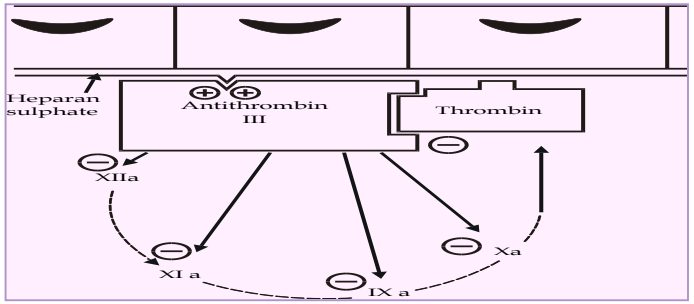
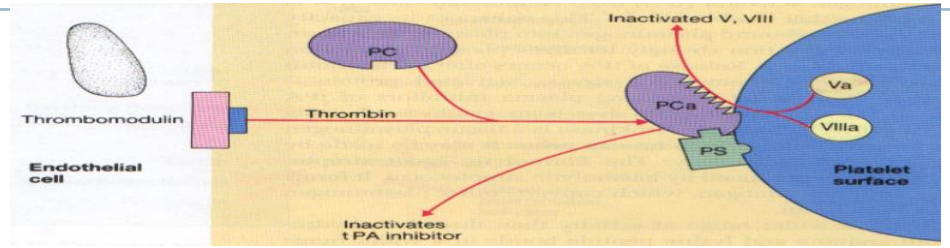
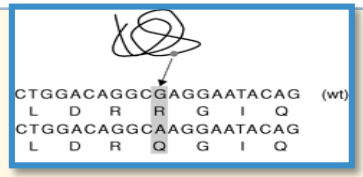
Role of CALCIUM ions in clotting

- No Ca^{++} → No clotting (needed in many steps)



Natural anticoagulants

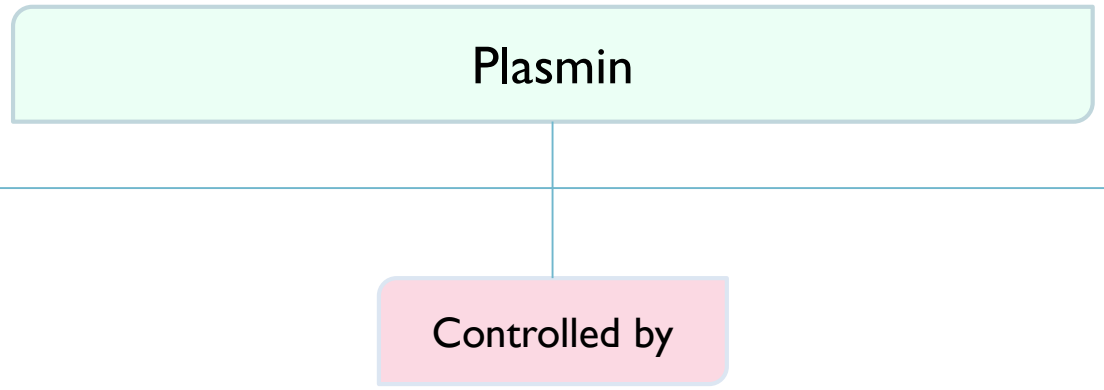
This slide is very Important

Antithrombin III		Protein C & S	
Synthesis	Hepatocytes & endothelial cells.	Protein C	- Vitamin K-dependent. - Synthesized by the hepatocytes Activated protein C resistance (APC-R): is mainly due to a genetic abnormality of clotting factor V called (factor V Leiden mutation).
Action	ATIII + thrombin → thrombin-ATIII complex. Heparin dramatically enhances this action. 	Action	 Note on the picture: point mutation in the factor V gene, G1691A in exon 10, leading to Arg506Gln. 

Natural intravascular anticoagulant (prevention of blood clotting in the normal vascular system and anticoagulant)

Endothelial Surface Factors	• Smoothness of Endothelium. • Glycocalyx Layers. • Thrombomodulin Protein binds to thrombin → Activates Protein C (with ProtS) → inactivates factors V & VIII and inactivates an inhibitor of tPA → increasing the formation of plasmin.
Antithrombin action of Fibrin and Antithrombin III	• 85-90 % Thrombin binds with Fibrin. • 10-15 % Thrombin binds with Antithrombin III. • Antithrombin III is a circulating protease blocking clot factors. • Antithrombin III, combines the remaining thrombin and removes it from blood.
Heparin	• vely charged conjugated polysaccharide. • Increase the effectiveness of Antithrombin III Produced by : Mast cell , Basophil cells , liver , lung. • Most widely used anticoagulant clinically e.g. in stroke. • $Alpha_2$ – Macrogobulin acts as a binding agent for several coagulation factors (combines with Antithrombin III and quickly removes thrombin from blood).
Fibrin fibers	adsorbs ~ 90% of thrombin to removes it from circulating blood.

Plasmin



- ✓ Is present in the blood in an inactive form plasminogen.
- ✓ Is activated by tissue plasminogen activators (t-PA) in blood.
- ✓ Digests intra & extra vascular deposit of Fibrin → fibrin degradation products (FDP).
- ✓ Unwanted effect of plasmin is the digestion of clotting factors.

- ✓ Tissue Plasminogen Activator Inhibitor (TPAI).
- ✓ Antiplasmin from the liver.

- ✓ Tissue Plasminogen Activator (TPA) used to activate plasminogen to dissolve coronary clots.

Hemostatic balance

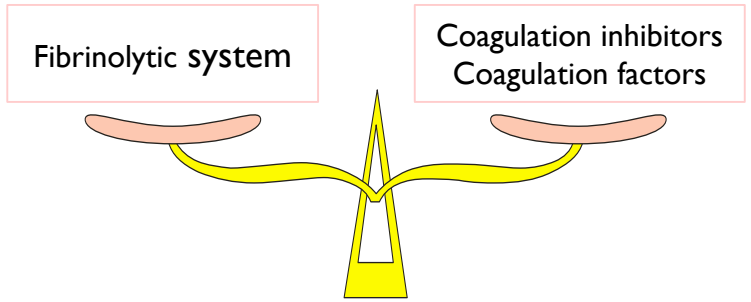
Only in Females' Slides

A crucial physiological balance exists between factors promoting coagulation (procoagulants) and factors inhibiting coagulation (anticoagulants).

Homeostasis of the clotting system:

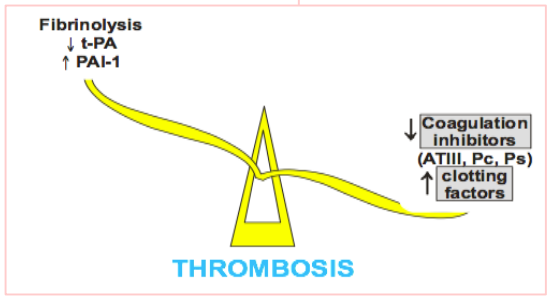
- A crucial physiological balance exists between factors favoring clotting and factors that oppose it.
- Disturbances in this balance can lead to thrombotic diseases or bleeding.

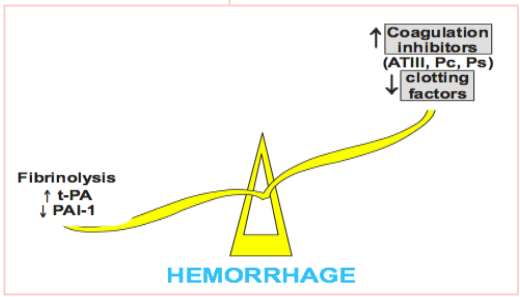
Coagulation of blood depends on the balance between these two factors.



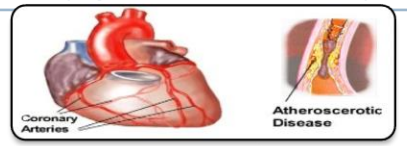
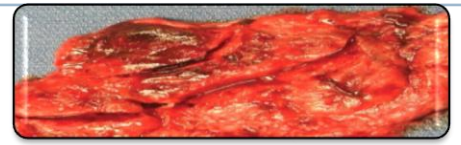
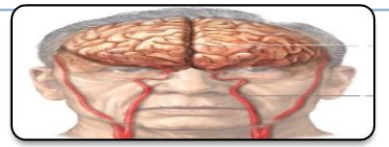
Disturbances in this balance could lead to:

- Thrombosis
- Bleeding





Hemostatic Disturbances

DVT & PE (Deep vein thrombosis & pulmonary embolism)	MI (Myocardial infraction)	Placental infraction Recurrent abortions	Stroke
			

Virchow Triads 1845

Etiological factors for thrombosis:

- Changes in blood flow (stasis).
- Changes in the endothelium.
- Changes in blood composition (Hypercoagulability).

An imbalance in one of these 3 can lead to hyper coagulability an imbalance between the pro and the anti.

Bleeding and clotting disorders (condition that cause excessive bleeding)

Hemophilia is very important

Thrombocytopenia

- ✓ Bleeding disorder & related to platelet problems.
- ✓ Very low numbers of platelets in blood (< 50,000/ul) may cause spontaneous bleeding.
- ✓ Less than 10,000 ⇢ Fatal.

Etiology

Decrease production:
- Aplastic anemia.
- Leukemia.
- Drugs.
- Infections (HIV, Measles).

Increased destruction:
- ITP (Idiopathic thrombocytopenic purpura).
- Drugs.
- Infections (HIV).

Clinical feature

Easy brusability, Epistaxis, Gum bleeding, Hemorrhage after minor trauma, Petechiae /Ecchymosis.

Diagnosis

Platelets decreased, B.T (bleeding time) increased.

Treatment

- ✓ Treatment of the underlying cause.
- ✓ Palates concentrates.
- ✓ Fresh whole blood transfusion.
- ✓ Splenectomy.

- ✓ Thrombocytopenia purpura, hemorrhages throughout all the body tissues.
- ✓ Idiopathic Thrombocytopenia, unknown cause.

Hemophilia

- Small Comp. → Hemophilia A → ↑PTT (Partial Thromboplastin Time).
- Large Comp. → Von-Willebrand's disease → ↑PTT & BT (bleeding time).

Hemophilia A:
- ✓ Classic hemophilia.
- ✓ 85% cases.
- ✓ Deficiency of factor VIII.

Hemophilia B:
- ✓ 15% case.
- ✓ Deficiency of factor IX.

Clinical feature

Easy bruising, massive bleeding after trauma or operation, hemorrhages in joints.

- ✓ Increase bleeding to tendency
- ✓ Genetic disorders (X-linked disease).
- ✓ Transmitted by female chromosome as recessive trait.
- ✓ Occurs exclusively in males, Females are carriers.
- ✓ Hemophilia is one of the clotting disorders are related to clotting problems.
- ✓ Remember that: in Hemophilia a PTT is increased, while in In Von-Willebrand's disease PTT and BT is increased.

Liver disease and vitamin-K deficiency

- ✓ e.g. Hepatitis, Cirrhosis, acute yellow atrophy, GI disease.
- ✓ Liver disease can have signs of bleeding and clotting together.

- ✓ Decreased formation of clotting factors.
- ✓ Increased clotting time.
- ✓ Vitamin K dependent factors:
- II (Prothrombin) ,VII, IX & X.

Vitamin-K :

- ✓ Fat soluble.
- ✓ vitamin Required by liver for formation:
- Prothrombin.
- Factor VII.
- Factor IX.
- Factor X.

Deficiency

- ✓ Malabsorption syndromes.
- ✓ Biliary obstruction.
- ✓ Broad spectrum antibiotics.
- ✓ Dietary deficiency (in Neonates).

Source

- ✓ Diet.
- ✓ Synthesized in the intestinal tract by bacteria.

Treatment

- ✓ Treat the underlying cause.
- ✓ Vit-K injections.

Hypercougulability

Only in Females' Slides

- ✓ The dynamic balance between procoagulant reactions & their downregulation by natural anticoagulants in conjunction with the fibrinolytic system should function within normal parameters to prevent abnormal thrombus formation or propagation.
- ✓ However, in some instances, alteration of just one variable in this complex series of interacting components will bring about a significant hypercoagulable (prothrombotic) state, which can manifest itself clinically as arterial and/or venous TE.

Definition	Is a laboratory phenotype whereby activation of the of clotting, fibrinolysis, endothelial cells and platelets are identified.

Hypercougulability / Prothrombotic States

Hereditory Hemostatic disorders

- ✓ Factor V Leidin (Deficincey).
- ✓ Prothrombin G20210A (Mutation).
- ✓ Hyperhomocysteinaema
- ✓ Deficiencies of AT III, Proteins C & S
- ✓ Increased FVIII.

Acquired Hemostatic disorders:

- ✓ Raised Levels of fibrinogen & FVII (With growth and pregnancy).
- ✓ Antiphosphlipid Antibodies (LA & ACAs).
- ✓ Oestrogen therapy (Contraception pills, infertility treatment).
- ✓ Pregnancy and its complications.
- ✓ Surgery and prolonged immobility.
- ✓ Major Trauma.
- ✓ Malignancy.
- ✓ Hyperviscosity.
- ✓ Nephrotic Syndrome
- ✓ Dehydration
- ✓ Thrombocytosis
- ✓ Polycycaemia
- ✓ Sepsis
- ✓ Smoking
- ✓ Obesity
- ✓ Age
- ✓ Varicose veins

Laboratory tests of hypercoagulability

Natural anticoagulant

- ✓ ATIII (Antithrombin 3)
- ✓ Protein C
- ✓ Protein S

Fibrinolysis

- ✓ PAI-1
- ✓ FDPs (D-Dimer)

Coagulation activation marker

- ✓ Thrombin-Antithrombin complexes (TAT).
- ✓ Prothrombin fraction 1+2.
- ✓ D-Dimer.

Activation protein C resistance (APCR)

- ✓ Functional Assay.
- ✓ Genetic assay (Factor V Leiden).

Genotyping

- ✓ Factor V Leiden.
- ✓ Prothrombin G20210A.
- ✓ Hyperhomocysteinaemia (MTHFR).

This slide is very Important

Questions'!

- What prevents blood from coagulating in normal (not injured) conditions? What are the natural intravascular anticoagulants?

1. Endothelial Surface Factors (Smoothness, Glycocalyx layers and action of Thrombomodulin Protein C and S).
2. Antithrombin action of Fibrin and Antithrombin III.
3. Heparin.
4. Alpha2 Macroglobulin.

What are the actions of Thrombomodulin, Protein C and S?

Thrombomodulin Protein binds to thrombin → Activates Protein C (with Protein S) → inactivates factors V & VIII and inactivates an inhibitor of TPA → increasing the formation of plasmin.

What aids in the mechanism of clot retraction?

The contractile property of platelets.

- Main ENDOTHELIAL factors that prevent platelets from aggregating?
  - PGI2
  - NO
  - ADP Phosphatase

- What are the actions of thrombin?

1. Stimulates conversion of Fibrinogen into Fibrin.
2. Activates Factor XIII (Fibrin Stabilizer).
3. Enhances its own activation(Prothrombin to Thrombin).
4. Enhances platelet aggregation.

- Main source of Heparin?

Mast cells and Basophils.

- How is the bleeding time changed in Haemophilia A?

It is normal. While in Von-Willebrand's disease it is increased.

Thank you!

اعمل لترسم بسمة، اعمل لتمسح دمعة، اعمل و أنت تعلم أن الله لا يضيع أجر من أحسن عملا.

The Physiology 436 Team:

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QUIZ

اقتراحات وشكاوي

References:

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- Ganong's Medical Physiology (25th Edition)
- Linda S. Costanzo (5th Edition).

اللهم اني استودعتك ما حفظت وما قرأت وما فهمت، فرده لي وقت حاجتي إليه إنّك على كل شيءٍ قدير.