
بسم الله الرحمن الرحيم

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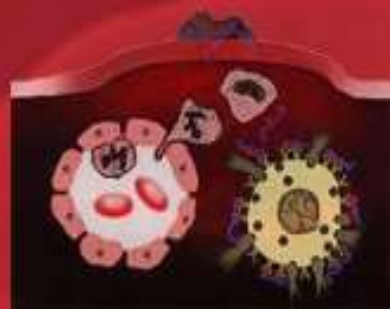
”قالوا سبحانك لا علم لنا إلا ما علمتنا إنك أنت العليم الحكيم“

صدق الله العظيم

6 - Hemostasis



Objectives;

Intended learning outcomes (ILOs)

After reviewing the PowerPoint presentation and the associated learning resources, the student should be able to:

- **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 hemostatis.**
- **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.**
- **Enumerate the different abnormalities for hemostasis and the tests commonly used to diagnose them.**

Def: prevention of blood loss after injury. By:

1 - Constriction of the blood vessel **(VC)**

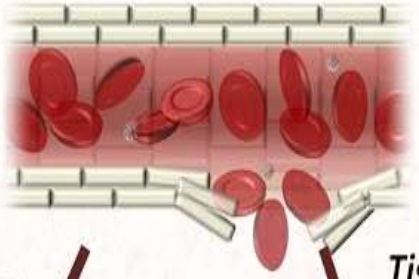
2 - Formation of temporary hemostatic plug **(Platelets)**

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.

Clot is dissolved to resume normal blood flow after tissue repair.

Major Components of Hemostasis



Vascular Injury

Collagen

Tissue factor

Vasoconstriction

Platelet Activation

Coagulation Cascade

Antithrombotic Control Mechanisms

vWF, fibrinogen

Thrombin

Platelet Plug

Fibrinogen → *Fibrin*

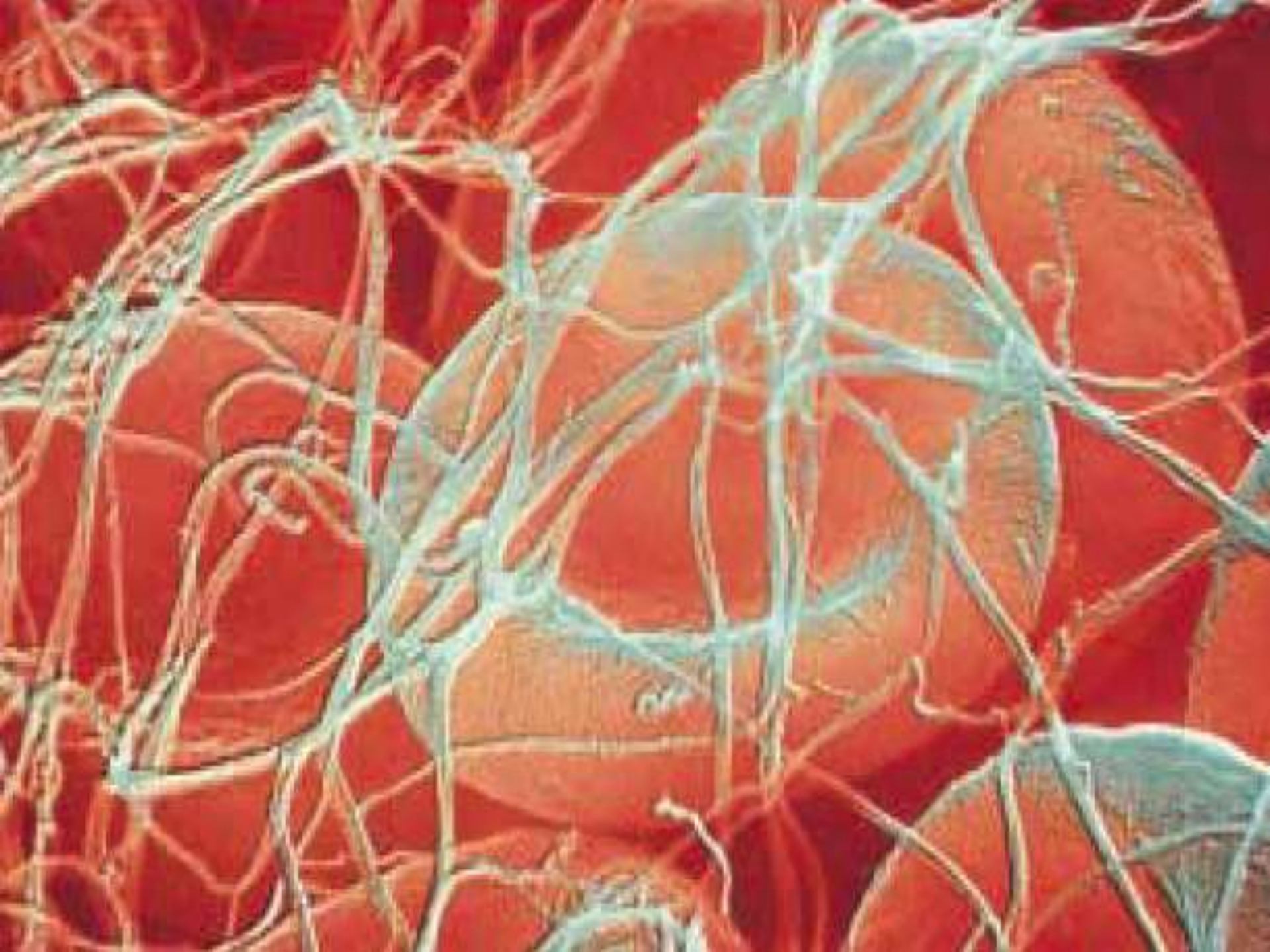
Blood Clot

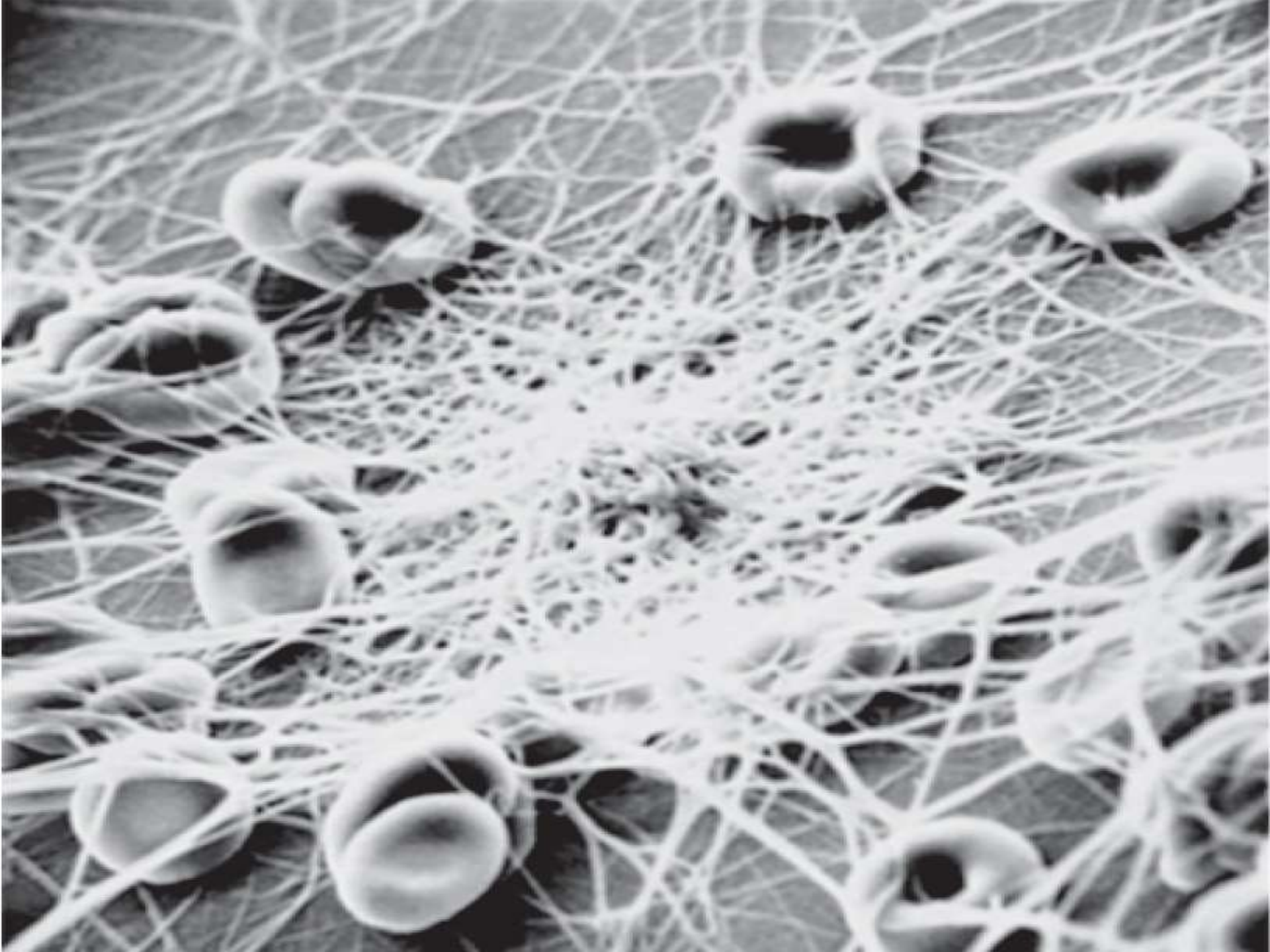
Plasmin

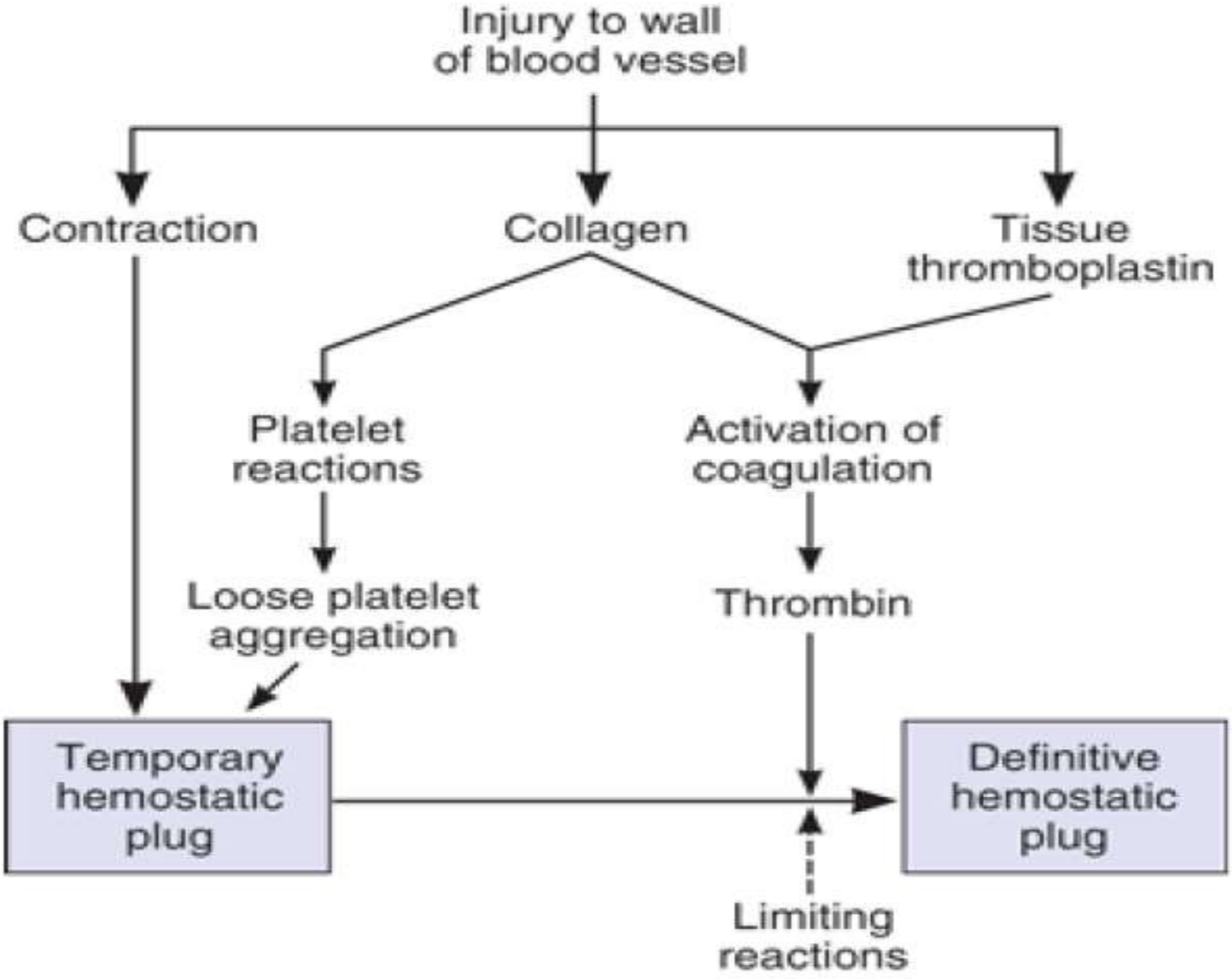
Fibrinolysis & Clot Degradation

Primary Hemostasis

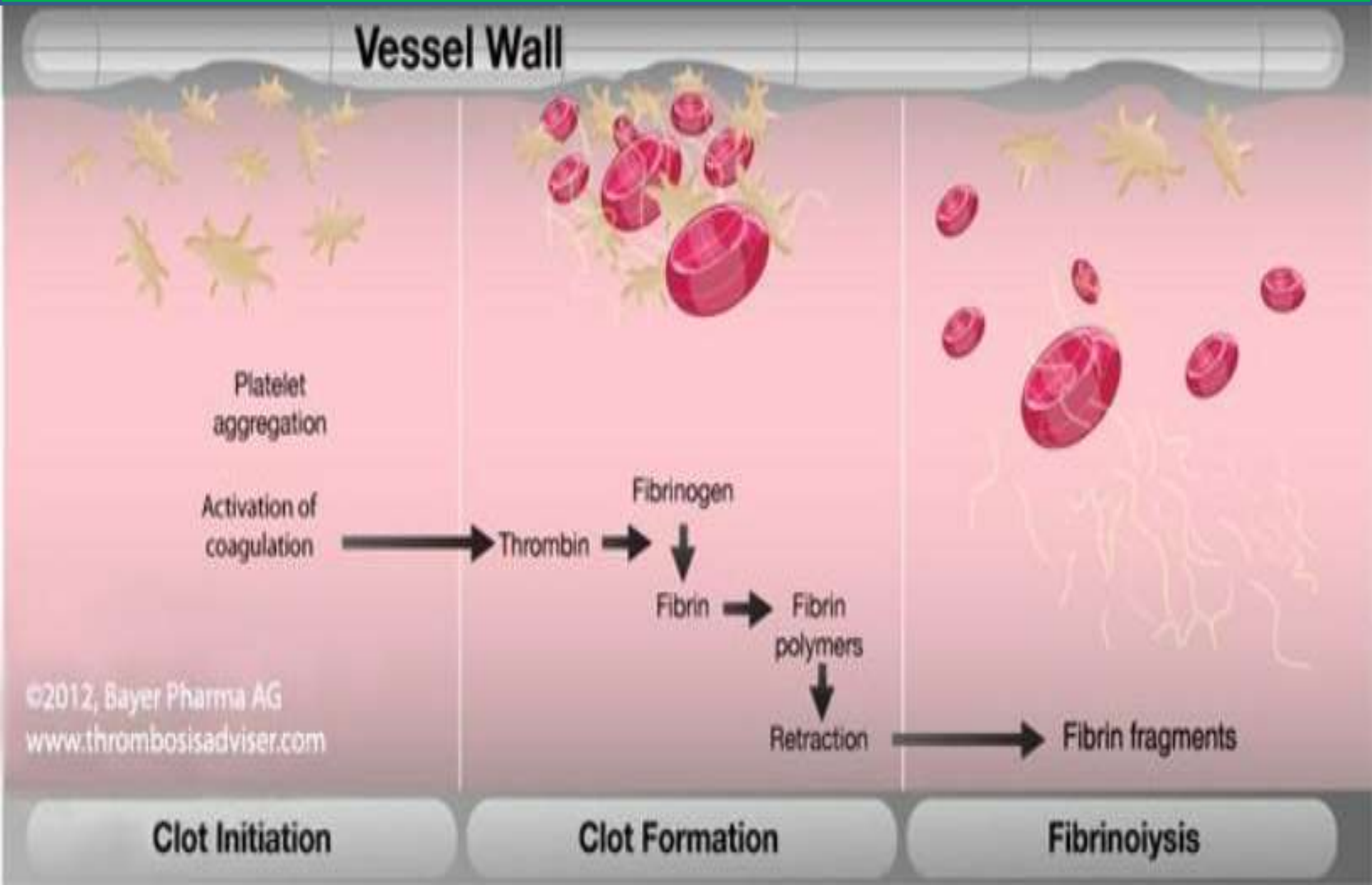
Secondary Hemostasis



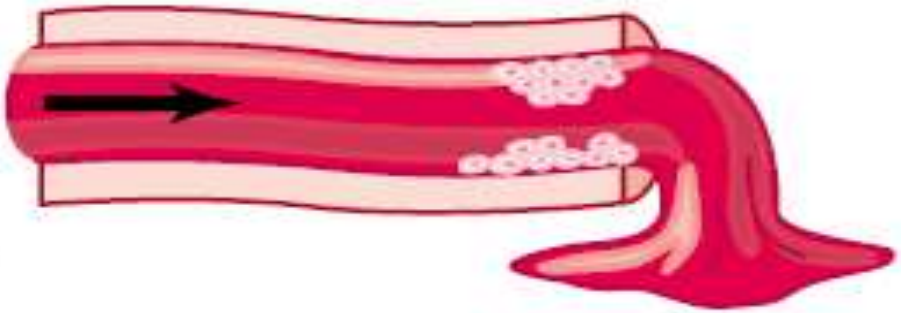



Injury to wall of blood vessel
Contraction
Collagen
Tissue thromboplastin
Platelet reactions
Activation of coagulation
Loose platelet aggregation
Thrombin
Temporary hemostatic plug
Definitive hemostatic plug
Limiting reactions

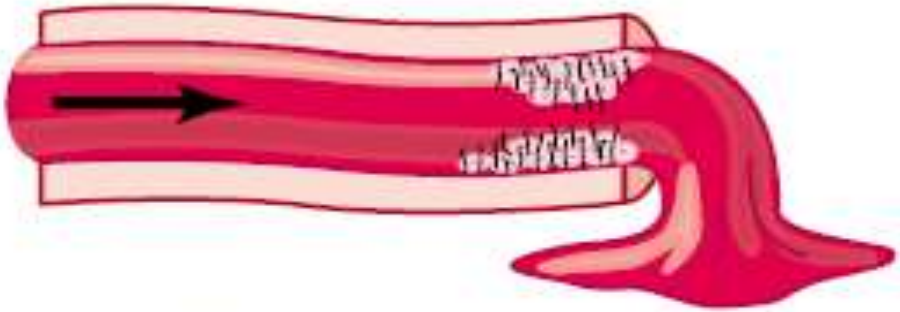
Stages of hemostasis



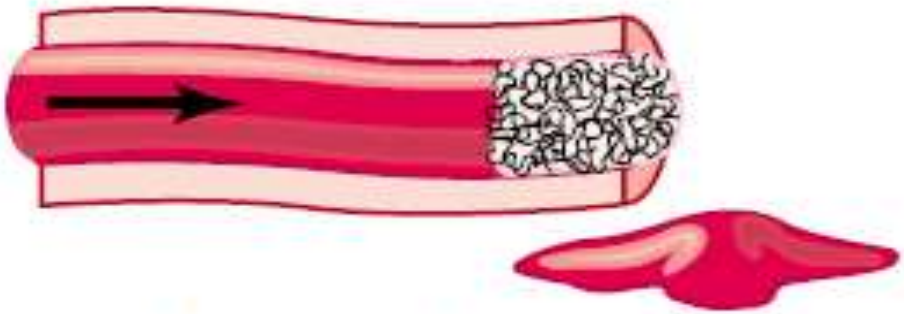
1. Severed vessel



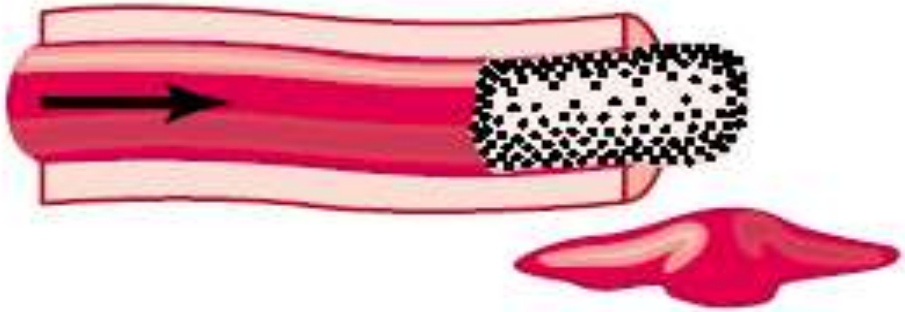
2. Platelets agglutinate



3. Fibrin appears



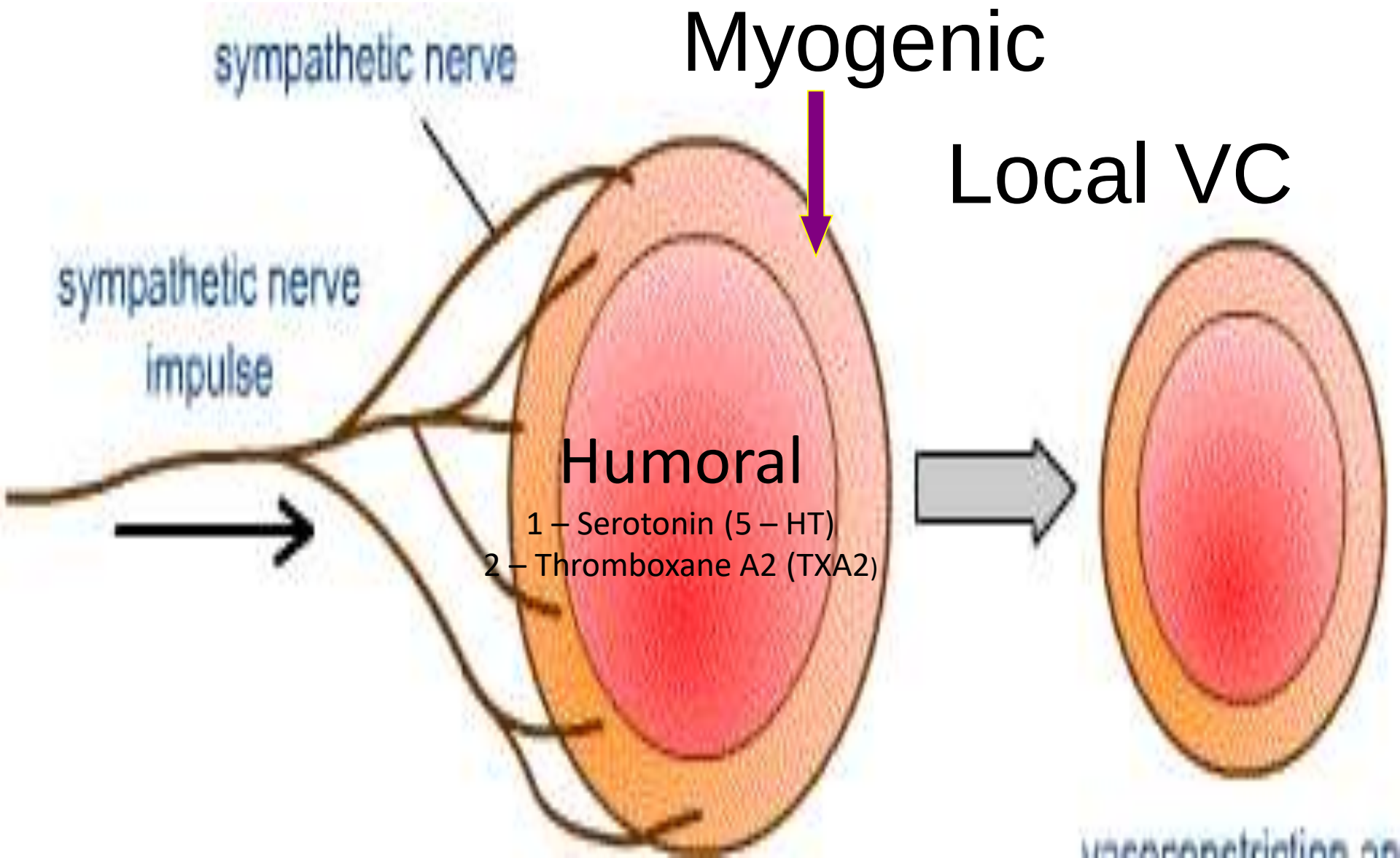
4. Fibrin clot forms



5. Clot retraction occurs

1 - Vasoconstriction

Nervous



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.

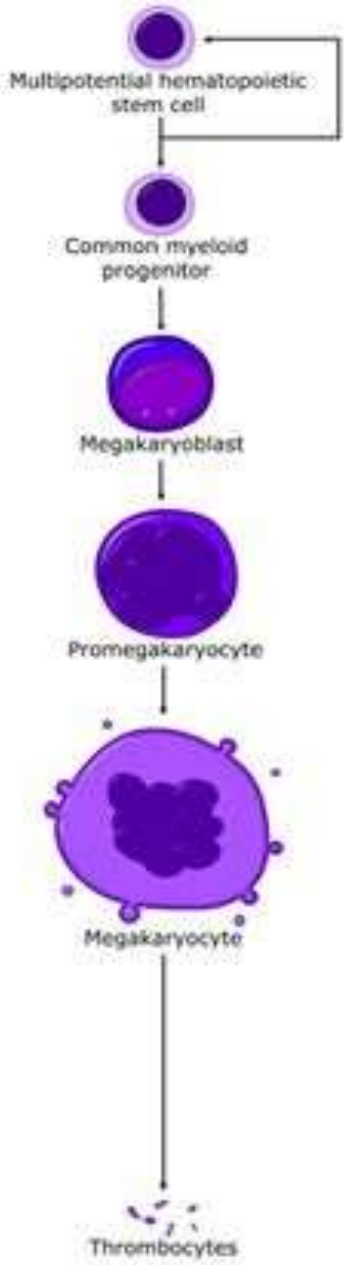
Platelets (Thrombocytes)

Small disc shaped **granulated**. Non nucleated structures.

Formation: Formed in the bone marrow under the effect of **Thrombopoietin.** From the precursor cell **megakaryocyte.**

Life span: 8 – 12 days

Normal platelet count: 150,000 – 300,000/cmm



Platelet reactions in hemostasis:

Platelet adhesion.

Platelet activation.

Platelet release reactions.

Platelet aggregation.

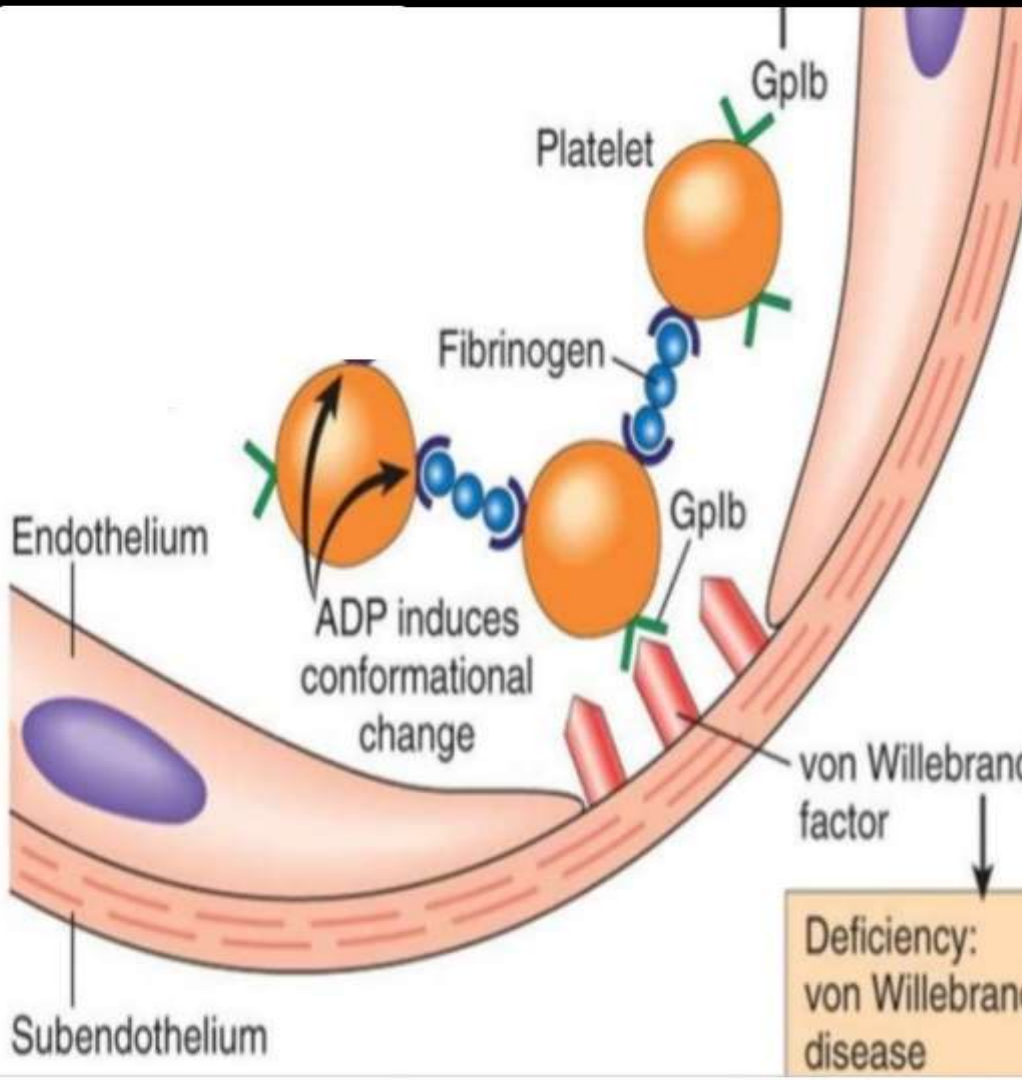
Platelet fusion.

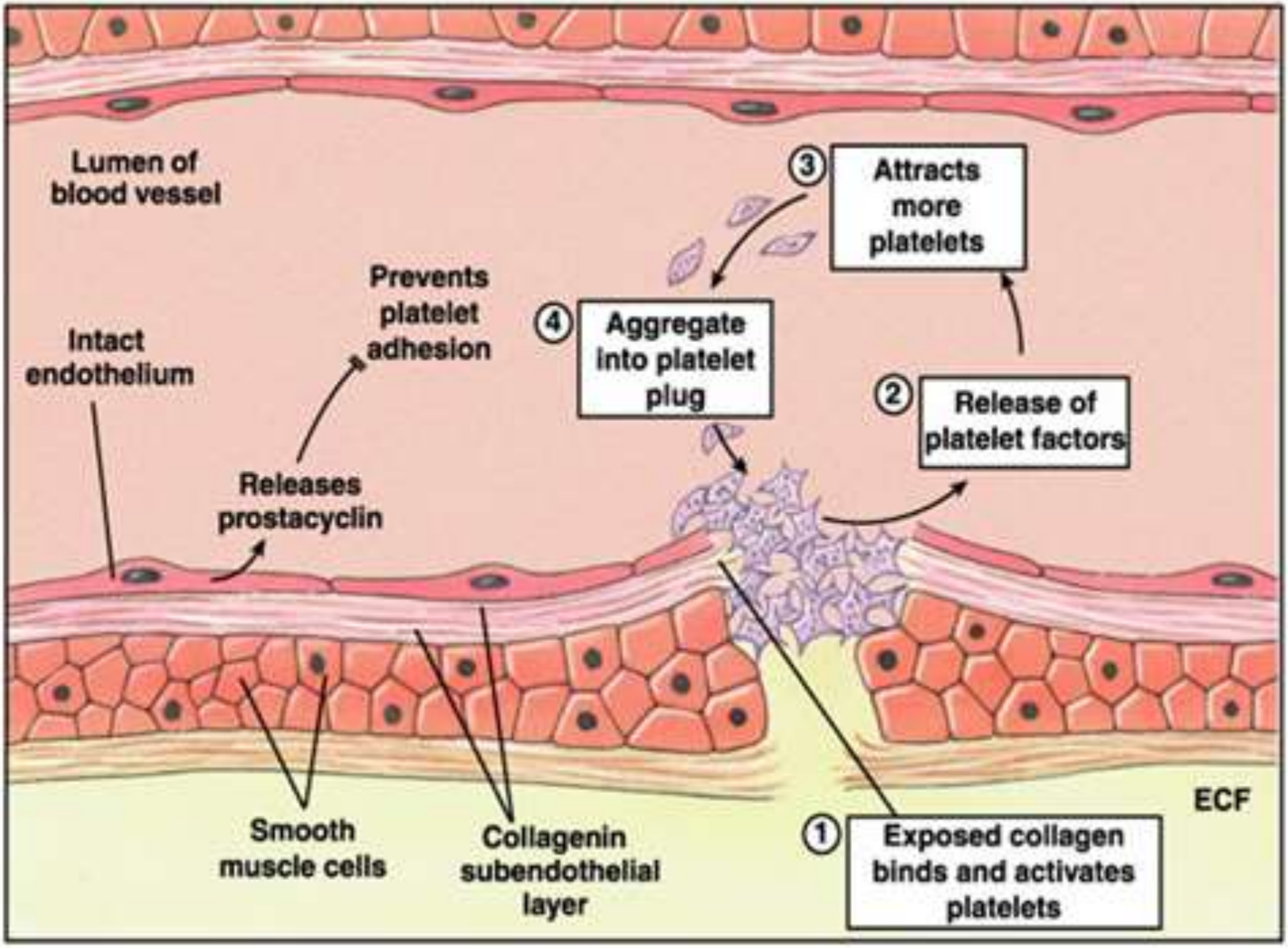
Clot retraction.

Steps	Substances involved	Characters
Platelet adhesion	Subendothelial collagen and Von Willeberand factor. ??	Occurs to the subendothelial tissue.
Platelet activation	ADP and 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.

Platelets adhere to the sub-endothelial tissues. Through the action of some receptors to sub-endothelial collagen and Von-Willeberand factor. Platelets do not adhere to the normal vascular endothelium under the normal physiological conditions.

Platelets adhesion

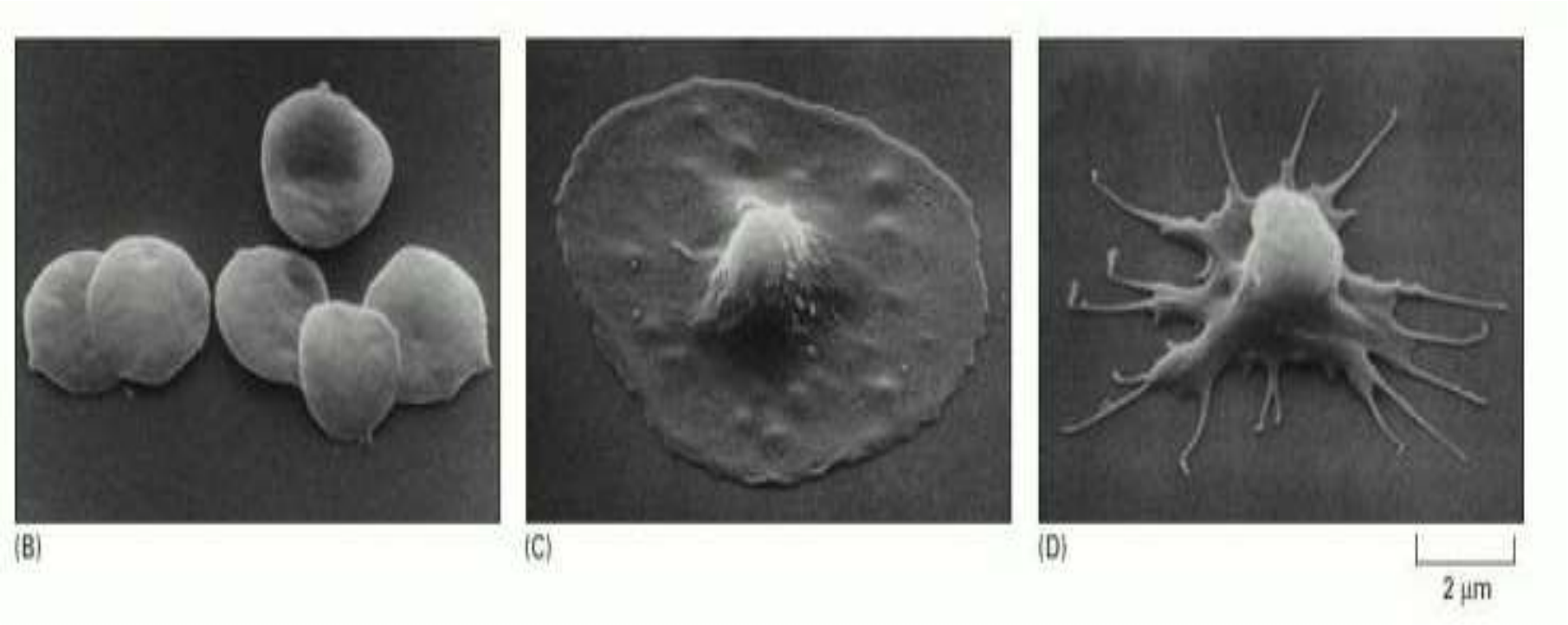



Lumen of blood vessel
3 Attracts more platelets
Prevents platelet adhesion
4 Aggregate into platelet plug
Intact endothelium
2 Release of platelet factors
Releases prostacyclin
ECF
Smooth muscle cells
Collagenin subendothelial layer
1 Exposed collagen binds and activates platelets

2- Platelets activation:

Swell change in shape put out pseudopodia

Stimulated by thrombin and ADP

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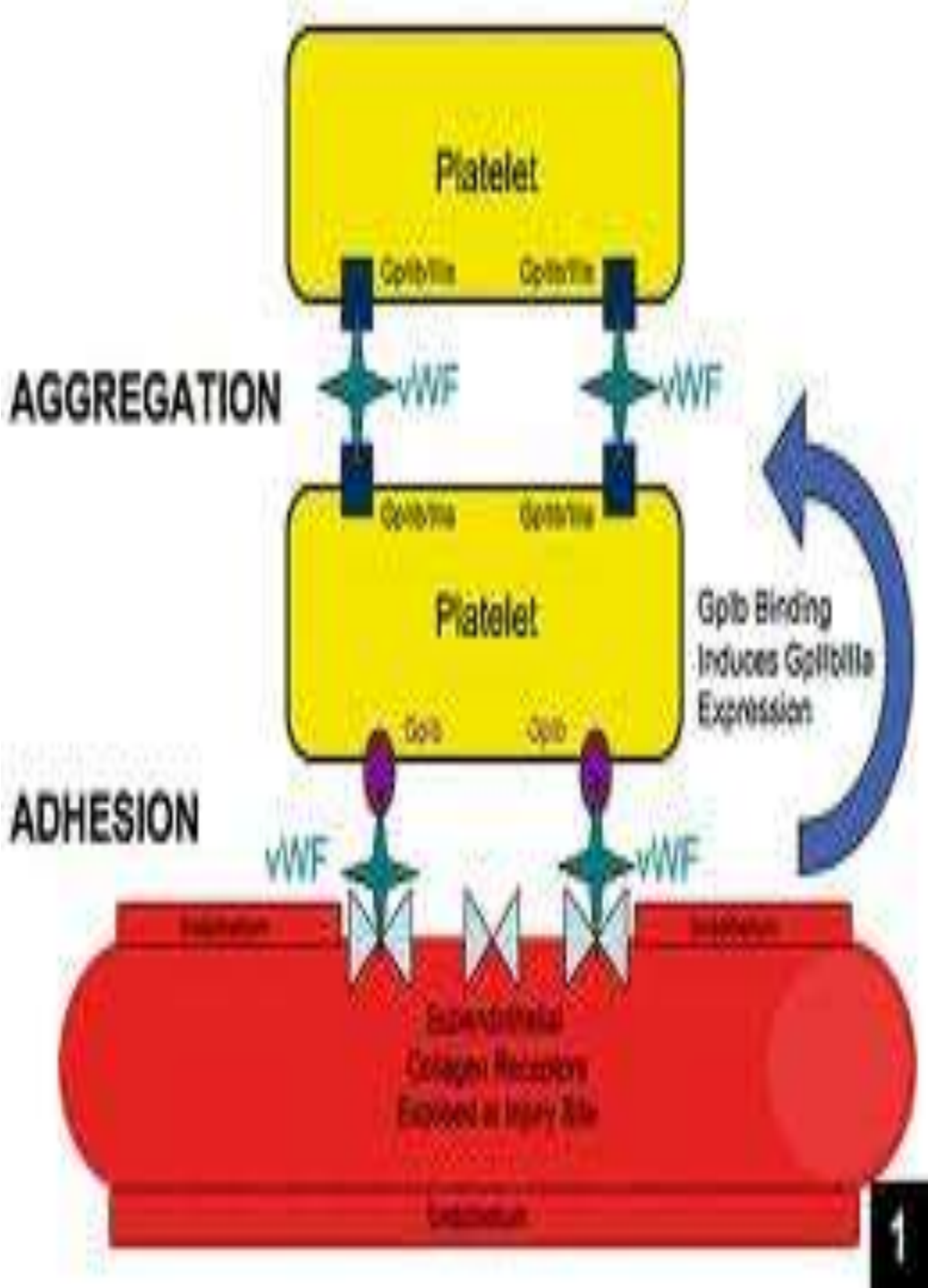
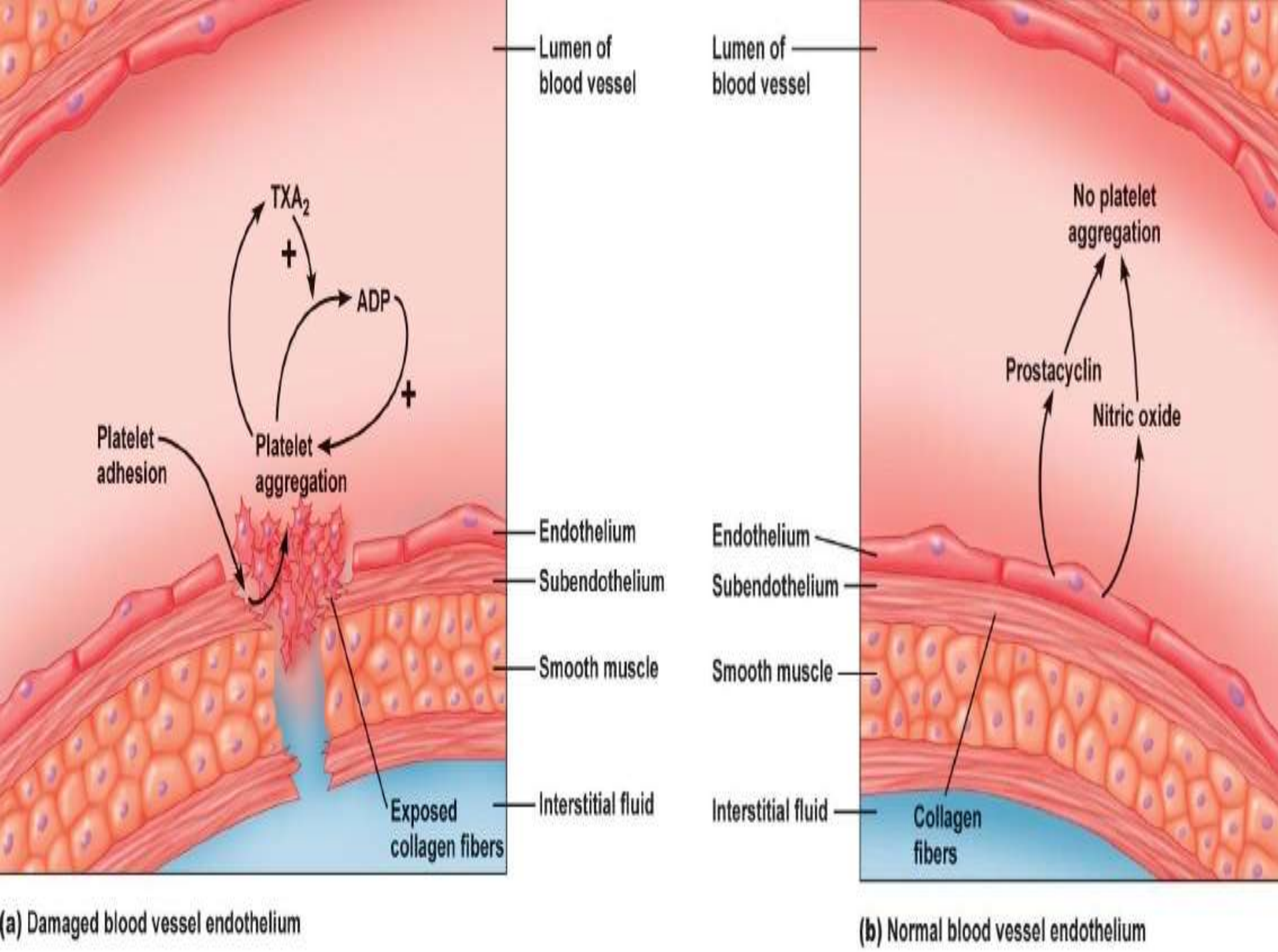
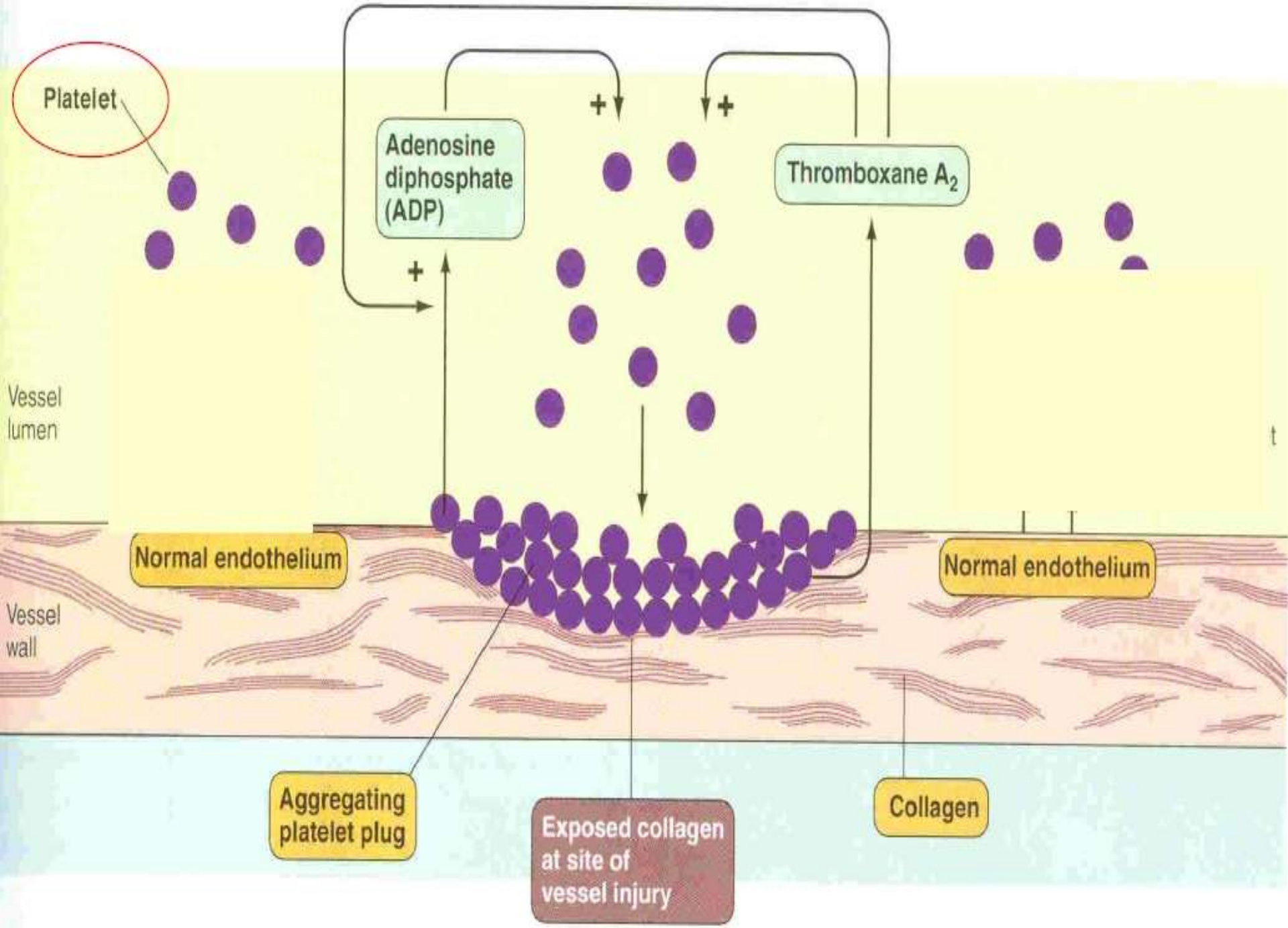
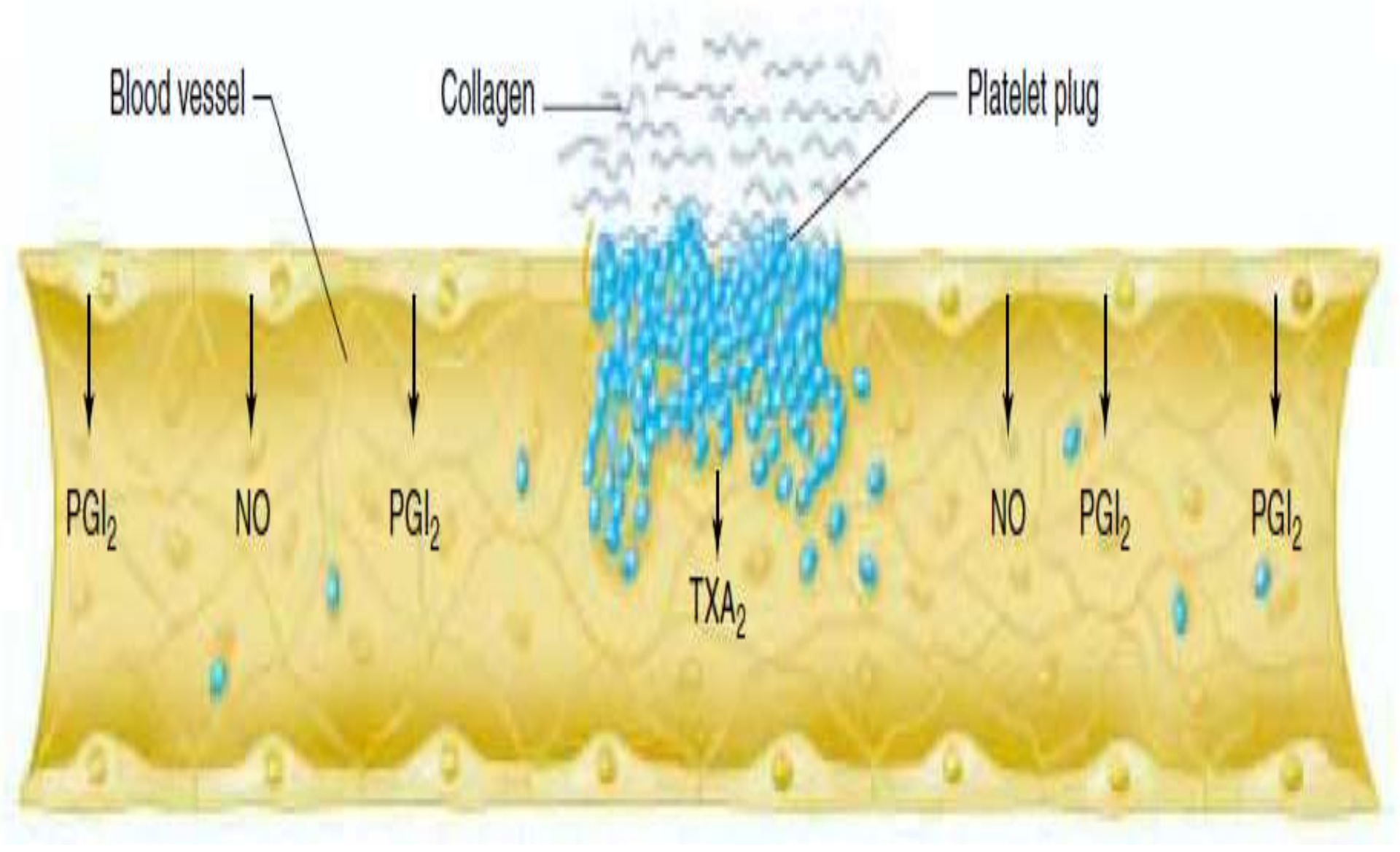
Platelets release TXA2 to help and increase the platelet aggregation and thrombus formation over the injured site. While the normal vascular endothelium releases Prostacyclin (PGI2) and Nitric oxide (NO) to prevents platelets aggregation over the normal site of the blood vessel.




Lumen of blood vessel
TXA_2
+
ADP
+
Platelet adhesion
Platelet aggregation
Endothelium
Subendothelium
Smooth muscle
Exposed collagen fibers
Interstitial fluid
(a) Damaged blood vessel endothelium
Lumen of blood vessel
No platelet aggregation
Prostacyclin
Nitric oxide
Endothelium
Subendothelium
Smooth muscle
Interstitial fluid
Collagen fibers
(b) Normal blood vessel endothelium


Platelet
Adenosine diphosphate (ADP)
Thromboxane A_2
+
+
+
Vessel lumen
Normal endothelium
Normal endothelium
Vessel wall
Aggregating platelet plug
Exposed collagen at site of vessel injury
Collagen

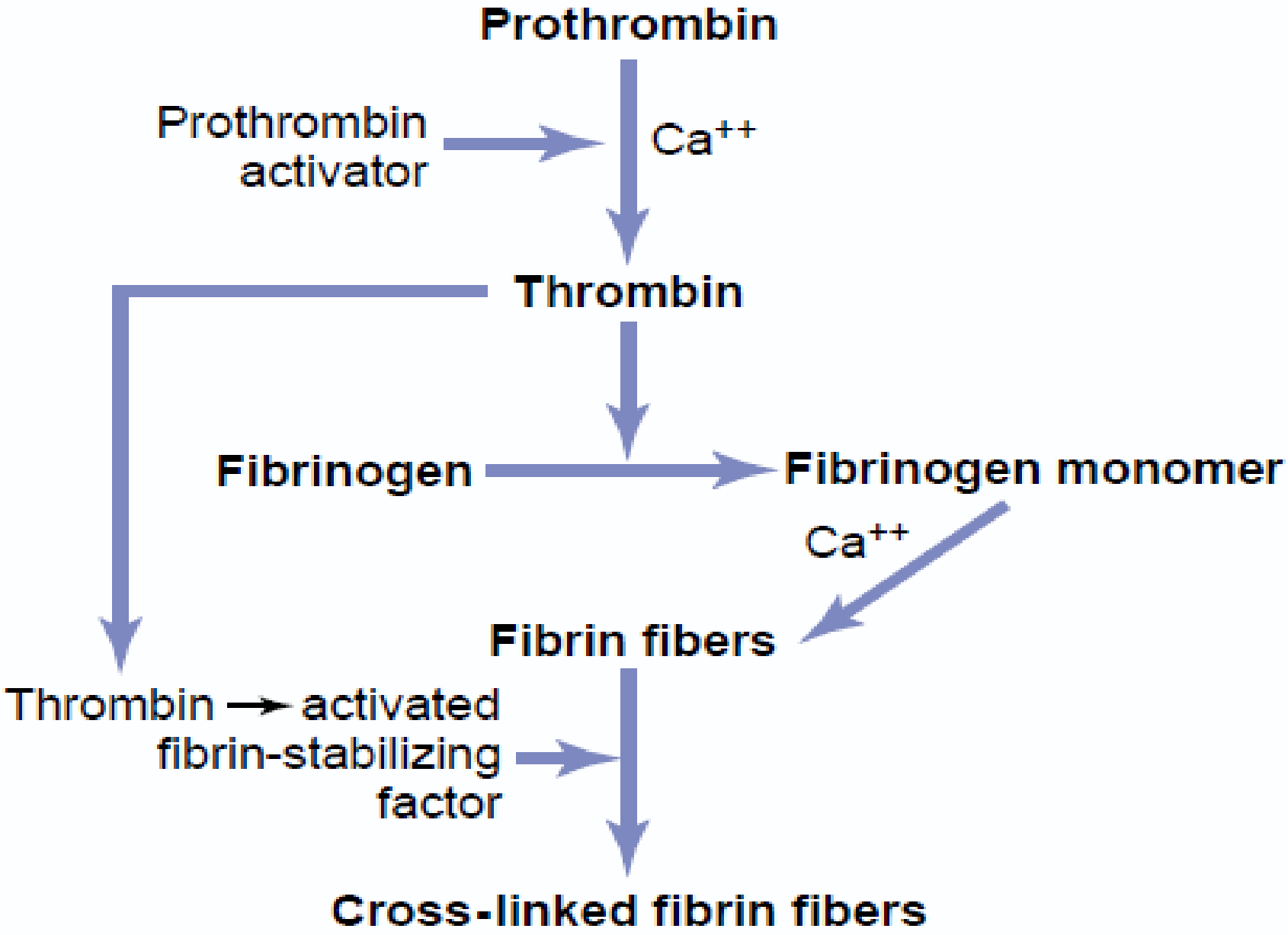


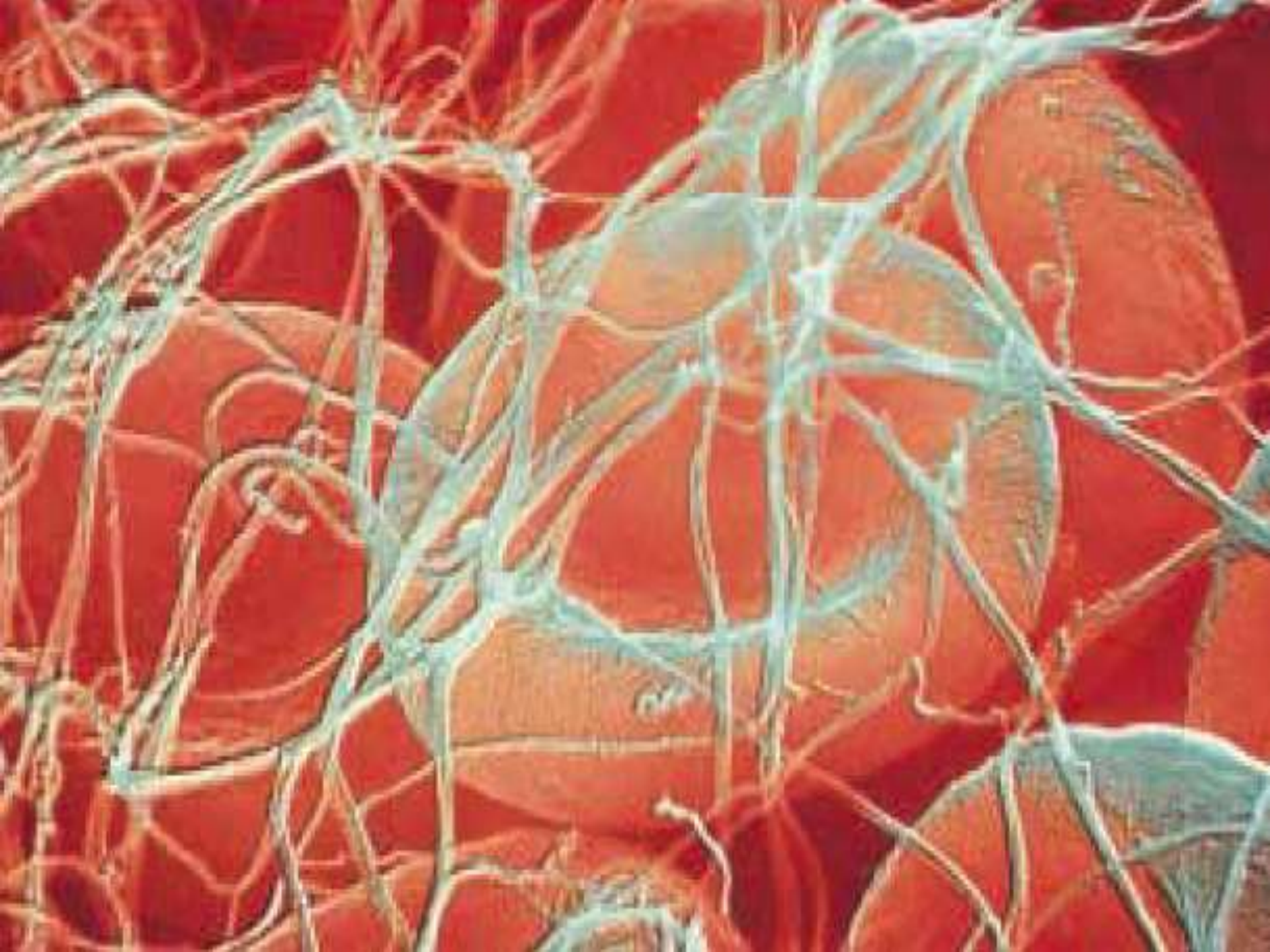
Clinical correlation

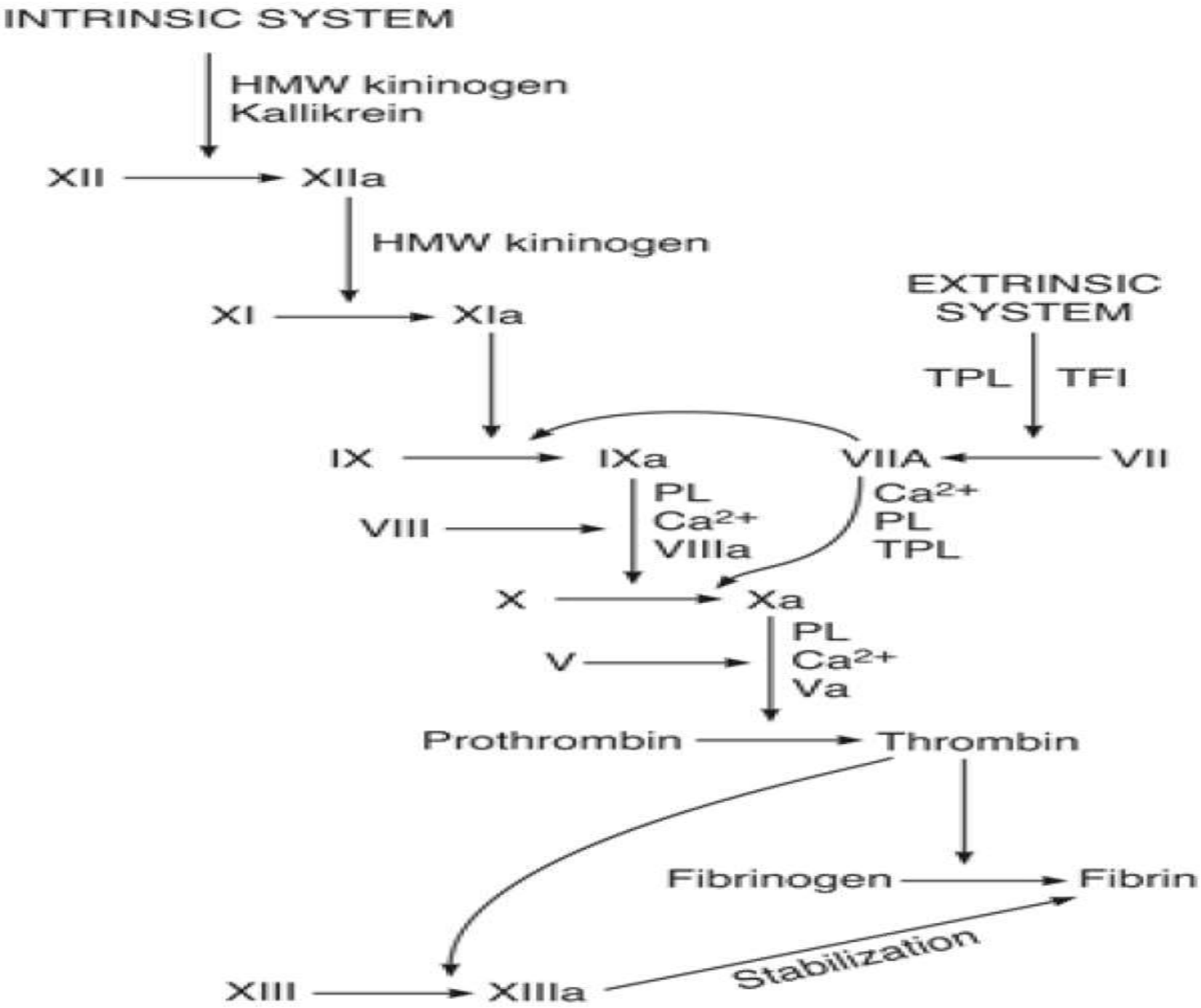
Acetyl salicylic acid (Aspirin) prevents platelet activity by inhibiting TXA2 so used in the prophylaxis against thrombus formation

Blood Coagulation

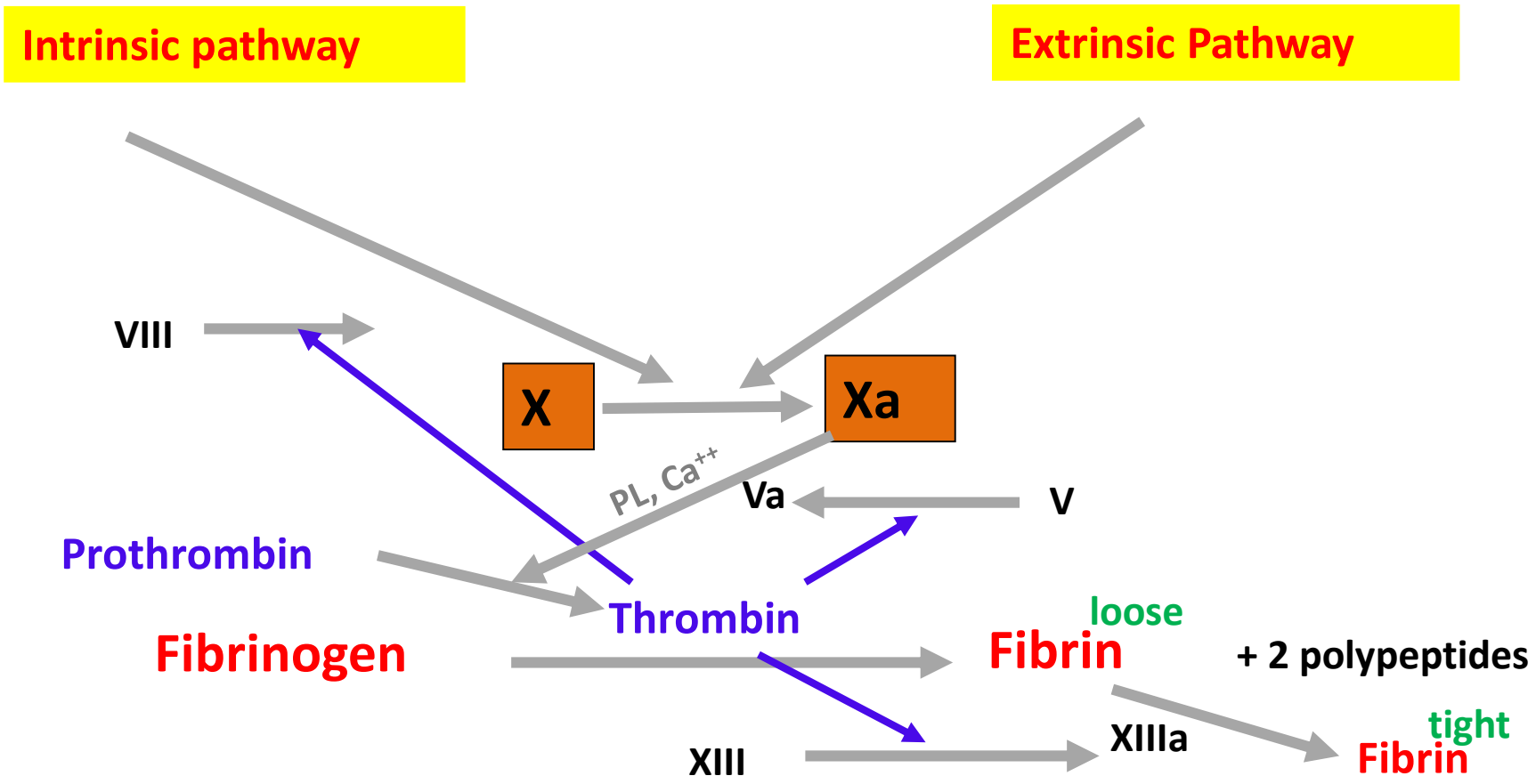
Factor	Name
I	Fibrinogen
II	Prothrombin
III	Thromboplastin
IV	Calcium
V	Proaccelerin, labile factor
VII	Proconvertin, stable factor
VIII	Antihemophilic globulin
IX	Christmas factor
X	Stuart-Power factor
XI	Plasma thromboplastin antecedent
XII	Hageman factor
XIII	Fibrin stabilizing factor
HMW-K	High molecular weight kininogen
Pre-K	Pre-kallikrein
Ka	Kallikrein
PL	Platelet phospholipids


Prothrombin
Prothrombin activator
Ca++
Thrombin
Fibrinogen
Fibrinogen monomer
Ca++
Fibrin fibers
Thrombin → activated fibrin-stabilizing factor
Cross-linked fibrin fibers

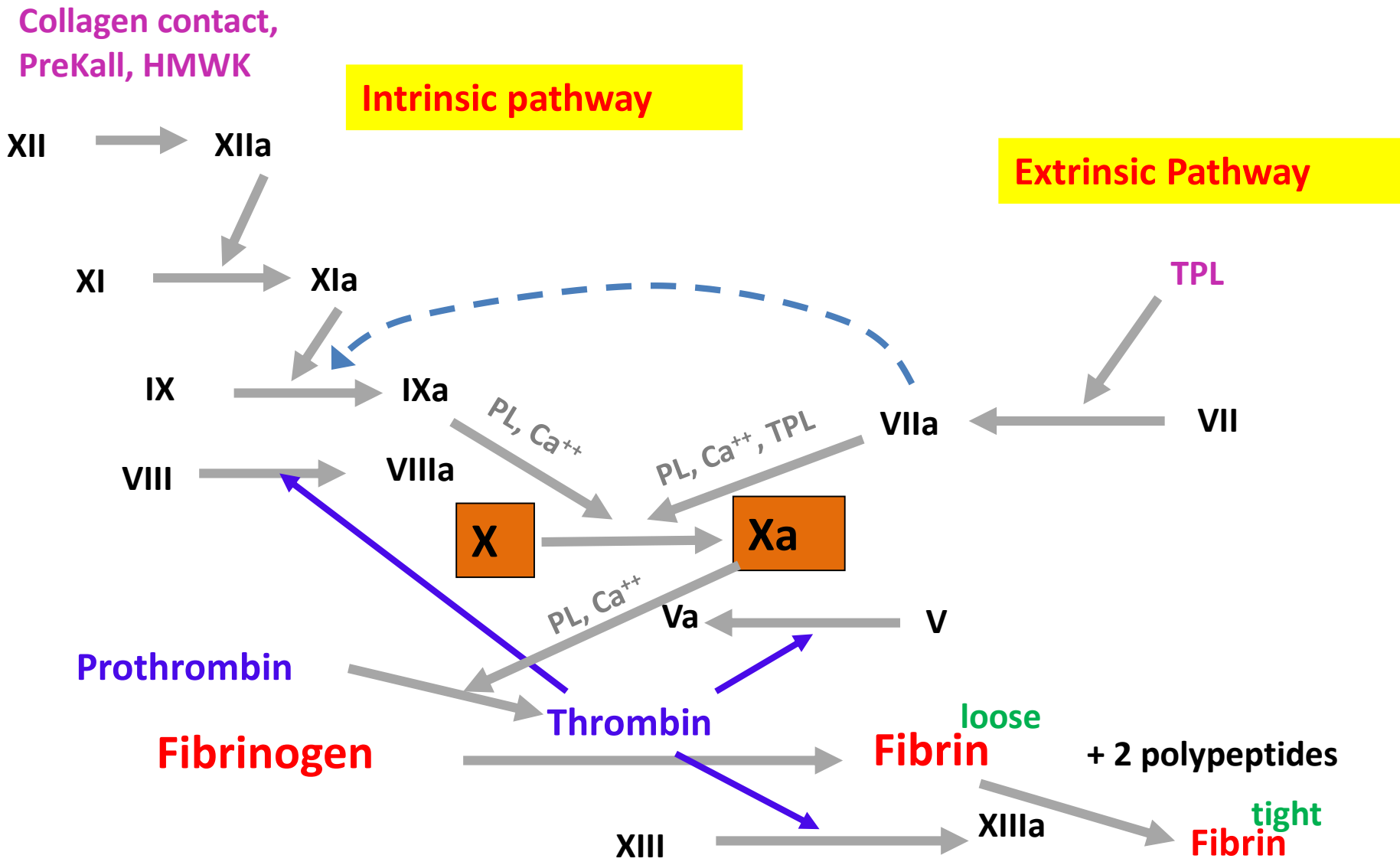



INTRINSIC SYSTEM
HMW kininogen
Kallikrein
XII
XIIa
HMW kininogen
XI
XIa
EXTRINSIC SYSTEM
TPL
TFI
IX
IXa
VIIA
VII
PL
Ca2+
VIIIa
VIII
Ca2+
PL
TPL
X
Xa
PL
Ca2+
Va
V
Prothrombin
Thrombin
Fibrinogen
Fibrin
XIII
XIIIa
Stabilization

Coagulation Cascade



Coagulation Cascade



	Extrinsic pathway	Intrinsic pathway
Duration	Rapid	Slow
	Weaker than the intrinsic pathway	More extensive. Forms more fibrin threads
Starts by	Factor III (Thromboplastin or tissue factor)	Factor XII (contact factor)
occurs	Only invivo	Both invivo and invitro
Tested by	Prothrombin time (PT)	Activated partial thromboplastin time (APTT)

NB: Role of thrombin in hemostasis
1 – Activates factors I, V, VIII, and XIII.
2 – essential for platelet activation, release reactions. Which are essential for platelet aggregation.
So inhibition of Thrombin leads to inhibition of blood clotting.

The anticlotting mechanisms (Limiting reactions)

The tendency of blood to clot is balanced in vivo by **limiting reactions.**

Aim: To prevent clotting inside the blood vessels and to 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).

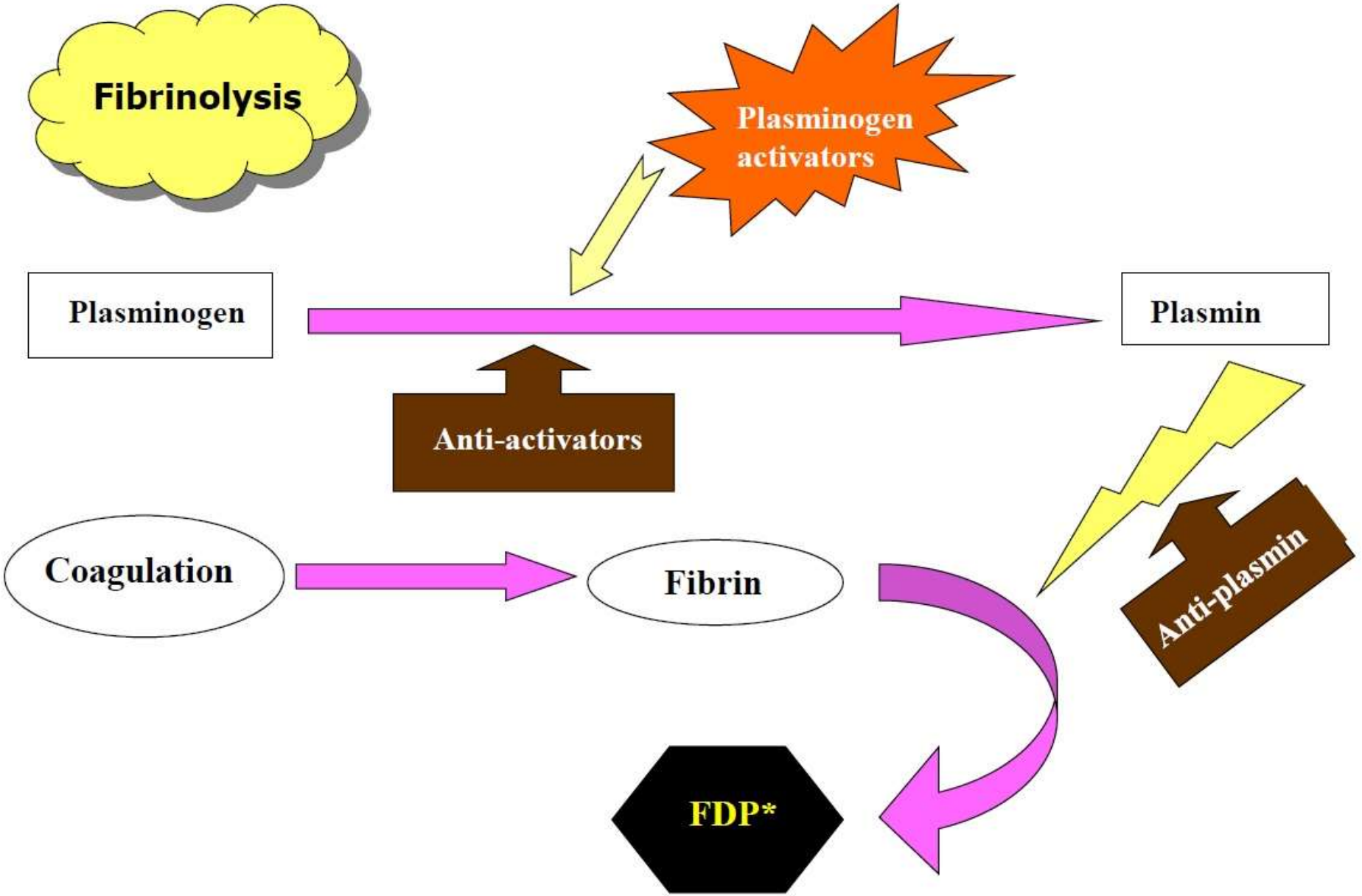
3 - The antithrombotic effects of **Prostacyclin and nitric oxide (NO).**

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

5 – Protein S (cofactor for protein C).

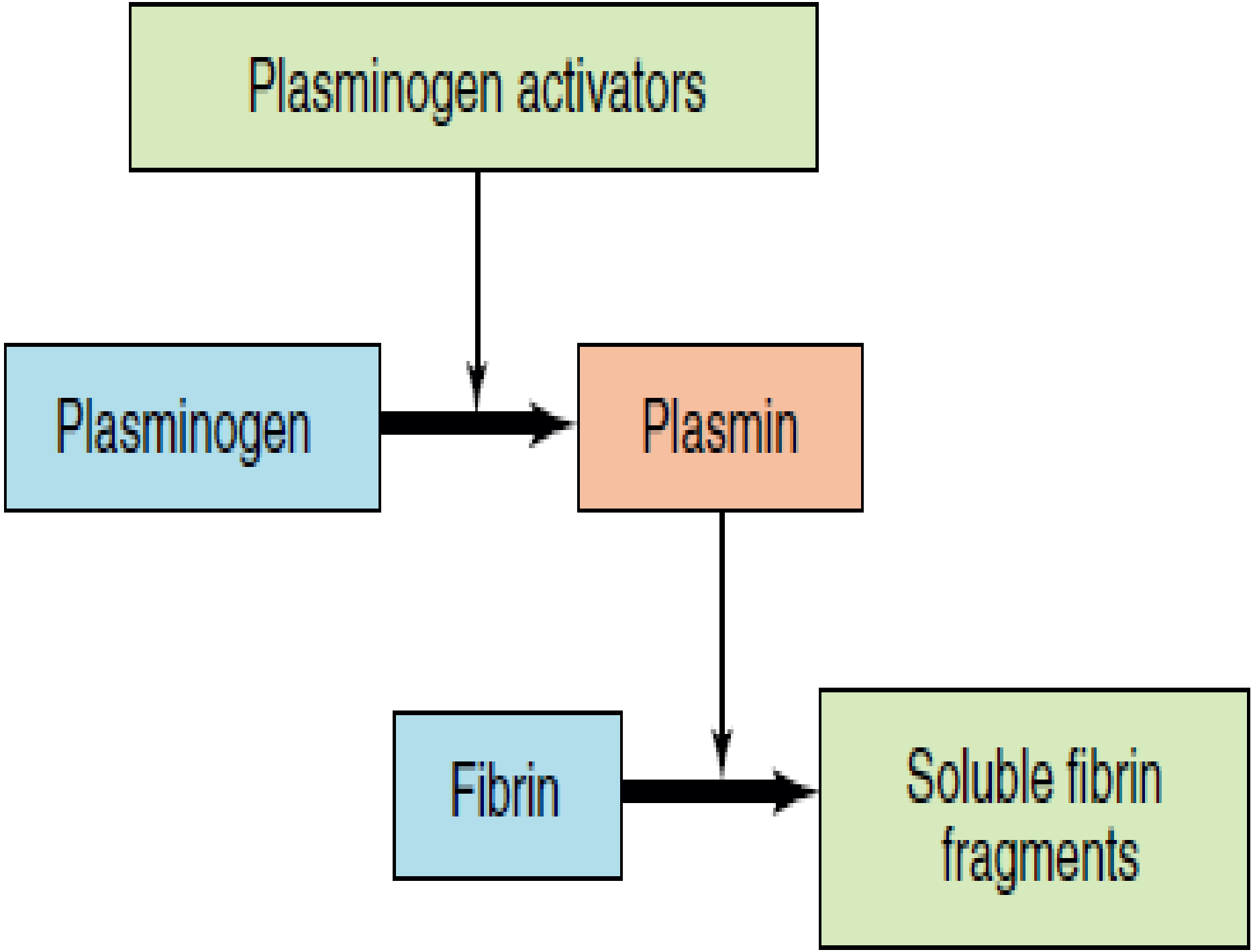
6 – Tissue factor inhibitor (TFI) which inhibits the activation of factor VII.

7 - The **fibrinolytic system.**



The fibrinolytic System

FDP*: Fibrin Degradation Products

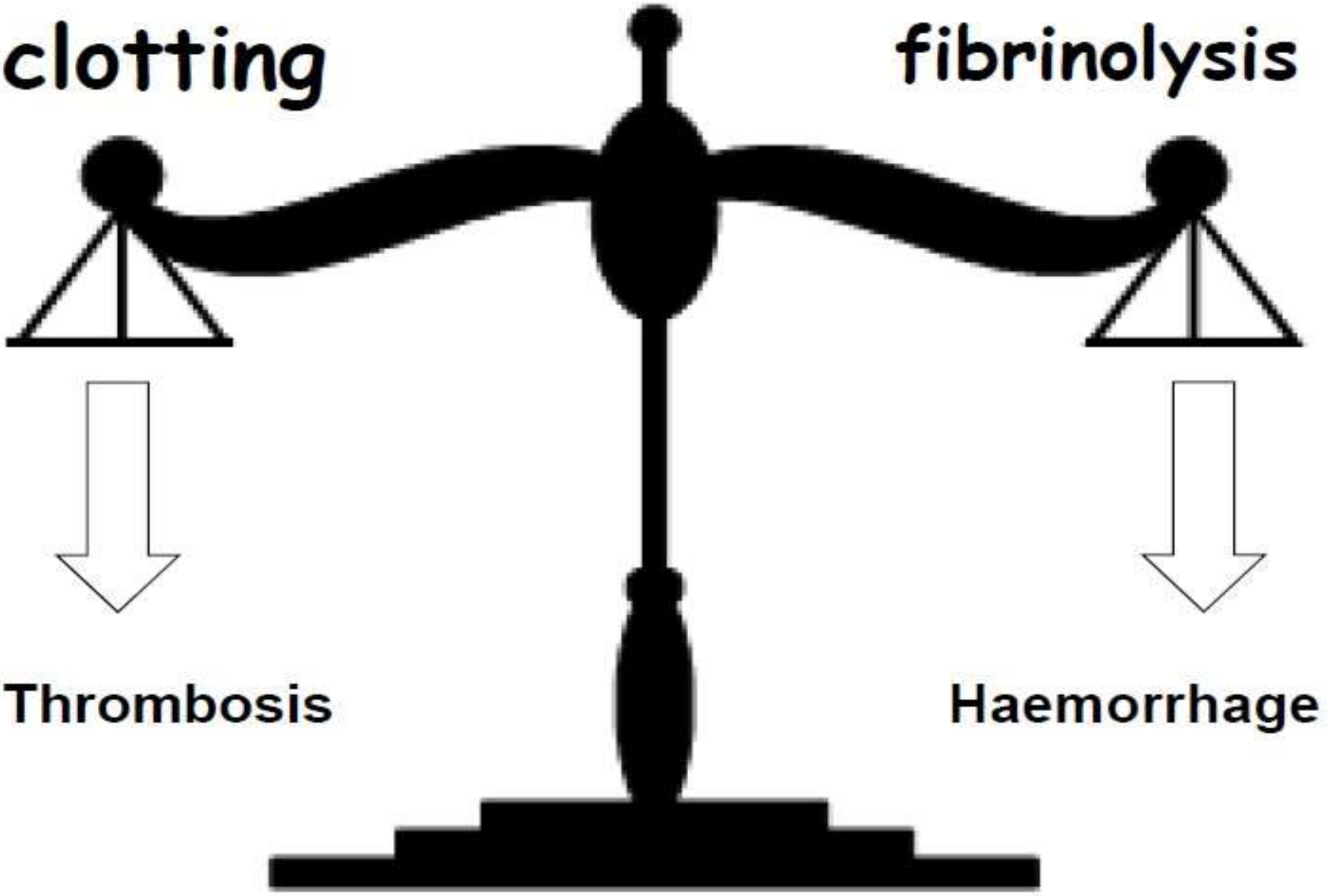

Plasminogen activators
Plasminogen
Plasmin
Fibrin
Soluble fibrin fragments

Fibrinolytic system

Tissue plasminogen activator increases the formation of plasmin from its precursor plasminogen. Which dissolves fibrin into FDPs (fibrin degradation products).

So tissue plasminogen activator is used to dissolve clots in cases of myocardial infarction.

Normally the tissue plasminogen activator is partially inhibited by antiplasmin secreted from the liver. Leading to a balance between the proclotting and the anticlotting factors.


clotting
fibrinolysis
Thrombosis
Haemorrhage

Hemostatic function tests

	Test for	Prolonged in
Bleeding time	Platelets function	Thrombocytopenia 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)

Abnormalities of hemostasis

Clotting disorders

Platelets disorders

Hemophilia

Vitamin K deficiency

Purpura

Platelets disorders (Purpura)

Cause:

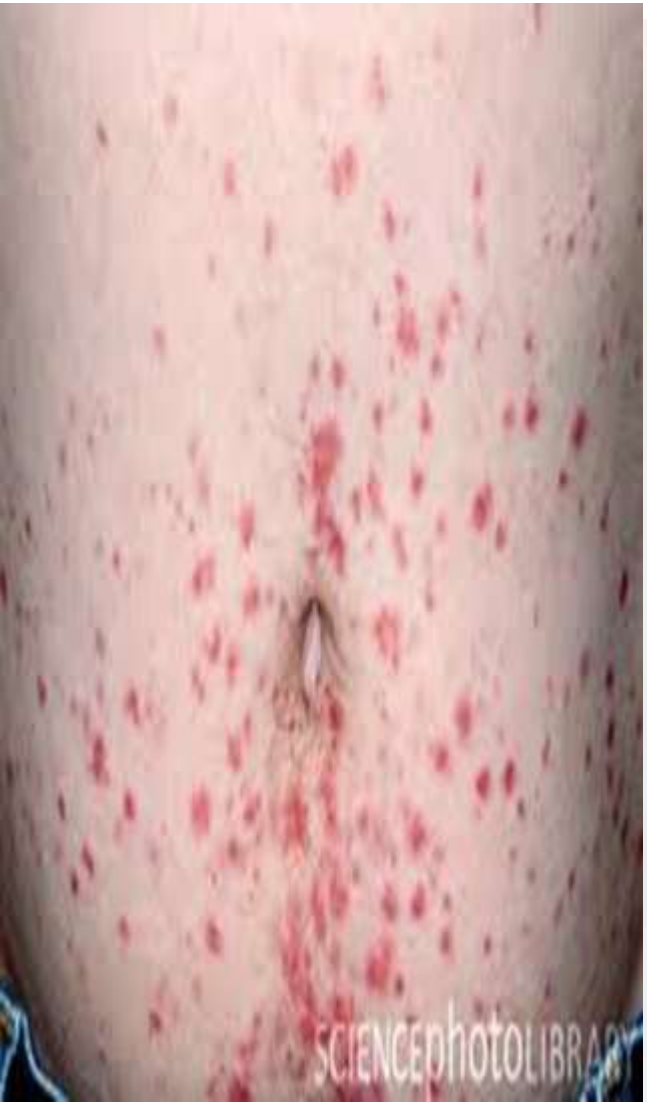
Thrombocytopenia (deficiency of platelets). Or thrombocytoasthenia.

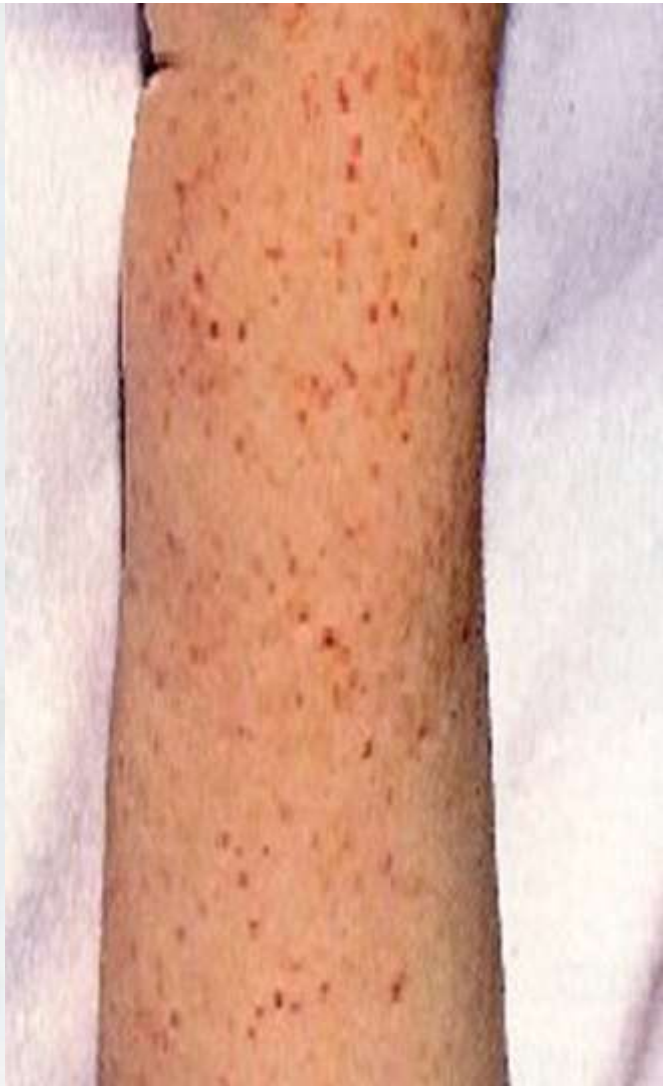
Characterized by:

the presence of many subcutaneous hemorrhages called **petechiae.**

And **prolongation of bleeding time**.

Thrombocytopenic purpura





Hemophilia

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

It is a sex linked recessive disease carried by females and manifested **almost always in males.**

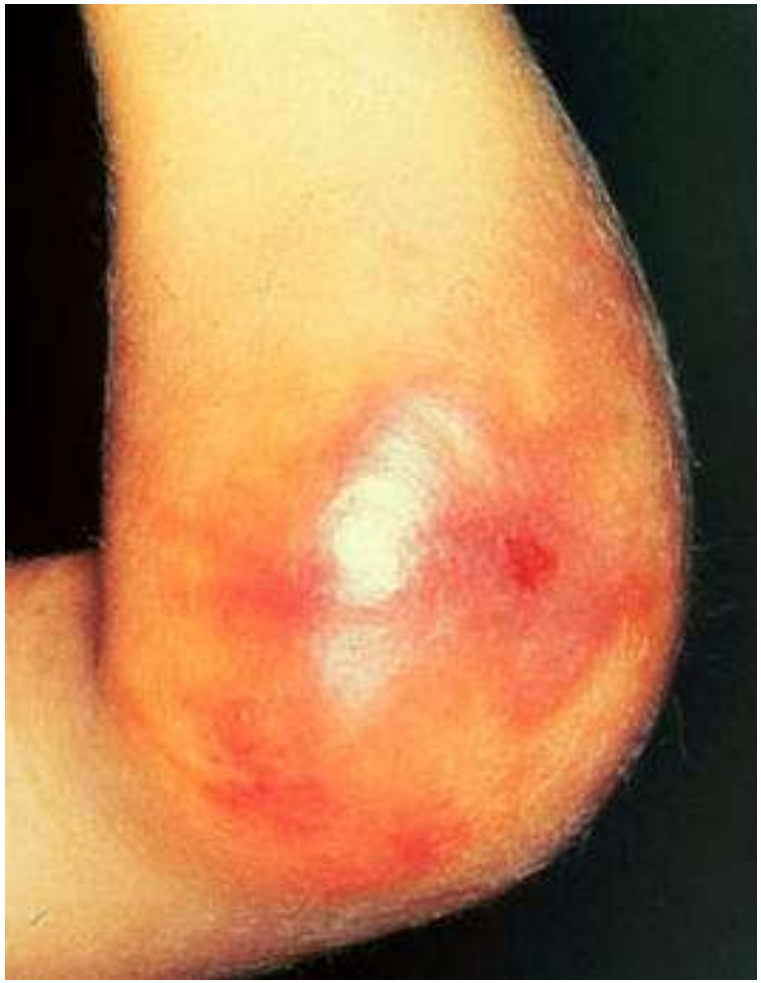
It causes prolongation of the **clotting time & APTT.**
There are 3 types of hemophilia:

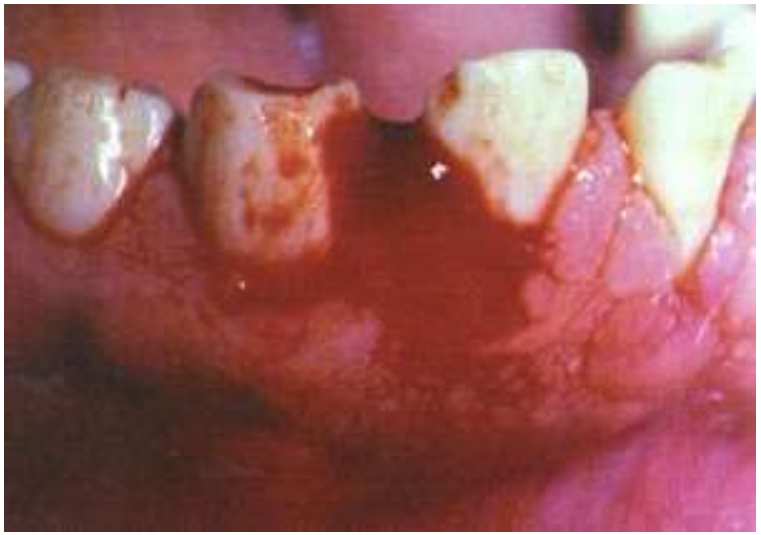
Hemophilia A: is the classic hemophilia which is caused by deficiency of factor **VIII** and represents 85% of cases of hemophilia.

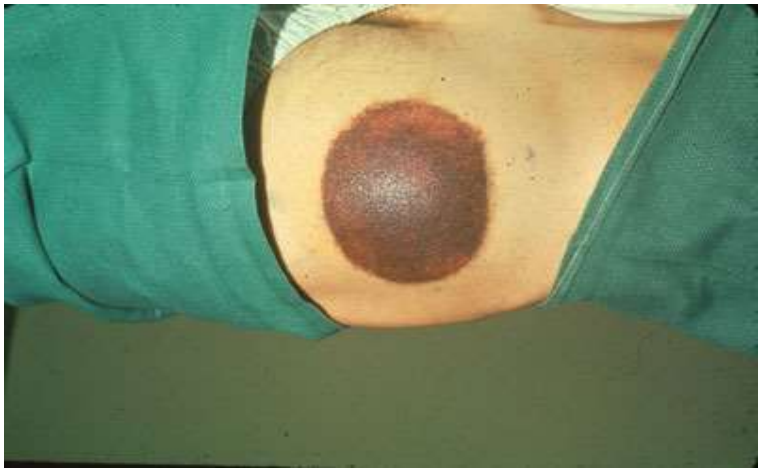
Hemophilia B: is due to absence of factor **IX.**

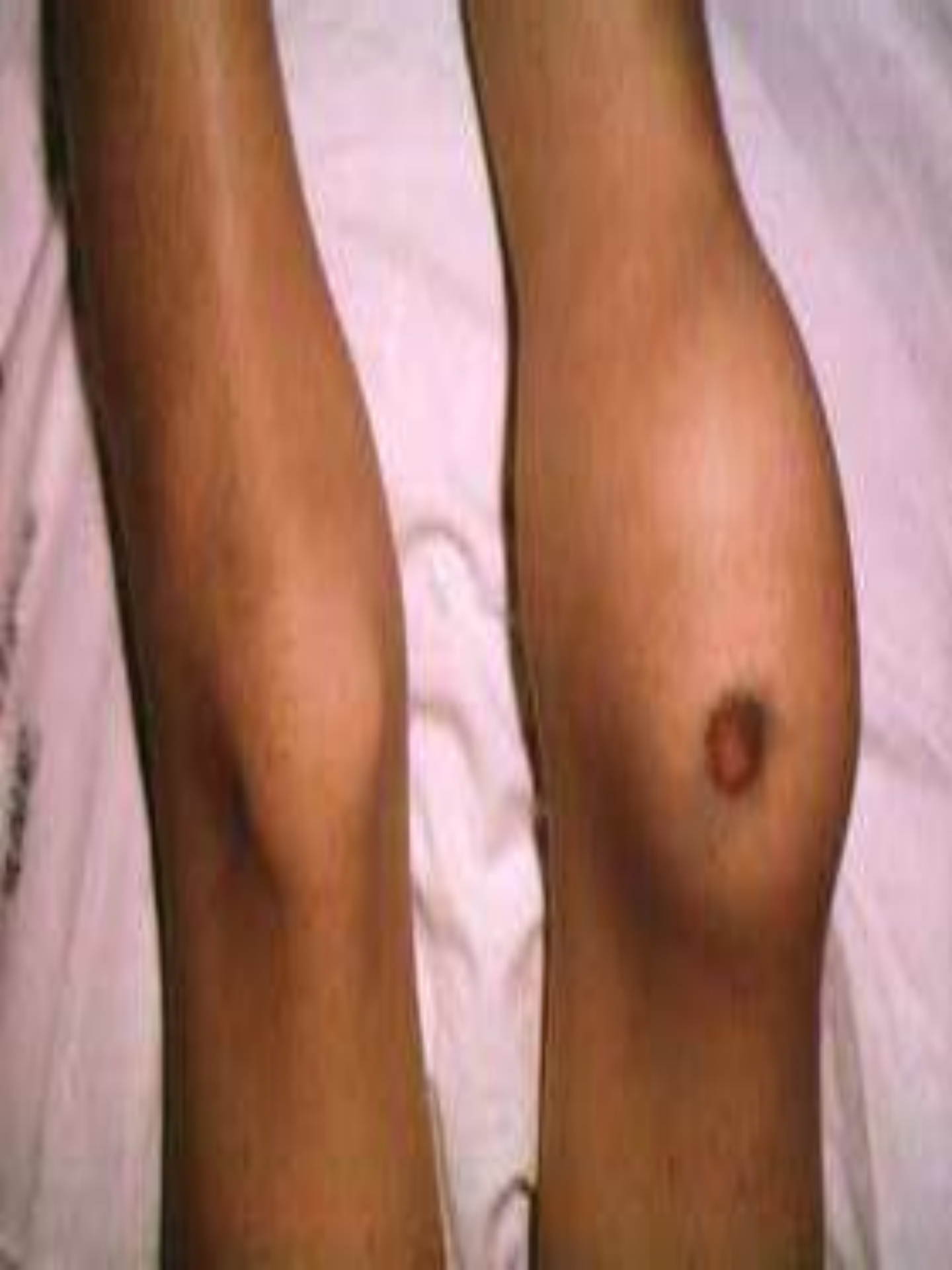
Hemophilia C: is due to absence of factor **XI.**

Hemophilia

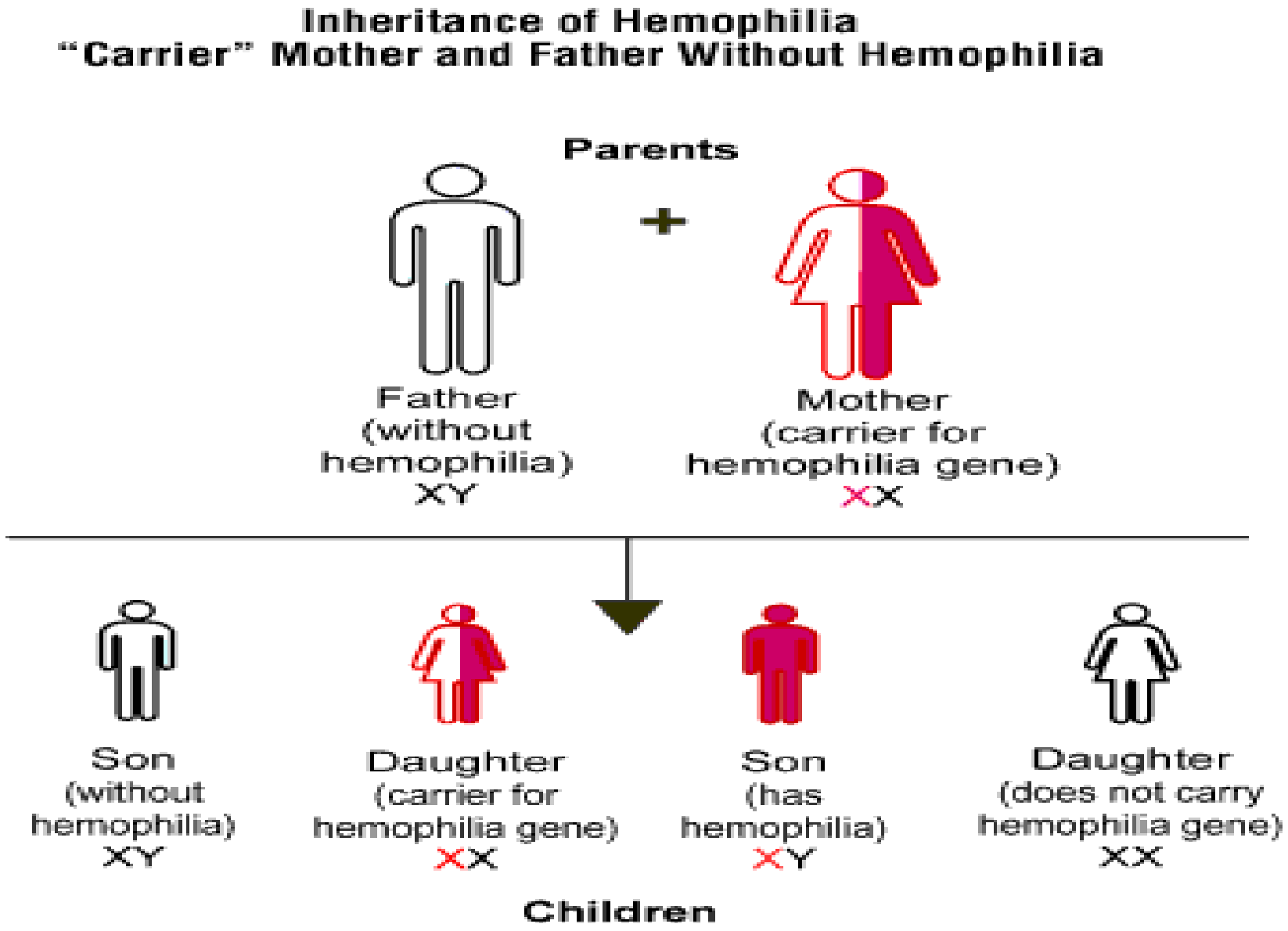


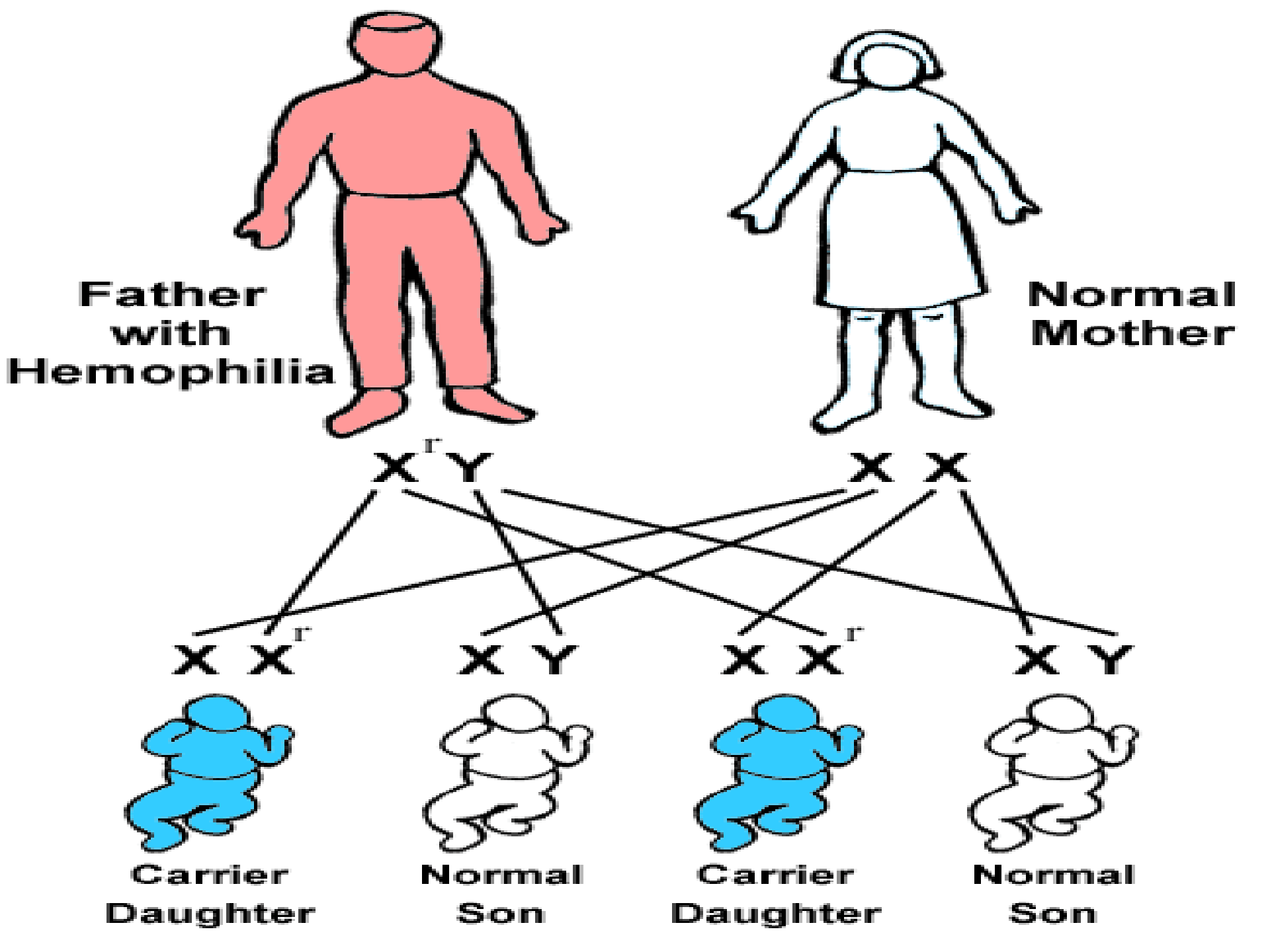


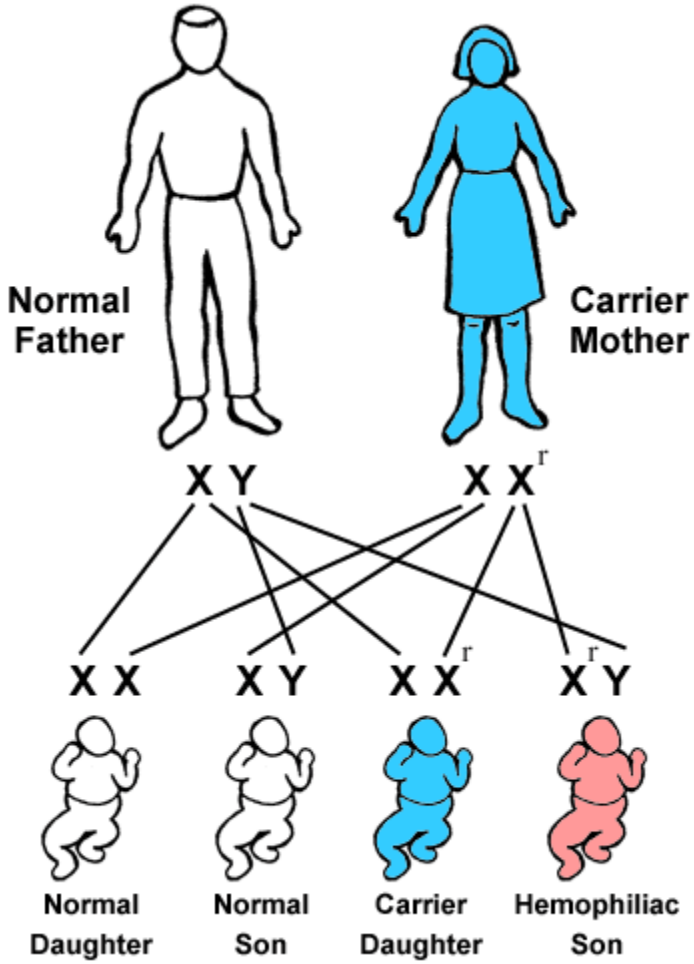




Inheritance of Hemophilia




Father with Hemophilia
Normal Mother
X r Y
X X
X X r
X Y
X X r
X Y
Carrier Daughter
Normal Son
Carrier Daughter
Normal Son


Normal
Father
Carrier
Mother
X Y
X X r
X X
X Y
X X r
X Y r
Normal
Daughter
Normal
Son
Carrier
Daughter
Hemophiliac
Son

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.**


Thank
You!