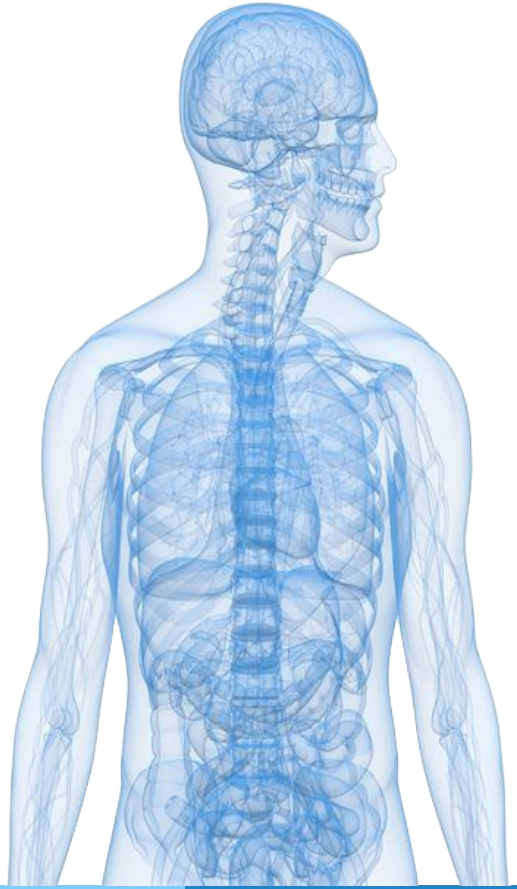

Hemostasis

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Red: Important
Black: In Male & Female slides
Blue: In male slides
Pink: In female slides
Green: Notes & extra information

Objectives

- Define hemostasis and enumerate steps of hemostasis.
- Discuss the platelet functions in hemostasis and the formation of the temporary hemostatic plug.
- Enumerate the different factors involved in the different steps of platelet reaction in Hemostatic.
- Recognize the different clotting factors and discuss the mechanism of blood clotting.
- Describe the clotting cascade and know the differences between the extrinsic and intrinsic pathways of blood clotting.
- Enumerate and describe the different limiting reactions and anticlotting mechanisms.
- Discuss the fibrinolytic system and function of plasmin
- Enumerate the different abnormalities for hemostasis and the tests commonly used to diagnose them.
- Describe formation and development of platelet
- Recognize the role of thrombin in coagulation.

Hemostasis

Definition: the spontaneous arrest of bleeding from ruptured blood vessels.
prevention of blood loss after injury. (Hemo=Blood, Stasis=stop)

Mechanisms of hemostasis:

1. **Constriction** of the blood vessel (vessel wall)
2. **Formation** of temporary hemostatic plug (Platelets)
3. **Conversion** of the temporary platelet plug into a definitive clot by fibrin threads produced by the process of blood coagulation.
4. **Limiting reactions**: Clotting is prevented over the normal endothelium (Fibrinoltic system).

((Clot is dissolved to resume normal blood flow after tissue repair))

1-vessel wall:

Vasoconstriction Immediately after injury localized.

Vasoconstriction mechanism:	Systemic release of adrenaline	Nervous factors	Local release of thromboxane A2 & 5HT by platelets

-Platelets:

Definition of platelet

(Thrombocytes) fragment of megakaryocytes. Small disc shaped granulated, Non nucleated structures.

Characteristic

Small disc shape—(150,300)x10^3 /ml— Life span 8-10 days — contain high Ca&ADP — Active cells contain contractile protein (actin & myosin)

Regulation

By Thrombopoietin. (secreted by kidney and liver)

Site of formation

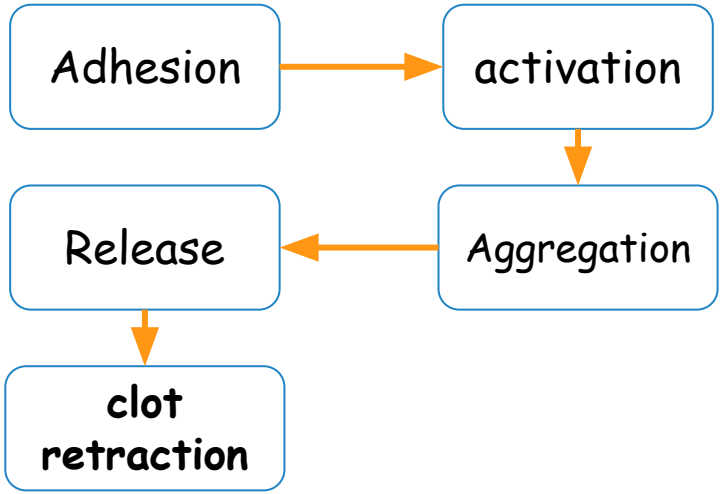
Formed in the bone marrow.

Steps of formation of platelets → Stem cell → megakaryoblast → megakaryocyte → platelets

2 - Formation of Temporary Hemostatic Plug:

- platelets form a mechanical plug to seal the vascular injury.
- If the cut in the vessel is small, the platelet plug by itself (can stop blood loss completely), but if the cut is large, a blood clot in addition is required to stop bleeding.

-Platelet reactions in hemostasis:

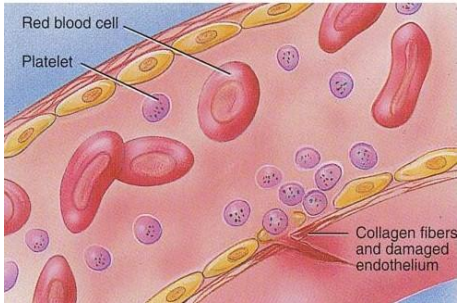


A- Platelet Adhesion:

- Exposed collagen attracts platelets, Platelets stick (adhere) to exposed collagen underlying damaged endothelial cells (sub-endothelial tissues and Von-Willebrand factor) in vessel wall Through the action of some receptors.

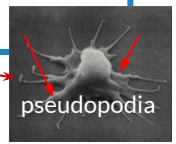
- Platelets do not adhere to the normal vascular endothelium under the normal physiological conditions.

- Platelets are activated by adhesion.
- Activated platelets will extend projections to make contact with each other.



B-Platelets activation:

Platelets activated by Adhesion → They extend projections (pseudopodia) to make contact with each other. → They release thromboxane A2 (TXA2), serotonin & ADP. → **Leading to** → Activation of other platelets.



Serotonin & thromboxane A2 (TXA2) are vasoconstrictors. They decrease blood flow through the injured vessel. While ADP causes stickiness

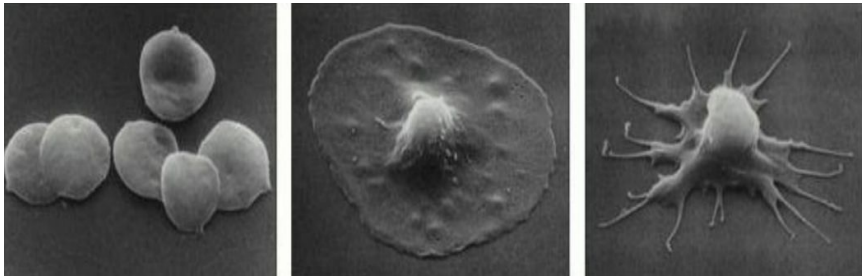
-when platelets are activated they:
1-swell
2-change shape
3-create pseudopodia.

Was only found in girl's slides

Activated Platelets Secrete:

- **5HT** which causes vasoconstriction.
- **ADP** (causes stickiness)
- **Platelet phospholipid** (PF3) which causes clot formation.
- **Thromboxane A2** (TXA2) is a prostaglandin formed from arachidonic acid.
  Functions:
  - vasoconstriction.
  - Platelet aggregation

  (TXA2 is inhibited by aspirin).



Helpful video

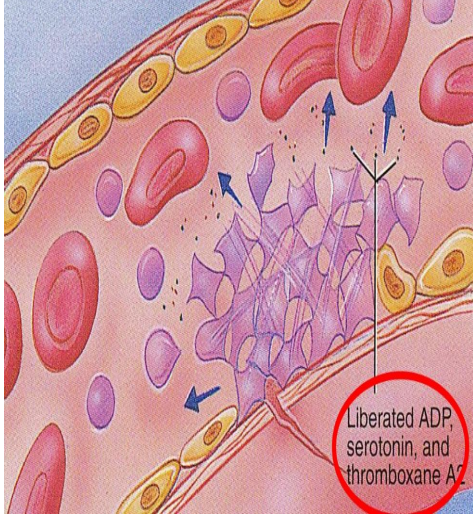
C-Release Reaction:

Activated platelets release Serotonin, ADP & Thromboxane A2 (TXA2)

↑ The stickiness of platelets

↑ Platelets aggregation

↑ plugging of the cut vessel

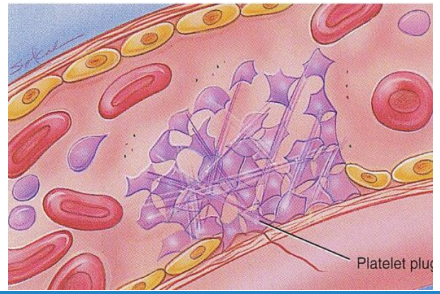


*Platelets release TXA2 to increase the platelet aggregation and thrombus formation over the injured site,
*normal vascular endothelium releases Prostacyclin (PGI2) and Nitric oxide (NO) to prevents platelets aggregation over the normal site of the blood vessel.

TXA2 Is one of the most powerful vasoconstrictors

D-Platelets aggregation:

- **Activated platelets stick together** and activate new platelets to form a mass called platelet plug.
- The plug is **reinforced by fibrin threads** formed during clotting process.



E-Clot Retraction:

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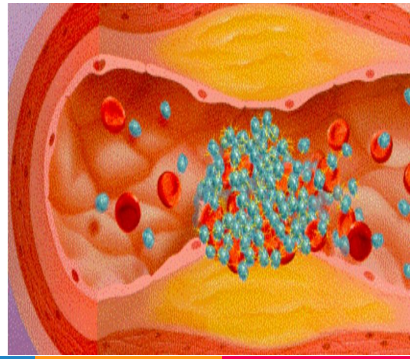
- Myosin and actin filaments in platelets are stimulated to contract during aggregation further reinforcing the plug and help release granule contents



Clinical correlation

This slide was only found in boy's slides

Acetylsalicylic acid (Aspirin) prevents platelet activity by inhibiting TXA2 which is used as a prophylaxis* against thrombus formation.

*Prophylaxis: action taken to prevent disease.

Platelets reactions in Hemostasis:

Steps	Substances involved	Process
Platelet adhesion	- Subendothelial collagen - Von Willebrand factor.	Occurs to the subendothelial tissue
Platelet activation	- ADP - Thrombin	Platelets enlarge and forms pseudopodia.
Release reaction	- Calcium ions	Calcium dependent process
Platelet aggregation	- ADP - Thromboxane A2 (TXA2) - Fibrinogen	This process is inhibited by Aspirin which inhibits the formation of TXA2.
Platelet fusion	- ADP	Irreversible process
Clot retraction	Actin and myosin contract to strengthen the plug.	Causes stabilization of the formed blood clot.

Blood Coagulation Factors

*Factor 6 is present but it's not mentioned due to its unimportance

Factors 2, 4 and 10 are extremely essential for the clotting process

Coagulation = Clotting
No difference, just another word

Fibrinogen is factor I and Thrombin converts it to Fibrin which will be called Factor Ia (When a factor is activated we add the letter a)

Why are these factors normally inactive?
Well, imagine that they are all activated. Fibrin will circulate in your blood and will form fibers in the blood vessels without any purpose. Thrombin will activate many factors constantly and will draw more platelets and that's where the problem is. Platelets won't find anything to clot hence they are normally inactive until we start bleeding

★ What you need to memorize

Clotting Factor Number	Clotting Factor Name	Extra information
★ I (1)	Fibrinogen	Made in the liver, fibrinogen in plasma is converted to fibrin by Thrombin
★ II (2)	Prothrombin	Converted into Thrombin (Activates factors I,V,VIII &XIII)
III (3)	Thromboplastin (Tissue Factor)	Released by dead tissues
IV (4)	Calcium (Ca)	Essential factor (That's why blood banks use binding agent to bind calcium to your blood so that it doesn't clot in the bag)
V (5)	Proaccelerin (Labile Factor)	-
VII (7)	Proconvertin (Stable Factor)	-
★ VIII (8)	Antihemophilic globulin	Assists in the conversion of prothrombin to thrombin
★ IX (9)	Christmas Factor	Named after a guy called Christmas :)
★ X (10)	Stuart-Power Factor	The common pathway in cascades (will be discussed in the next slide)
XI (11)	Plasma Thromboplastin Antecedent	It is a Serine protease (protein)
XII (12)	Hageman Factor	HMW-K & Ka dependent
★ XIII (13)	Fibrin Stabilizing Factor	Crosslinks fibrin and stabilize it
HMW-K	High Molecular Weight Kininogen	-
Pre-K	Pre-Kallikrein	-
Ka	Kallikrein	-
PL	Platelet Phospholipids	-

3-Coagulation cascade

I recommend seeing the table made in the next slide before studying this slide

A really helpful video

Extrinsic Pathway

III → IIIa (3)

VII → VIIa (7)

Intrinsic Pathway

XII → XIIa

(Positive feedback)

Platelets → XII → XIIa (12)

XI → XIa (11)

IX → IXa (9)

FVIII
PLTs
Ca +

X → Xa(10)

Common pathway

PL, CA & TPL

Fibrin mesh (Network)

VIII → VIIIa(8)

V → Va(5)

XIII → XIIIa(13)

CoFactor

Cofactor

PL & Ca

II → IIa(2) → I → Ia(1)

Legends

- Factor activates a factor
- Factor acting as a cofactor
- Intermediate factors
- Common pathway

- Factor X is the common Factor (two pathways meet at factor X)

in every activation. the inactive factor will become active and we indicate its activity by adding "a"
For example, XII will catalyze XI but before that, XII will be activated and will be called XIIa then will catalyze factor XI to become XIa and so on with the rest of the factors.

- TPL is Thromboplastin, Ca is Calcium and PL is Platelet Phospholipids
- Extrinsic pathway starts first but intrinsic pathway does most of the work

Extrinsic and Intrinsic pathways comparison

This slide was only found in boy's slides

	Extrinsic Pathway	Intrinsic Pathway
Duration	Rapid	Slow
efficiency	Weaker	More extensive, forms more fibrin threads
Starts by	Factor III (3) (also called tissue factor)	Factor XII (12) (contact factor)
Occurs	Only invivo (It's called the tissue factor because it's present in tissues. And Factor 3 starts the extrinsic factor hence it's invivo (in tissues only)	Both invivo and invitro (in tissues and blood)
Tested by	Prothrombin Time	Activated Partial Thromboplastin Time (APTT)

*Both pathways occur simultaneously (at the same time)

Importance of Thrombin in hemostasis

1- **Activates factor I, V, VIII & XIII**

طريقة لحفظها = 1x (5 + 8) = 13

2- **Essential for platelet activation and release reactions**. Which are essential for platelet aggregation

- So inhibition of Thrombin leads to inhibition of blood clotting
- Thrombin is activated from both pathways and is our final factor before activating factor I (Fibrin)

Just to make it clear! Prothrombin (Inactive factor 2) when activated becomes Thrombin (Activated factor 2)

Role of Calcium (Ca++) ions in clotting:

- If there is no calcium then there is no clotting.

- Blood samples are prevented from clotting by adding:

Citrate ions → Deionization of Ca++

Oxalate ions → ppt the Ca++

Role of Thrombin in clotting:

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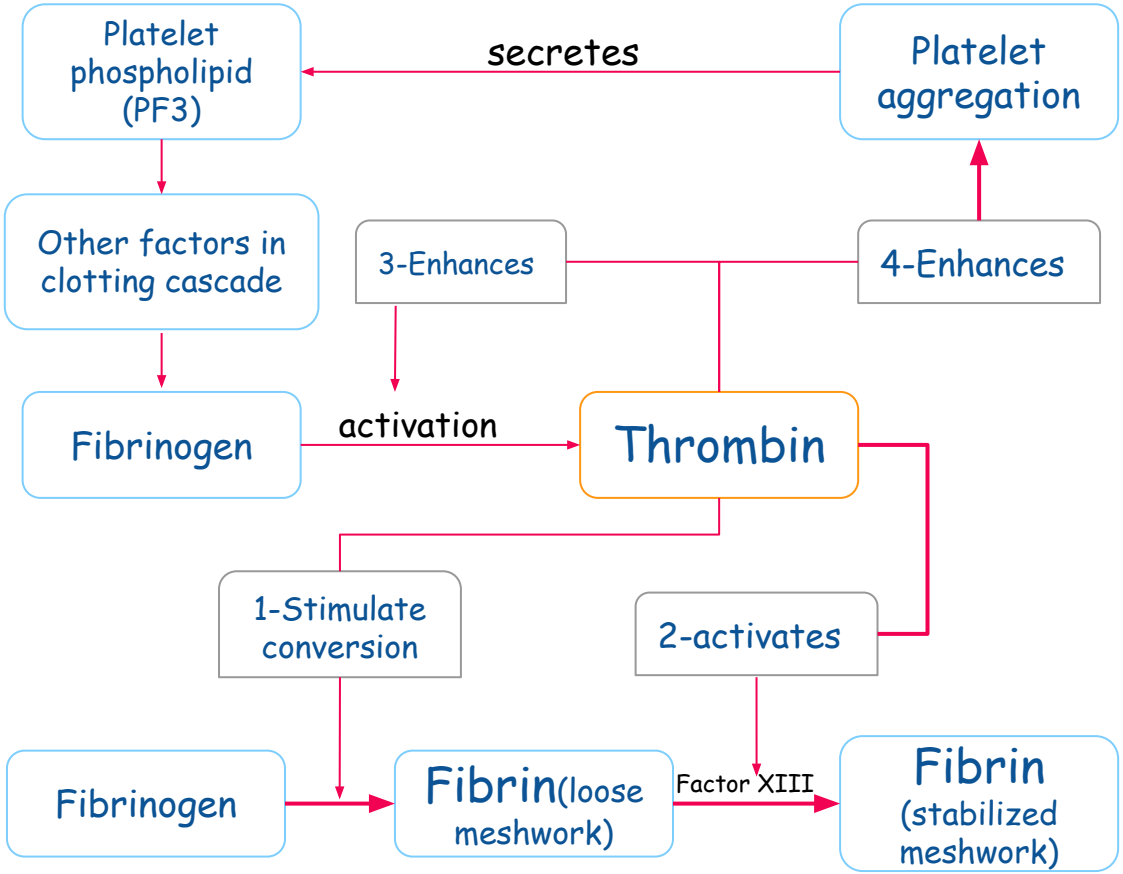
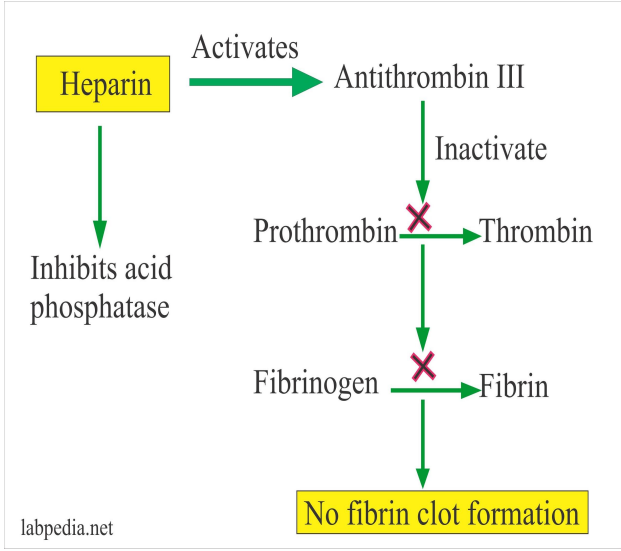


The anticlotting mechanisms (Limiting reactions)



The tendency of blood to clot is balanced invivo by limiting reactions.

Aim:

- prevent clotting inside the blood vessels.
- break down any formed clots after vascular repair.

Mechanisms:

1 - **Smooth vascular endothelium** thus there is no activation of factor XII or platelets.

2 - **Presence of heparin**, which is a naturally occurring anticoagulant (Antithrombin).

3 - The antithrombotic effects of **Prostacyclin and nitric oxide** (NO).

4 – **Protein C** which inhibits factors V & VIII. And activates plasmin.

5 – **Protein S** (cofactor for protein C).

6 – Tissue factor inhibitor (TFI) which inhibits the activation of factor VII (Because factor VII is activated by Factor III (the tissue factor) hence inhibiting factor 3 will inhibit factor 7) " شفتوا الطب بيشتغل ازاي "

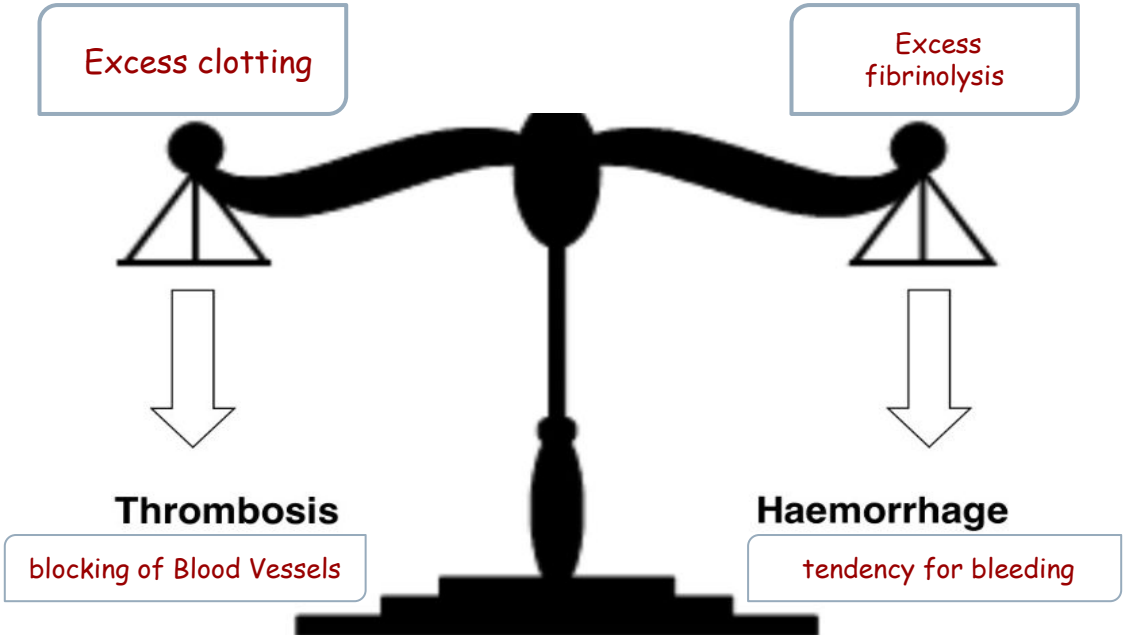
-**7 -** The **fibrinolytic system**

Fibrinolysis

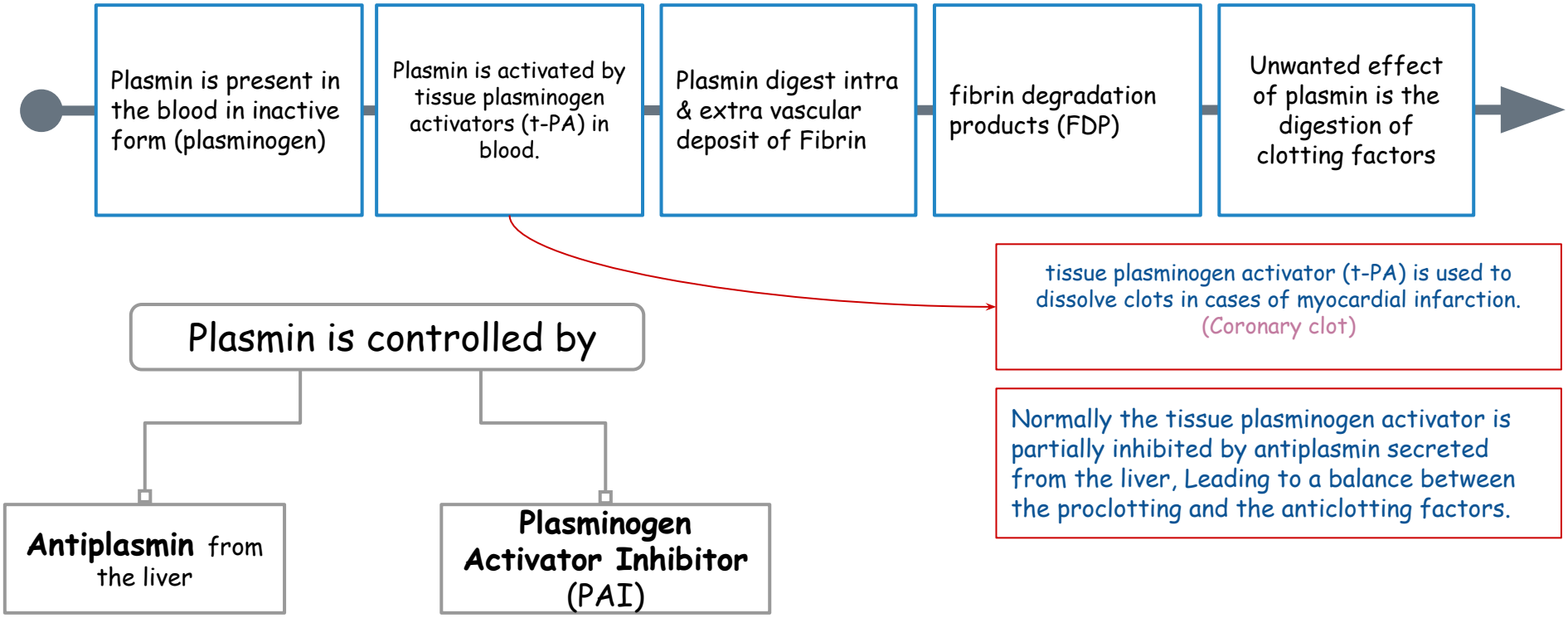
(there is balance between clotting and fibrinolysis)

This slide was only found at girl's slides.

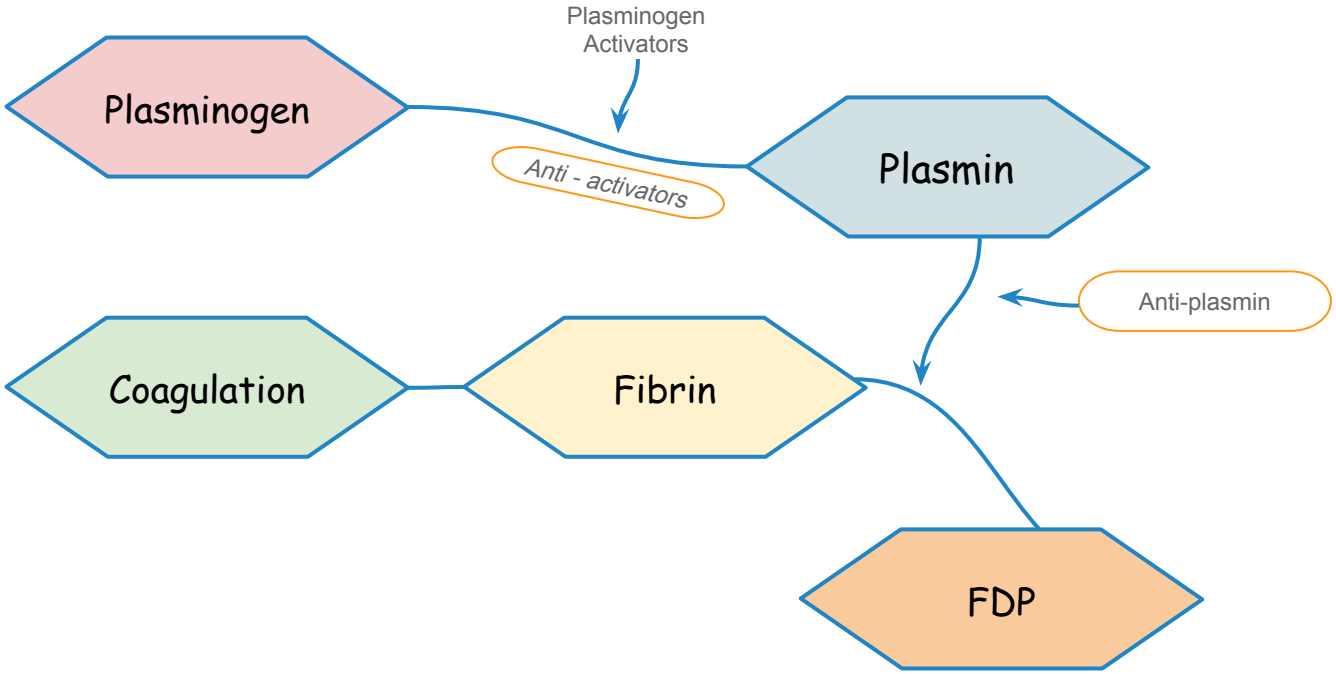
- Formed blood clot can either become fibrous or dissolve.
- Fibrinolysis (dissolving) = Breaking down of fibrin by naturally occurring enzyme plasmin therefore prevent intravascular blocking .



4-Fibrinolytic system



Fibrinolytic system



FDP : Fibrin Degradation Products

Hemostatic function tests

	Test for	Prolonged in
Bleeding time	Platelets function	1-Thrombocytopenia. 2-Thrombocytoasthenia.
Coagulation (clotting time)	Coagulation cascade	All disorders of coagulation (Hemophilia – Vitamin K deficiency).
Prothrombin time (PT)	Extrinsic pathway	Abnormalities of the extrinsic pathway (Vitamin K deficiency).
Activated partial prothrombin time (APTT)	Intrinsic pathway	Abnormalities of the intrinsic pathway (Hemophilia).

Platelets disorders (Purpura)

Cause

- Thrombocyto asthenia
- Thrombocytopenia (deficiency of platelets)
  - PLT count upto 50,000 ul
  - Less than 10,000 --> Fatal

Characterized by

- the presence of many subcutaneous hemorrhages called **petechiae**.
- prolongation of bleeding time.

ETIOLOGY

Decreased production :

- Aplastic anemia
- Leukemia
- Drugs
- Infections (HIV, Measles)

Clinical Features :

- Easy bruisability
- Epistaxis
- Gum bleeding
- Hemorrhage after minor trauma
- Petechiae/Ecchymosis

Diagnosis :

- PLT decreased
- Bleeding Time increased

Rx :

- Rx of the underlying cause
- PLT concentrates
- Fresh whole blood transfusion
- Splenectomy

Clotting (coagulation) disorders

Hemophilia

Congenital disease carried by females (X linked) and manifested almost always in males

characterized by a **tendency for severe bleeding** after mild trauma.

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

It **causes prolongation of the clotting time** & **APTT**.

Hemophilia (A)

is the classic hemophilia which is caused by deficiency of factor VIII and represents 85% of cases of hemophilia.

Hemophilia (B)

is due to absence of factor IX (Christmas factor)
(represents 15%)

Hemophilia (C)

is due to absence of factor XI.

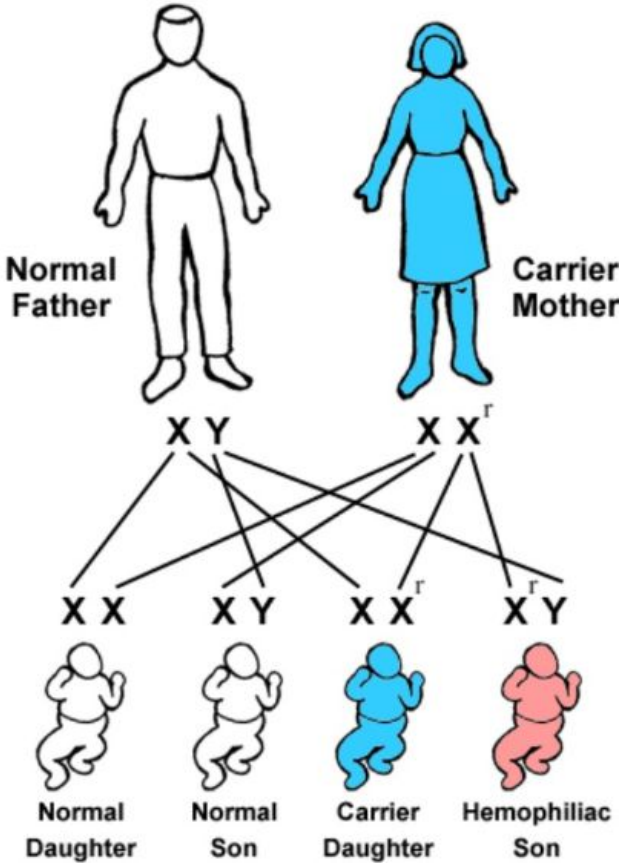
Vitamin K Deficiency

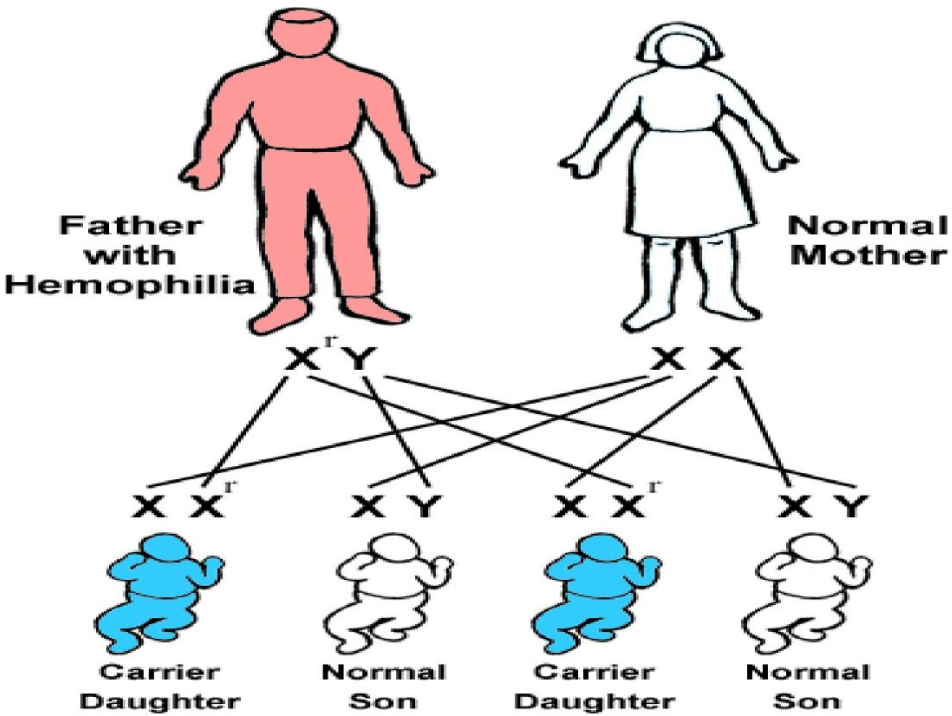
Vitamin K is a fat soluble vitamin synthesized by the intestinal bacterial flora.

It is needed for the formation of factors, II, VII, IX and X by the liver.

Deficiency is associated with **prolongation of the clotting time**.

Inheritance of Hemophilia





QUIZ!

Q-BANK : https://forms.gle/BhJpyn5vneEvqRKM6

MCQs

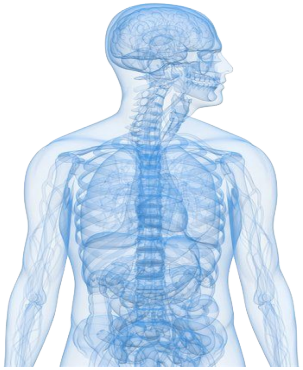
Q1: Hemophilia type (A) represents .....% of cases of hemophilia.			
A) 15%	B) 58	C)85	D) 99
Q2: Platelets are activated by....			
A) Retraction	B) aggregation	C) Adhesion	D) stickiness
Q3: Thrombin activates factors:			
A) I, V ,IX & XI	B) I, X, XI & XIII	C) III, IX, X AND VII	D) I, V, VIII & XIII
Q4 : Platelets stick (adhere) to:			
A)liver	B) sub-endothelial tissues	C) epidermis	D) dermis

SAQ

Q1: If factor VII gets inhibited it will affect the blood clotting, which pathway specifically will be inhibited?

MCQs key answer :
1) C
2) C
3) D
4) B

SAQ answer key :
1) Extrinsic pathway



Thank You

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- حصة العليان
- شذى الظهير
- سمو الزير
- نورة الشثري
- سارة القحطاني
- ريناد الحميدي
- ياسمين القرني
- يارا الزهراني
- لمى الأحمدي
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