Physiology Team 439

MED439
KING SAUD UNIVERSITY

Revised & Approved
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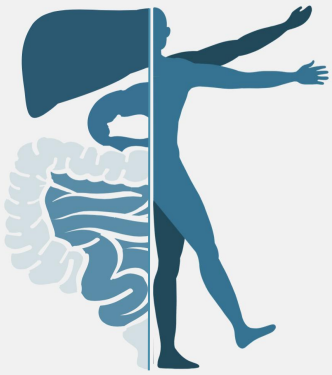


Coagulation mechanism

Special thanks to Sarah Alobaid

Objectives:

- Recognize the different clotting factors.
- Understand the role of calcium ions during clotting cascades.
- Describe the cascades of intrinsic and extrinsic pathways for clotting.
- Recognize process of fibrinolysis & function of plasmin. Recognize some conditions causing excessive bleeding or hypercoagulation.
- Understand some important anticoagulants & their mechanism of action.
- Recognize different stages of haemostasis
- Explain the role of platelets in haemostasis.
- Recognize different clotting factors & cascade of clotting.
- Describe the intrinsic, extrinsic and common pathway.
- Recognize the role of thrombin in coagulation
- The role of anticoagulants and their mechanism of action

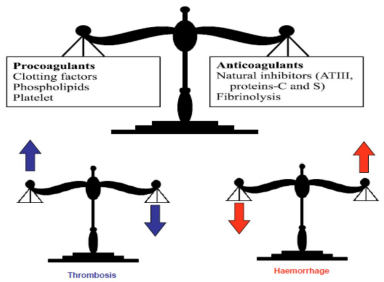
Color index:

- Important.
- Girls slide only.
- Boys slide only.
- Dr's note.
- Extra information.

Editing File

Introduction Only in girls slides

- A crucial physiological **balance** exists between factors promoting coagulation (procoagulants) and factors inhibiting coagulation (anticoagulants).
- Coagulation of blood depends on the balance between these two factors.
- Disturbances in this balance could lead to **thrombosis** or **bleeding** both are disasters, and sometimes the patient has thrombosis and bleeding. For example, Disseminated intravascular coagulation (DIC) which is very serious and fetal.
- **Procoagulants:** clotting factors, phospholipids and platelets
- **Anticoagulants:** Natural inhibitors (AT Ⅰ Ⅰ Ⅰ, proteins-C and S) and fibrinolysis.
- **Thrombosis:** If Procoagulant is > Anticoagulant
- **Hemorrhage:** If Anticoagulant is > Procoagulant



Hemostasis:
Prevention or stoppage of blood loss.
The spontaneous arrest of bleeding from ruptured blood vessels

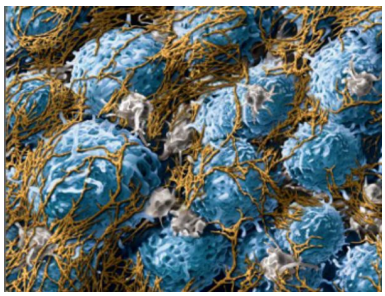
Hemostatic mechanisms

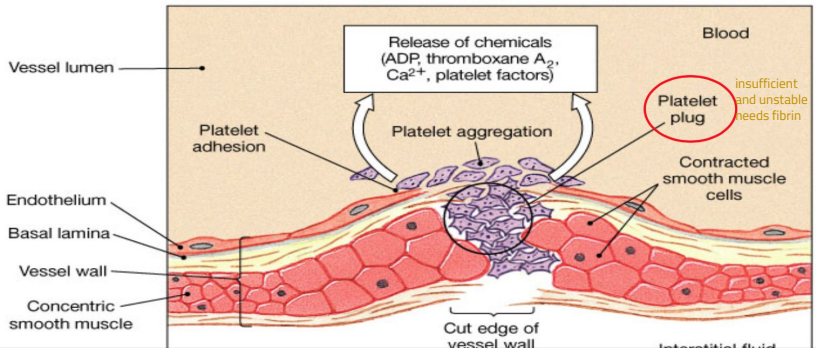
Not all steps are required. If bleeding is stopped in phase 1, The rest won't be activated. It depends on the severity of the injury

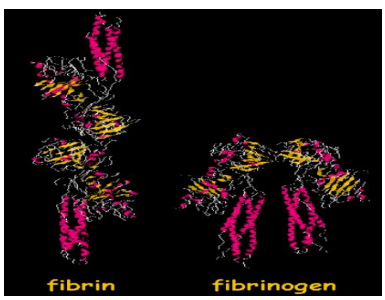
1. **Vessel wall** (Vasoconstriction)
2. **Platelets** (Production & activation, Platelets Plug formation)
3. **Blood coagulation** Clot formation and clot retraction (intrinsic/extrinsic/common pathways).
   Produce fibrin to stabilize primary hemostatic plug (which is from platelets), then Fibrinolysis
4. **Fibrinolysis** "important step some students forget it"

Coagulation: Formation of fibrin meshwork (Threads) to form a blood CLOT.*

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







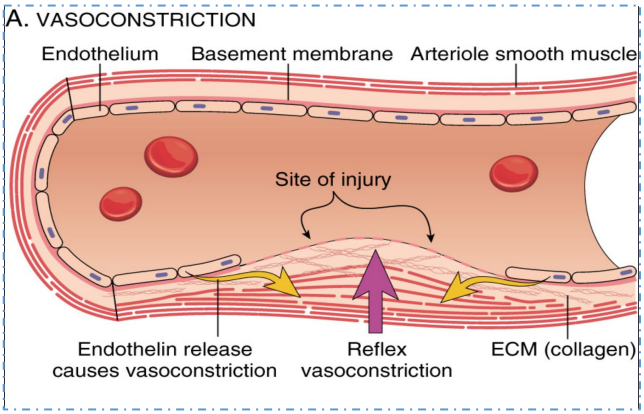
1- Vascular spasm (vascular constriction) *

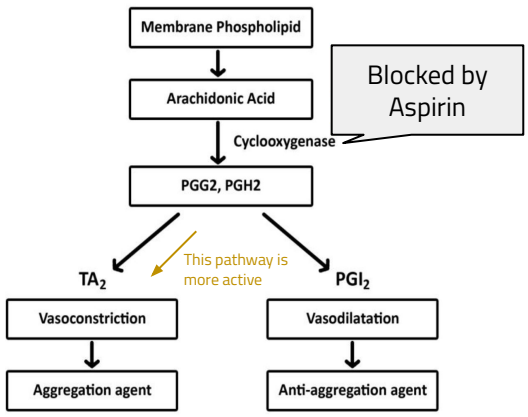
Immediately After injury there is localized Vasoconstriction.

- **Causative factors are three (3):**
  - Nervous reflexes
  - Local myogenic spasm
  - Local humoral factors....Platelets → Thromboxane A2 [TXA2] **(Vasoconstrictor)**

- **Importance:**
  Crushing injuries → Intense spasm → No lethal loss of blood

The bigger the area of injury, the more the vasospasm and vice versa.
-Small area (knife cut): Minimal vasospasm not enough to stop the bleeding
-Large area (crushing of the whole arm): massive vasospasm leading to minimal or no bleeding at all



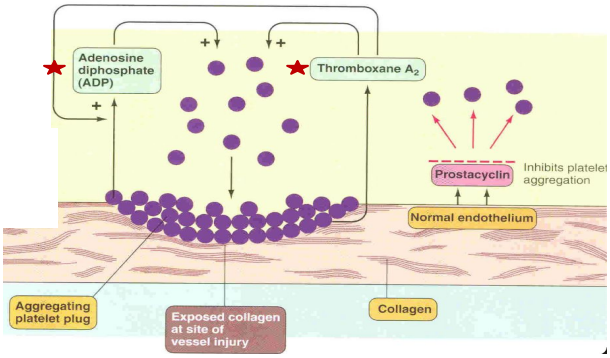


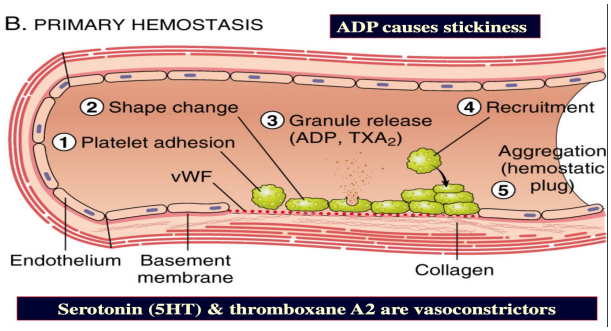
2-Formation of platelet plug (primary hemostasis)*

- **Importance:** enough to stop bleeding from small vascular damage
- **Normal endothelium secretes:**
  (Anti-aggregation agents)
  - Prostacyclin (PGI2)
  - NO
  - ADP phosphatase

- **Platelets secrete:**
  - ADP
  - Thromboxane A2
  - Serotonin

Thromboxane A2 and ADP enhance platelet aggregation
Thromboxane A2 and serotonin are vasoconstrictors



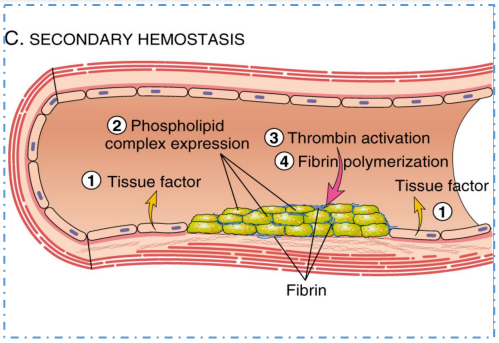


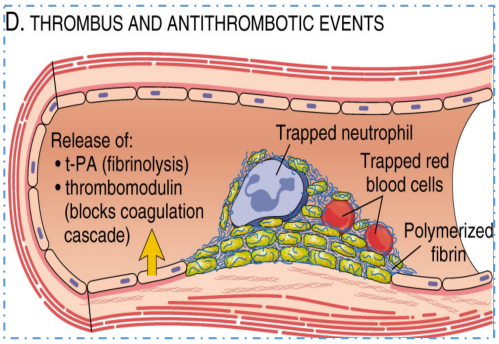
3- Blood coagulation (secondary hemostasis)
formation of clot or thrombus

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

- **Pathway**:
  - Intrinsic
  - Extrinsic

- Begins to develop in* :
  - 1-2 min → minor trauma
  - 15-20 sec → Severe trauma





Clotting Factors:

Boys Dr. said they are hard to memorize but he did mention some of them. (will be highlighted in bold)

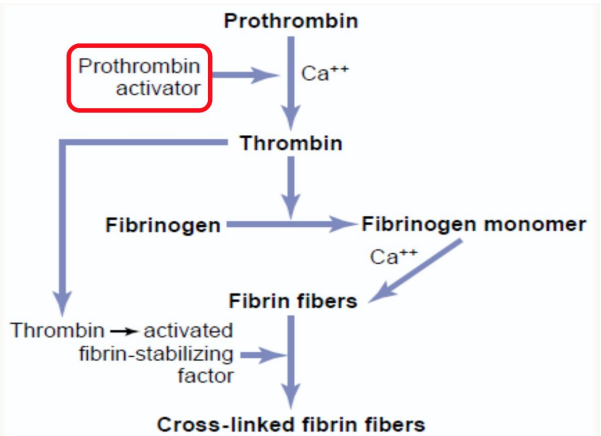
Most of them are formed in the liver, and they are inactive in the circulation. Once the person get injured the become active.

Factors	Names / Synonyms
1. I	Fibrinogen percurcer of fibrin
2. II	Prothrombin
3. III	Thromboplastin (tissue factor)
4. IV	Calcium
5. V	Labile factor; Proaccelerin; Ac-globulin(Ac-G)
7. VII	Stable factor; Serum prothrombin conversion accelerator (SPCA); Proconvertin
8. VIII	Antihemophilic factor A; Antihemophilic globulin
9. IX	Antihemophilic factor B; Plasma thromboplastin component (PTC); Christmas factor
10. X	Stuart-Prower factor
11. XI	Antihemophilic factor C; Plasma thromboplastin antecedent (PTA)
12. XII	Hageman factor "glass factor" because it is responsible for the blood coagulation in a test tube (discussed later)
13. XIII	Fibrin stabilizing factors

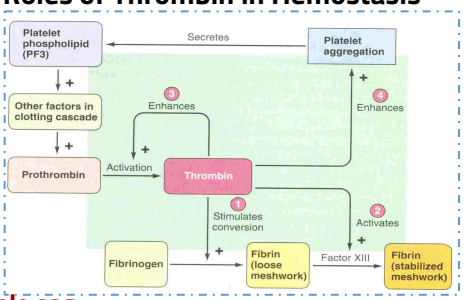
Features of some factors

Factors	Prothrombin (II) Pro: Thrombin المادة الأولية لل	Thrombin* From factor II (prothrombin).	Fibrinogen (I) Fibrin المادة الأولية لل	Fibrin-Stabilizing factor(XIII)*
Characteristics	- Plasma protein (Alpha2 globulin),* Mol. Wt. - 68,700،* Plasma conc. - 15 mg/dl* Any patient has liver disease (liver fibrosis, malignancy and metastasis) will have problems in coagulation. - Unstable protein that can be split easily into thrombin Key enzyme in the coagulation system - Lack of vit K or liver disease can decrease prothrombin formation to a very low level → bleeding.*	- Is a protein enzyme with proteolytic capabilities. - It acts on fibrinogen to form one molecule of fibrin monomer - Fibrin monomers polymerize with one another to form fibrin fibers. - Thrombin is essential in platelet morphological changes to form primary plug. - **Thrombin stimulates platelets to release ADP & thromboxane A2; both stimulate further platelets aggregation** - Activates factor XIII Activates clotting factors: - XIII to crosslink fibrin. - **Activates Intrinsic pathway via factor X.** - Cofactor of the activation of factors V & VIII	- Is a high molecular weight plasma protein* Mol. Wt. – 340,000 * Plasma conc. – 100 – 700mg/dl* - Little or no fibrinogen leads to blood leak from vessels*	- A plasma protein. - Released from platelets that is entrapped in the clot. - It must be activated before it affects the fibrin fibers. - Activated XIII factor operates as an enzyme causing additional strength of fibrin meshwork.
Site of synthesis	Synthesized by liver, and **Vitamin-K is required for synthesis** 4 clotting factors depend in vitamin k in their synthesis (2,7,9,10).	Activated form of prothrombin	Continually formed by the liver	megakaryocytes (platelets)

ACTION OF THROMBIN ON FIBRINOGEN TO FORM FIBRIN



Roles of Thrombin in Hemostasis



Possible saq:
"what are the main 4 actions of thrombin ?"

1- Thrombin stimulates conversion of fibrinogen to fibrin
2- Activation of Factor 13
3- Enhances its own activation (Positive feedback)
4- Causes platelet aggregation

Procoagulant actions of thrombin enzyme:

1. **Activates clotting factors:**
   a. Xiii to cross link fibrin (to stabilize fibrin)
   b. Intrinsic pathway via factor Xi.
   c. Cofactor of the activation of factors V & Viii.

2. **Stimulates platelet activation.** Thrombin stimulate platelet aggregation, and platelet release factors stimulate coagulation= يعني الاثنين يتعاونون

Blood Coagulation (clot formation)

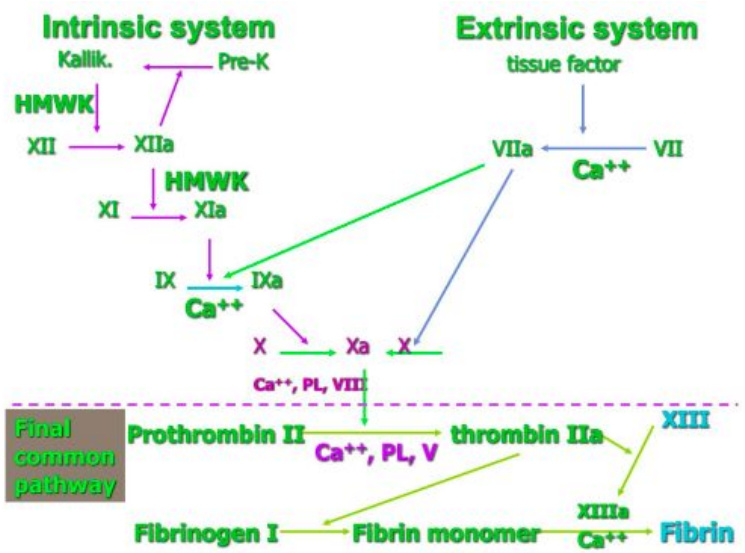
1. A series of biochemical reactions leading to the formation of a blood clot within few seconds after injury.

2. Formation of Prothrombin activator complex (Xa+Ca+PF-3+V) by short Extrinsic & long Intrinsic Pathways leading to Common Pathway

3. This reaction leads to the activation of thrombin enzyme from inactive form prothrombin.

4. Thrombin will change fibrinogen (plasma protein) into fibrin (insoluble protein). (First fibrin become soluble, and need factor XIII to become insoluble) important
   Fibrin converts to stable fibrin polymer

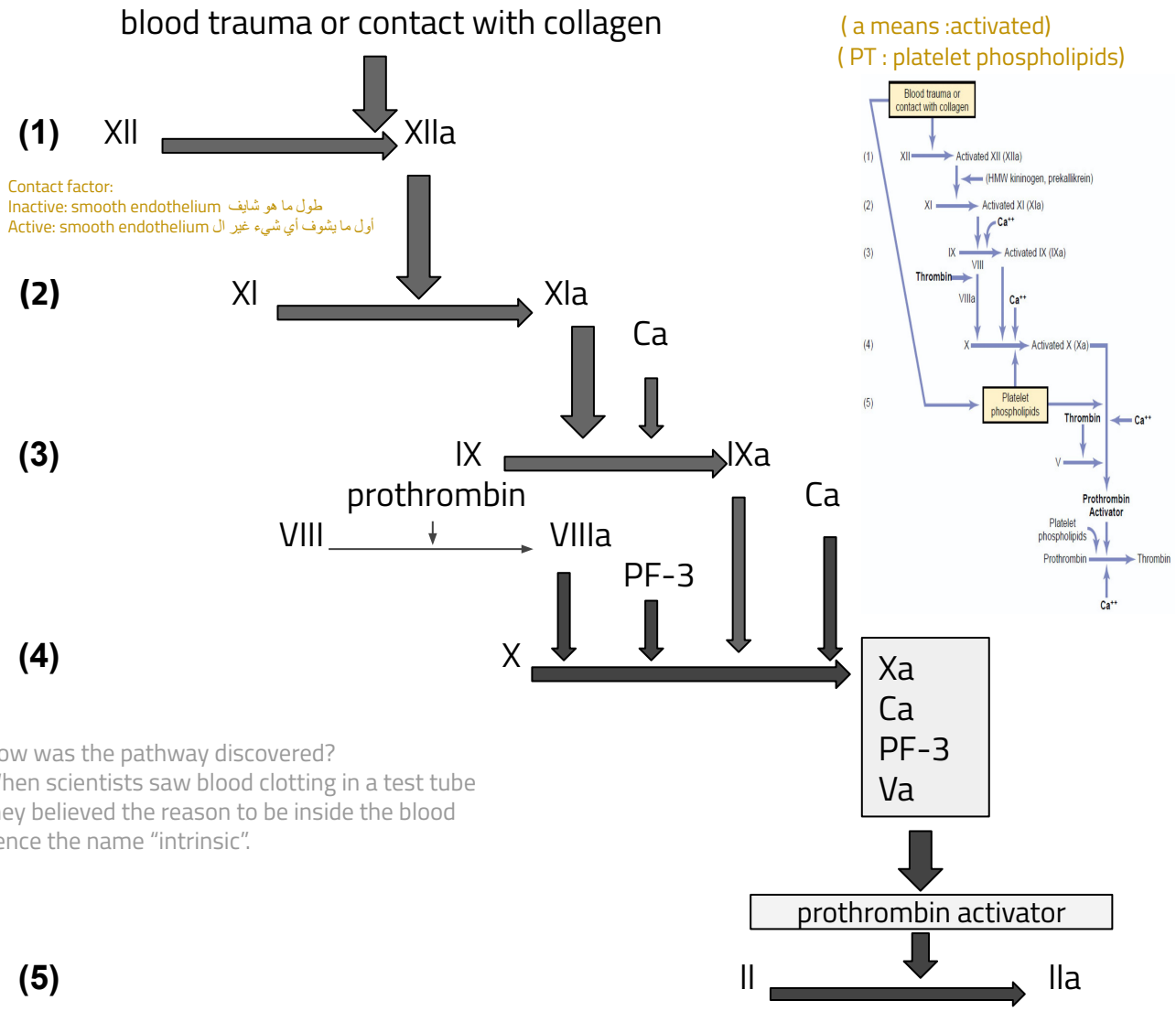
Coagulation Cascade: Classical model



Intrinsic pathway

كل ال factors اللي محتاجها جوا الدم

- The trigger is the activation of factor XII by trauma to the blood itself or by contact with collagen (from a traumatized blood vessel wall),foreign surface and glass.
- Activated factor XII will activate factor XI.
- Activated factor XI will activate factor IX.
- Activated factor IX + factor VIII + platelet phospholipid factor 3 + Ca ions (prothrombin activator complex) will activate factor X.
- following this step the pathway is common for both intrinsic and extrinsic.
- All clotting factor present in the blood.
- Blocked by Heparin
- If you take a blood sample from a patient and put it in a test tube. By which pathway is it going to clot? Intrinsic pathway
- In Vitro, the intrinsic pathway is initiated when fresh whole blood is placed in a glass tube. The negative charge of the glass initiates the 'Contract Pathway' where FXII is activated and then FXIa cleaves FIX to FIXa. The extrinsic pathway is triggered when tissue factor, phospholipid, and calcium are added to plasma anti coagulated with citrate. In vitro, FVII is activated and TF-FVIIa preferentially converts FX to FXa activated the common pathway. Taken from ppt notes



How was the pathway discovered?
When scientists saw blood clotting in a test tube they believed the reason to be inside the blood hence the name "intrinsic".

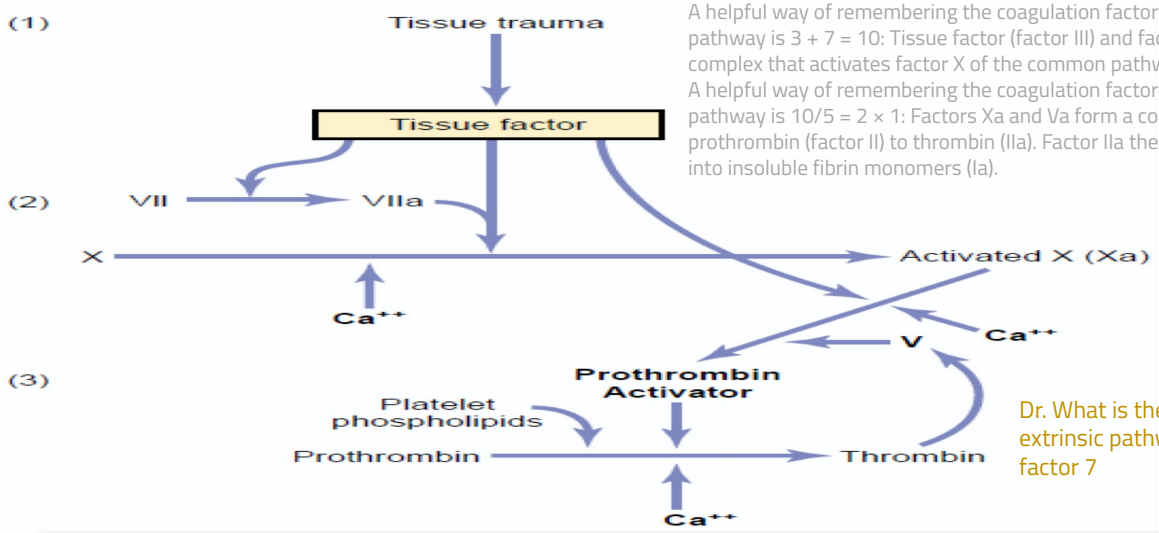
- Activated Partial Thromboplastin Time (APTT or PTT) is a test used to check the activity of the intrinsic pathways (Used to monitor the dose of heparin)
- Prothrombin Time (PT) is a test used to check the activity of the extrinsic pathways (Used to monitor the dose of Warfarin)

extrinsic pathway

واحد نحتاجه برا الدم جاي من لل tissue factors

- Triggered by factor released from damaged tissues (tissue thromboplastin - TF)
- Tissue thromboplastin + VII + Ca ⟶ activate X
- TF includes phospholipids from the membrane of the tissue plus a lipoprotein complex that functions mainly as proteolytic enzyme.
- Faster due to fewer steps
- **Extrinsic pathway is blocked by Warfarin**

How was the pathway discovered?
In an experiment, They added anti coagulants to the blood in the test tube and then added a tissue sample which made the blood clot.
So, the other pathway was named "extrinsic or **Tissue factor** pathway"



A helpful way of remembering the coagulation factors of the extrinsic pathway is 3 + 7 = 10: Tissue factor (factor III) and factor VII form a complex that activates factor X of the common pathway.
A helpful way of remembering the coagulation factors of the common pathway is 10/5 = 2 × 1: Factors Xa and Va form a complex that cleaves prothrombin (factor II) to thrombin (IIa). Factor IIa then cleaves fibrinogen (I) into insoluble fibrin monomers (Ia).

Dr. What is the first step in the extrinsic pathway? activation of factor 7

Common pathway only in girls slides

- Activated factor X + factor V + PF-3 +Ca will activate prothrombin activator (proteolytic enzyme) which activates prothrombin .
- Activated prothrombin activates thrombin.
- Thrombin acts on fibrinogen and change it into fibrin monomers (soluble + unstable and weak).
- Factor Xlll + Ca ⟶ stonge fibrin multimers (strong clot).

Cell based model only in girls slides

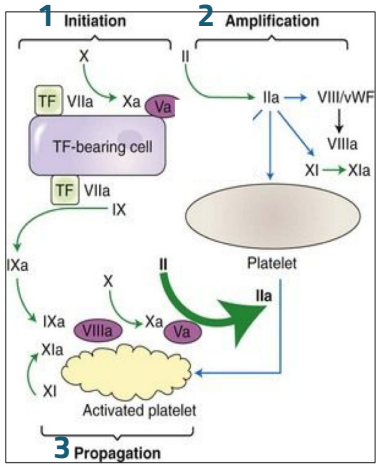
#438 Teamwork

معناها ان العملية هذه تحصل على سطح الخلايا الموجودة بالدم واللي هي platelets and endothelial cells

- Damaged tissues express tissue factor on their surfaces, tissue factor acts as a receptor and an activator for factor VII, together they form a complex that activates factor X (much like the extrinsic pathway), and a non-specific activation of small amounts of factor IX. Activated factor X is expressed on the cell surface where it attracts factor V, together they activate small amounts of thrombin, this concludes **the initiation phase.**

- Thrombin then acts on platelets causing their activation, activated platelets release chemotactic factors attracting other coagulation factors that attach to the cell's surface, like factor VIII and factor XI, these factors were shown to be activated by the released thrombin. Activated factor VIII combines with factor IX from the initiation phase, and they activate larger amount of thrombin, this concludes **the amplification phase.**

- Thrombin activates more platelets, and attracts more coagulation factors and the process of the previous stage is repeated, this is the **propagation phase.**



Clot retraction

- when clot retract (contract) it expresses most of the fluid from the clot within 20-60 min called ⟶ serum
- serum cannot clot
- Role of platelet in clot formation and retraction they are contractile.
- Fate of clot : lysis or fibrous tissue formation.

Fibrinolysis

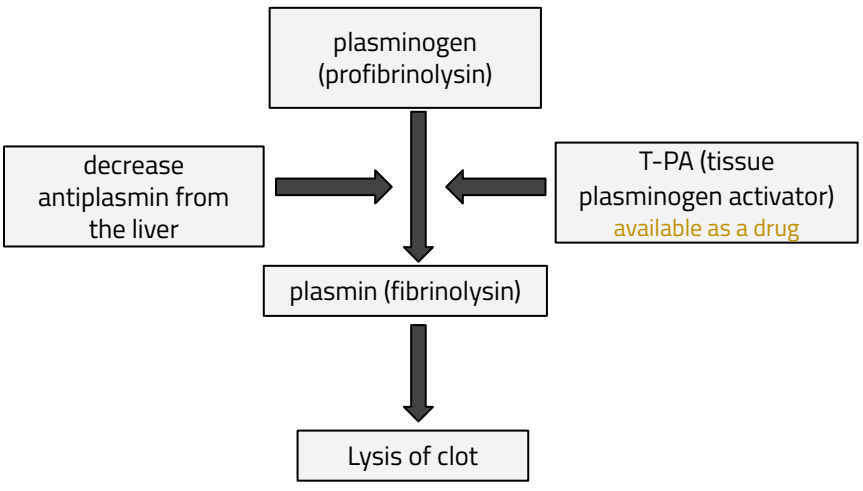
- Formed blood clot can either become fibrous (if it's too large) or dissolved by Fibrinolysis.
- Fibrinolysis (dissolving) breakdown of fibrin by naturally occurring enzyme plasmin (Key enzyme of Fibrinolysis) therefore prevent intravascular blocking.
- There is balance between clotting and fibrinolysis :
  -Excess clotting ⟶ blocking of blood vessels.
  -Excess fibrinolysis ⟶ tendency for bleeding.

Plasmin

- It present in the blood in an inactive form (plasminogen)
- It is activated by tissue plasminogen activators (T-PA) in blood.(1)
- Digest intra and extra vascular deposit of fibrin⟶ fibrin degradation products (FDP).
- Unwanted effect of plasmin is the digestion of clotting factors.
- It is controlled by:

1) tissue plasminogen activator inhibitor (TPAI).
2) Antiplasmin from the liver.

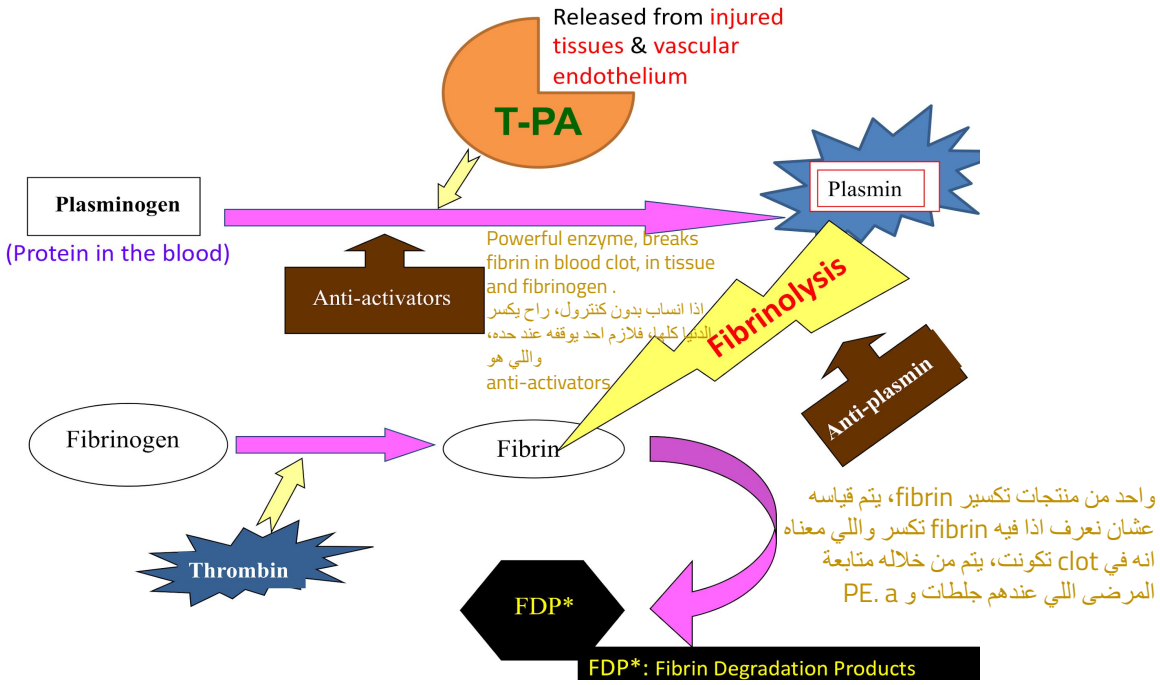
- Tissue plasminogen activator is used to activate plasminogen to dissolve coronary/cerebral clots.



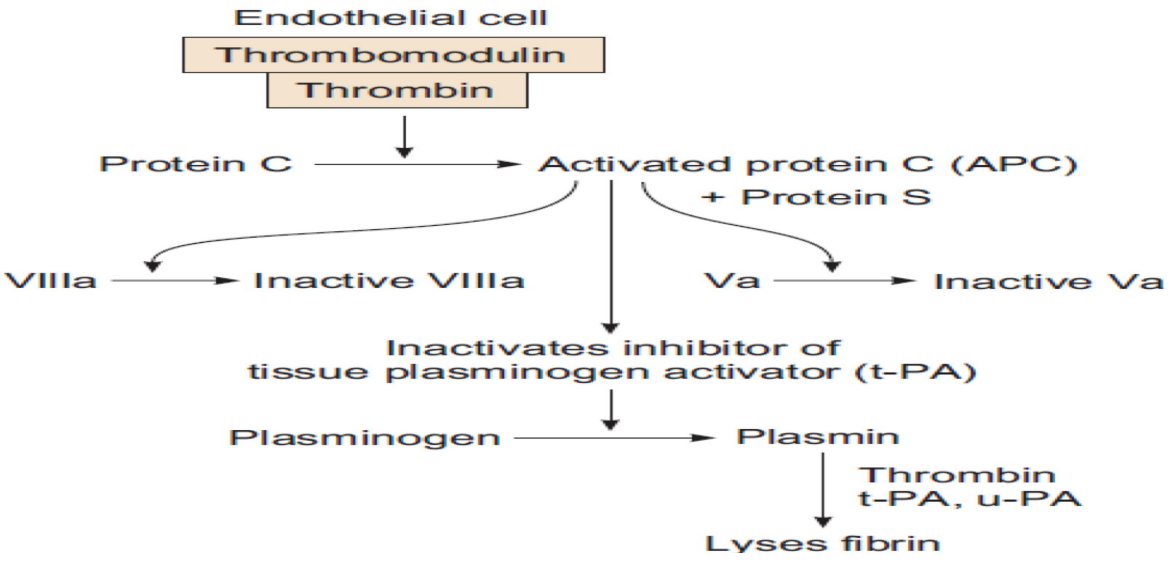
(1): t-PA team:

هو تيم مسؤول عن تحديد اذا المريض اللي جاي ال ER يشتكي من اعراض (coronary heart disease/ M - cerebral thrombus) هل حصلت ال thrombus خلال ثلاث ساعات اللي فاتت ؟
اذا خلال الثلاث ساعات اللي فاتت يعطونه t-PA واللي بدوره يحول plasminogen الى plasmin ويروح يكسر التجلط بدون damage of the brain or heart.
لكن لو عدت الثلاث ساعات ما يقدرون يعطونه t-PA ، ليه ؟
بدل ما يموت بالجلطة راح يموت من النزيف لان plasmin راح يكسر fibrin بكل مكان.
لذلك فريق t-PA مسؤول عن تحديد هل مرت ثلاث ساعات على الجلطة او أكثر؟ هل نعطيه t-PA او لا ؟

Cont. Fibrinolysis



The fibrinolytic system and its regulation by protein C only in boys slides



Prevention of Blood Clotting and Anticoagulants

Endothelial Surface Factors

- Smoothness of the endothelial cell surface (ECS)
- Glycocalyx layer
- Thrombomodulin protein
- 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

Fibrin Fibers

- Adsorbs ~90% of thrombin to removes it from circulating blood.
- Alpha2 – Macrogobulin
- Synthesized mainly in liver and acts as a binding agent for several coagulation factors and inhibits thrombin

Antithrombin action of Fibrin and Antithrombin III

- Antithrombin III is a circulating protease blocking clot factors
- 85-90% Thrombin binds with Fibrin
- 10-15% Thrombin binds with Antithrombin III
- Removes the remaining thrombin from blood

Heparin

Increase the effectiveness of Of antithrombin III

- Combines with **Antithrombin** (anticoagulant) **III increasing its effectiveness** & quickly removes thrombin from blood (endothelial cells Liver, lungs, mast cells, basophils)
- A negatively charged conjugated polysaccharide
- Produced by:Mast cells, Basophil cells
- Most widely used anticoagulant clinically e.g.in stroke
  - Found naturally in the blood
  - Can be given I.V or subcutaneous but not orally because it will be digested.

Natural anticoagulant Proteins *

Protein C:

- Activate protein c (APC) degrades factors Va & VIIIa.
- Activated protein C also indirectly promotes fibrinolysis.

Protein S :Is a cofactor for protein C.

Only in boys slides

ANTICOAGULANTS

Used in vivo

Parenteral

Heparin → Combines with antithrombin III and ↑ its effectiveness by 100-1000 fold, Also remove Factors XII, XI, X, and IX (Monitored by PTT time) → CANNOT BE TAKEN ORALLY

Oral

Warfarin: decrease production of Vit K dependent clotting factors (II, VII, IX and X) by liver (Monitored by PT time) →
IS ALWAYS TAKEN ORALLY

Used in vitro

No Ca++ → no Clotting (needed in many steps).
- Citrate ions → Deionization of Ca++
- Oxalate ions → Precipitate the Ca++
- Ethylenediaminetetraacetic acid (EDTA) → chelates (binds) calcium ions
- Heparin → Binds to AT III

Conditions that cause excessive Bleeding

1- Vitamin K Deficiency

- vitamin K Required for synthesis of prothrombin, factor VII factor IX, and factor X.
- It leads to:decreased formation of clotting factors, increased clotting time
- Fat soluble vitamin
- Sources:Diet,Synthesized in the intestinal tract by bacteria.
- Deficiency is rare but maybe seen in: Hepatitis, Cirrhosis,Malabsorption syndromes,Biliary obstruction,Broad spectrum antibiotics.Dietary def (Neonates) and GIT disease.

2- Hemophilia

- ↑ Bleeding tendency.
- X-linked disease, Genetic disorders.
- Hem A & B are inherited in X linked recessive pattern.
- Occurs exclusively in males Females are carriers.
- Hem C is autosomal recessive.
- VWD autosomal dominant.
- **Types**:
- **1.** Hemophilia A (Classic Hemophilia) due to deficiency of factor VIII small component(85%).
- **2.** Hemophilia B (Christmas disease) due to factor IX deficiency(15%) .
- **3.** Hemophilia C (Rosenthal syndrome) due to factor XI deficiency and it affects both sexes.
  - Small Comp. → Hemophilia A ►↑PTT
  - Large Comp. → Von-Willebrand's disease ►↑PTT & BT
- Clinical Features: Easy bruising, massive bleeding after trauma or operation, hemorrhages in joints

3- Thrombocytopenia نقص عدد ال platelets

- Very low number of platelets in blood (<50,000/µl and < 10,000 is fatal)
- Idiopathic thrombocytopenia: unknown cause.
- Thrombocytopenia purpura: hemorrhages throughout all the body tissues.
- **Etiology:**
  1. Decreased production such as Aplastic anemia, Leukemia, Drugs, Infections (HIV,Measles).
  2. Increased destruction such as Immune Thrombocytopenia purpura, Drugs, Infections (HIV)
- **Clinical features include:**Easy bruising, epistaxis,gum bleeding, hemorrhage after minor trauma, petechiae/Ecchymosis.
- **Diagnosis:**
  1. PLT count decreased. 2. Bleeding time increased.
- **Treatment:** Treatment of the underlying cause,Platelets concentrates,Fresh whole blood Transfusion,Splenectomy.
- **Pseudothrombocytopenia:**
  1- Partial clotting of specimen 2- EDTA-platelet clumping 3-Platelet satellitism around WBCs 4-Cold agglutinins 5-Giant platelets

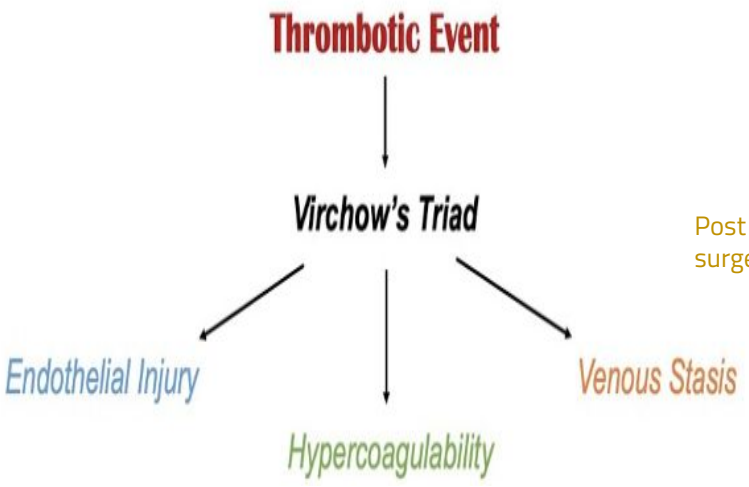
4- Hypercoagulability

- Increased risk of thromboembolism.
- **Causes:**
  1- Primary (genetic):
  (Thrombophilia)
  2- Secondary (acquired): for example nephrotic syndrome

Congenital factors | **Acquired factors**

Congenital factors
- Resistance to activated protein C (Leiden Factor V)
- Mutation of the prothrombin gene (G20210A)
- Protein C deficit
- Protein S deficit
- Antithrombin III deficit
- Factor VIII increase (>1500 UI)
- Heparin Cofactor II deficiency
- Disfibrogenemia
- Plasminogen congenital deficiency
- Thrombomodulin mutation
- Sticky platelet syndrome
- Sickle cell anemia

Acquired factors
- Hepatic or endothelial pathology
- Vitamin C deficit
- Oral contraceptives
- Alcohol
- Tobacco
- Special situations:
  - Menopause
  - Pregnancy
  - Immobilization
  - Surgery
  - Traumatisms
- Diseases:
  - Cancer, myeloproliferative diseases
  - PTT
  - Disseminated intravascular coagulation
  - Sepsis
  - Hyperhomocysteinemia
  - Anti phospholipid antibody syndrome



Post operative: specially in orthopedic surgery > لانه ما يقدر يتحرك

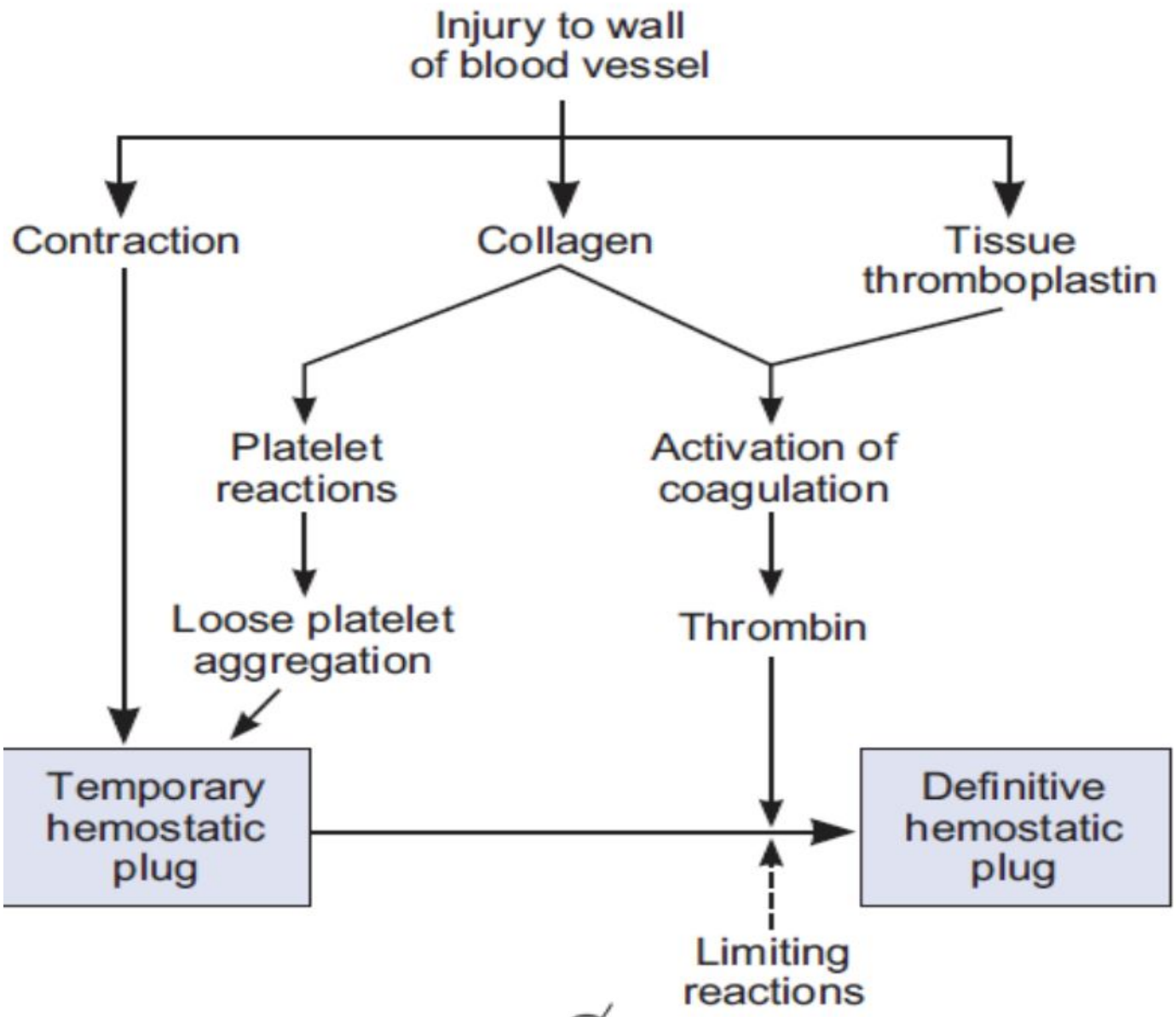
Screening tests

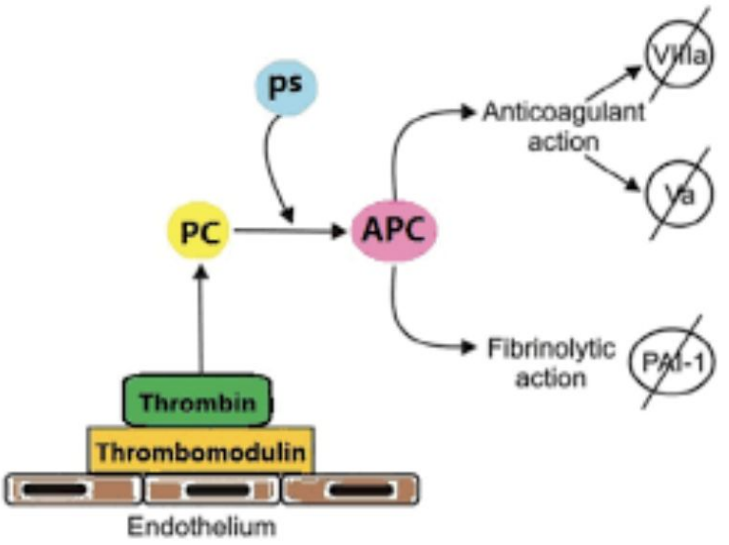
	Mechanism Tested	Normal Value	Disorder
Prothrombin time (PT)	Extrinsic and common pathway	<12s beyond neonate, 12-18s in-term neonate	Liver disease, defect in vitamin K-dependent factors, disseminated intravascular coagulation (DIC)
Activated partial thromboplastin time (aPTT)	Intrinsic and common pathway	25-40s beyond neonate, 70s in-term neonate	DIC, von Willebrand disease, hemophilia
Platelet count	Platelet number	150000-450000 cells per millimeter cubed	Thrombocytopenia
Bleeding time (BT)	Hemostasis, capillary and platelet function	3-7 minutes beyond neonate	Thrombocytopenia, von Willebrand disease

Hemostasis in hereditary coagulation disorders

	Hemophilia A	Hemophilia B	vW disease
Bleeding time (BT)	Normal	Normal	Prolonged
Prothrombin time (PT)	Normal	Normal	Normal
Activated partial thromboplastin time (aPTT)	Prolonged	Prolonged	Prolonged
Factor VIII	Low	Normal	Low or normal
Factor IX	Normal	Low	Normal
vW Factor	Normal	Normal	Low

Summary of reactions involved in hemostasis.





MCQ & SAQ:

Q1: Which of the following minerals found naturally in the body plays an essential role in the coagulation cascade?

A. Gold
B. Aluminum
C. Magnesium
D. Calcium

Q2: What is the function of factor VIIa in the coagulation cascade?

A. Activation of factor X
B. Fibrin stabilization
C. conversion of prothrombin to thrombin
D. Activation of factor VII

Q3: Which of the following coagulation factors is vitamin K dependent ?

A. Plasma thromboplastin antecedent
B. Prothrombin
C. Thromboplastin
D. Proaccelerin

Q4: If you take a blood sample from a patient and put it in a test tube. By which pathway is it going to clot?

A. Intrinsic pathway.
B. Extrinsic pathway
C. -
D.-

Q5: What is the first step in the extrinsic pathway?

A. Activation of factor 7
B. Activation of factor 5
C. The release of tissue thromboplastin
D. Conversion of prekallikrein to kallikrein

Q6: The most common cause for hemophilia is an X- linked deficiency encoding which of the following factors?

A. Factor IV
B. Antihemophilic Factor B
C. Factor VIII
D. Factor III

answer key:
1: D
2: A
3: B
4: A
5: A
6: C

1- What are the main 4 actions of thrombin ?

2- Name two factors that are activated by thrombin

3- Name three physiological anticoagulants

4- List three conditions that can cause excessive bleeding

A1: 1- Thrombin stimulates conversion of fibrinogen to fibrin 2- Activation of Factor 13 3- Enhances its own activation (Positive feedback) 4- Causes platelet aggregation

A2: Factor V and XIII

A3: Heparin, protein C and and antithrombin III

A4: Vitamin K deficiency, thrombocytopenia and haemophilia

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