

بِسْمِ اللّٰهِ الرَّحْمٰنِ الرَّحِیْمِ



Haemostasis

At the end of this lecture student should be able to:

1. Recognize different stages of hemostasis
2. Describe formation and development of platelet
3. Describe the role of platelets in hemostasis.
4. Recognize different clotting factors
5. Describe the cascade of clotting .

Haemostasis

5. Describe the cascade of intrinsic pathway.
6. Describe the cascade of extrinsic and common pathways.
7. Recognize the role of thrombin in coagulation
8. Recognize process of fibrinolysis and function of plasmin

Haemostasis

Terms:

- Primary haemostatic plug?
- Aggregation?
- Coagulation?
- Secondary haemostatic plug?
- Fibrinolysis?

Haemostasis

the spontaneous arrest of
bleeding from ruptured
blood vessels



Hemostasis:

the spontaneous arrest of bleeding from ruptured blood vessels



Mechanisms:

1. Vessel wall
2. Platelet
3. Blood coagulation
4. Fibrinolytic system

Hemostatic Mechanisms- cont

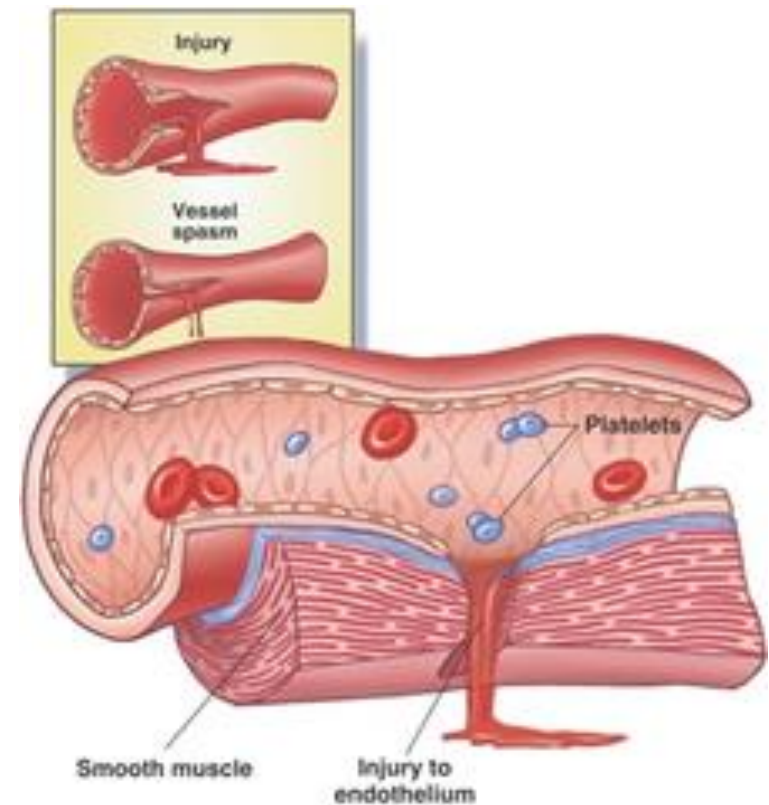
1. Vessel wall

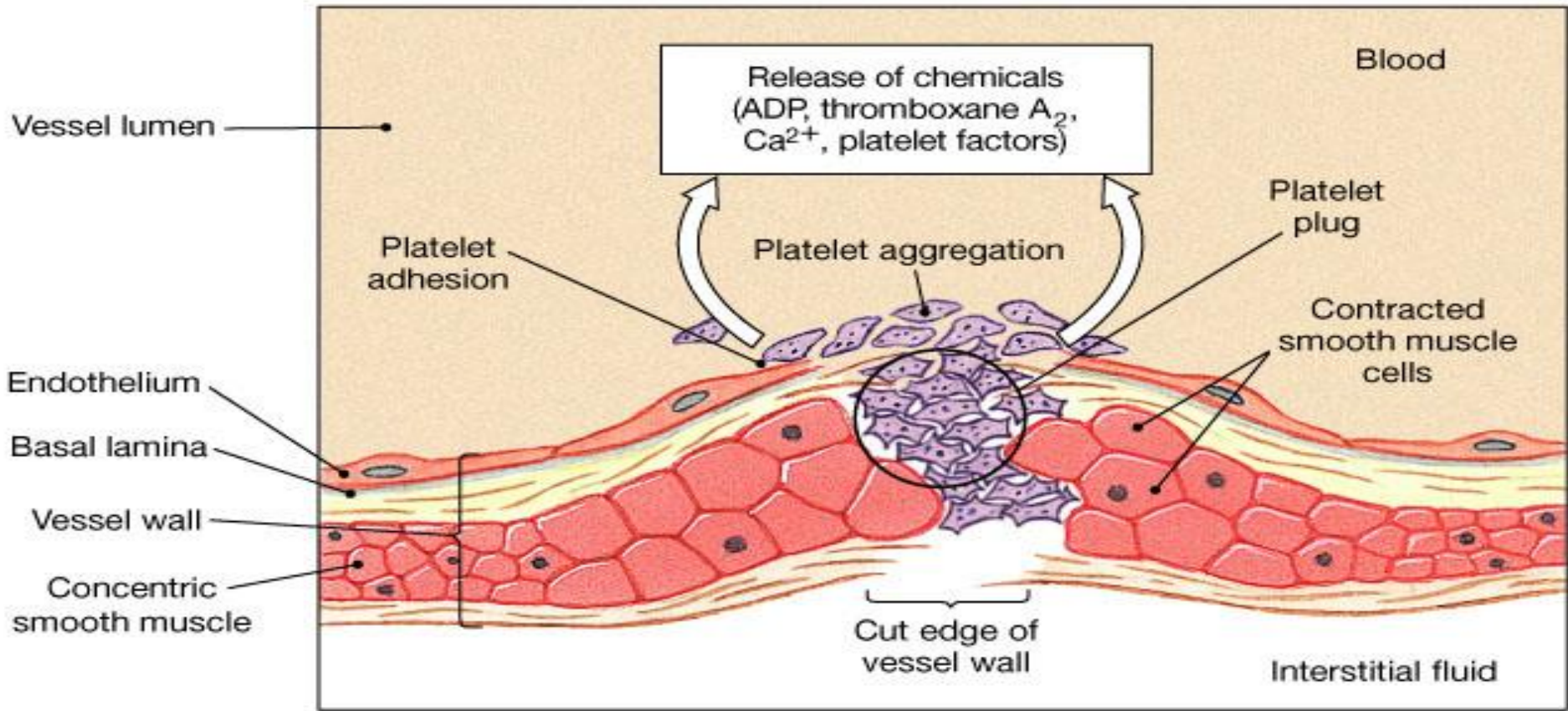
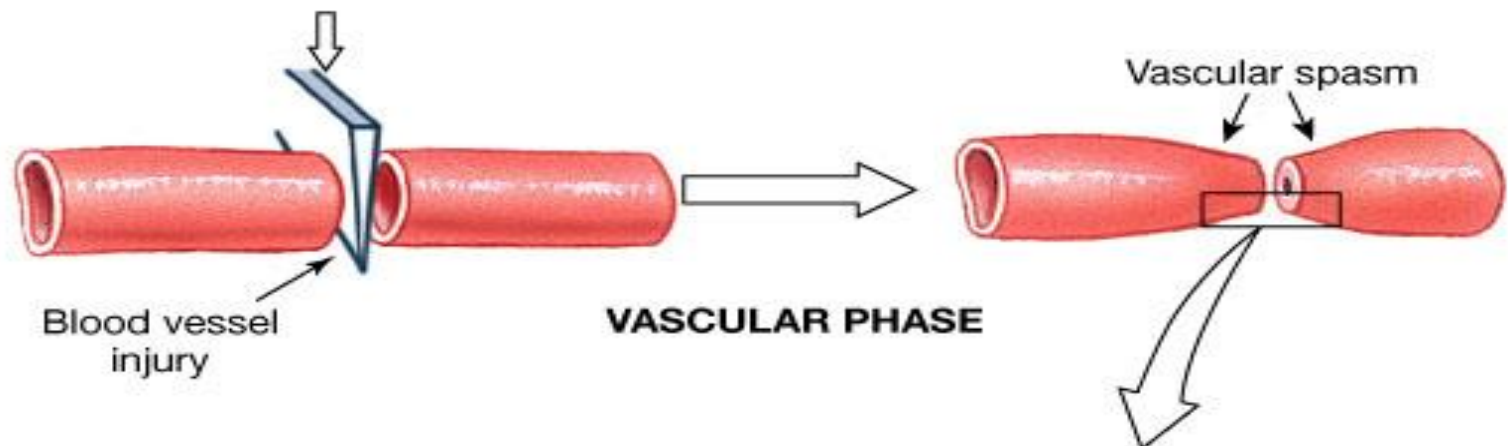
• Immediately After injury a localized

Vasoconstriction

• Mechanism:

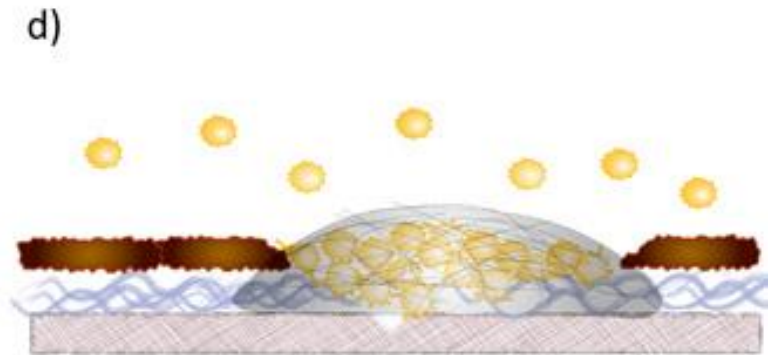
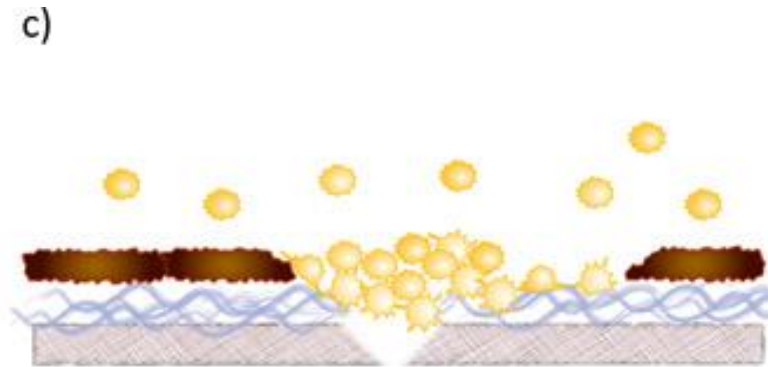
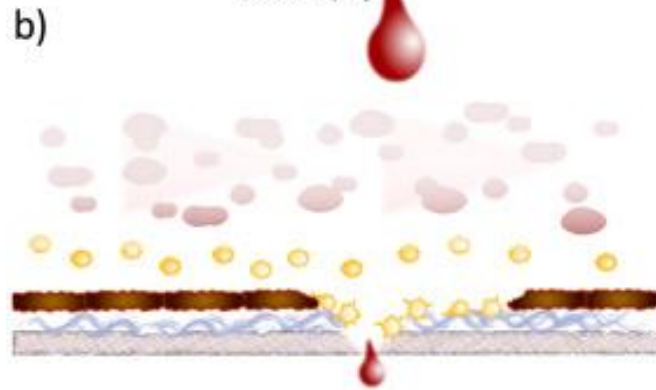
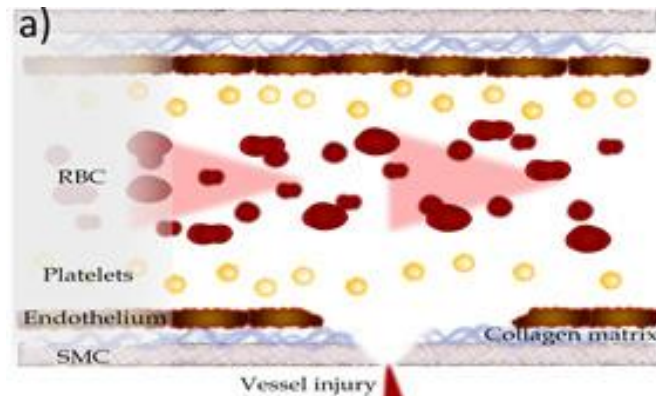
- Myogenic spasm
- Nervous factors
- Humoral factors:
 - Systemic release of adrenaline
 - local release of thromboxane





PLATELET PHASE

Platelet haemostatic plug formation

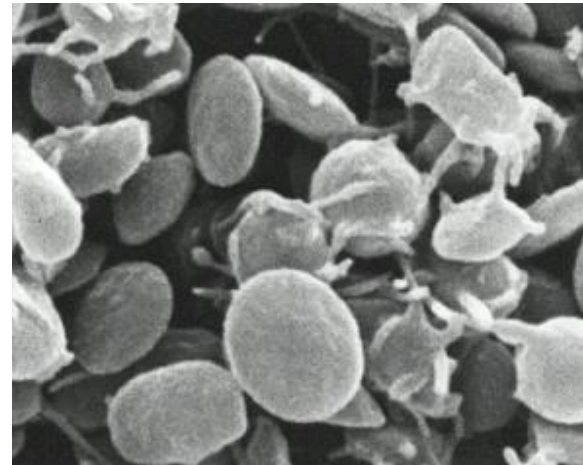
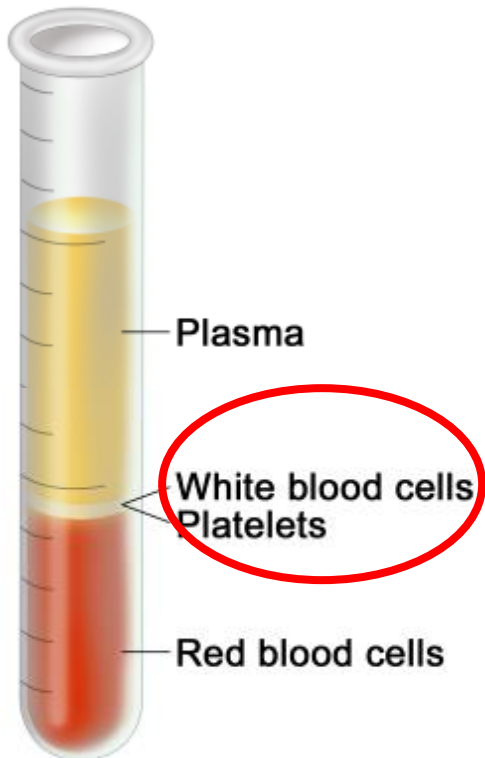


Na Pali Coast, Kaua'i



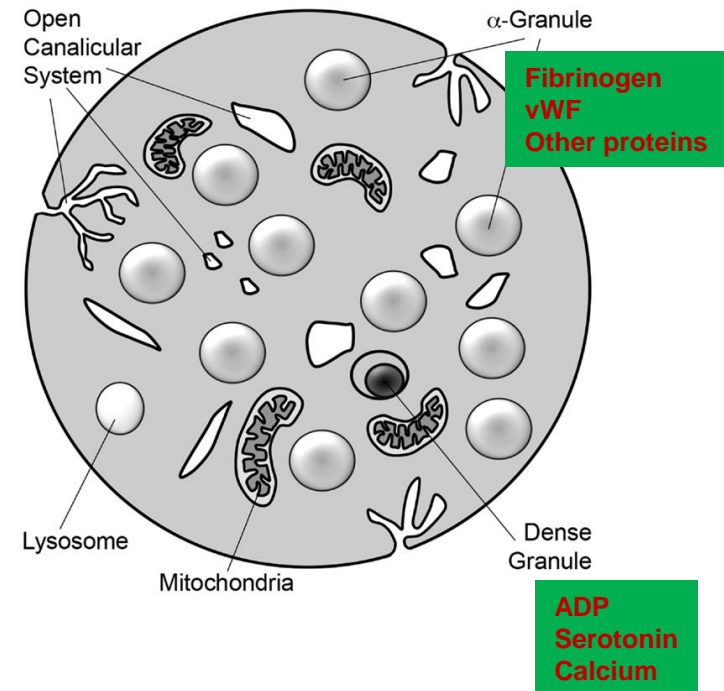
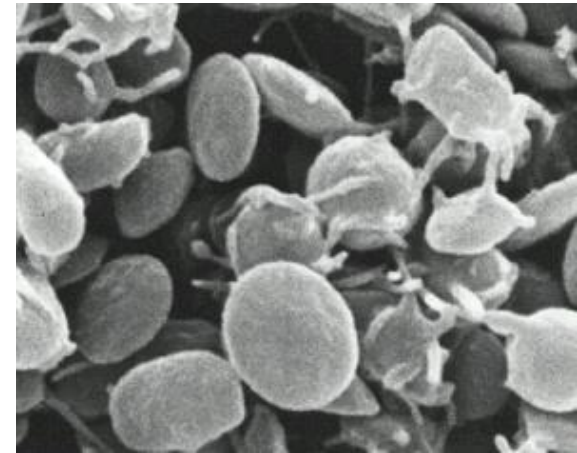
Platelets (PLT)

(Thrombocytes)

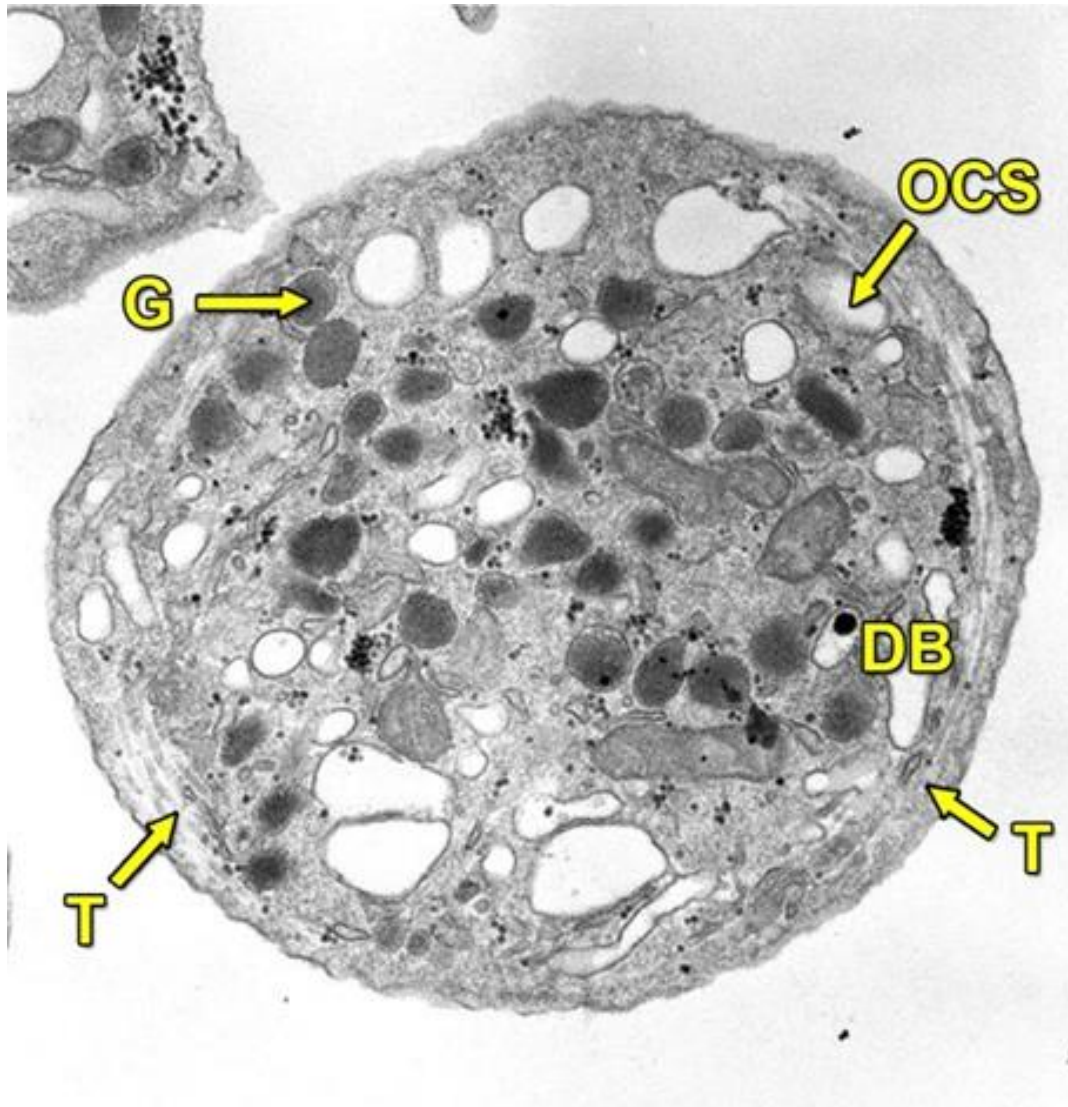


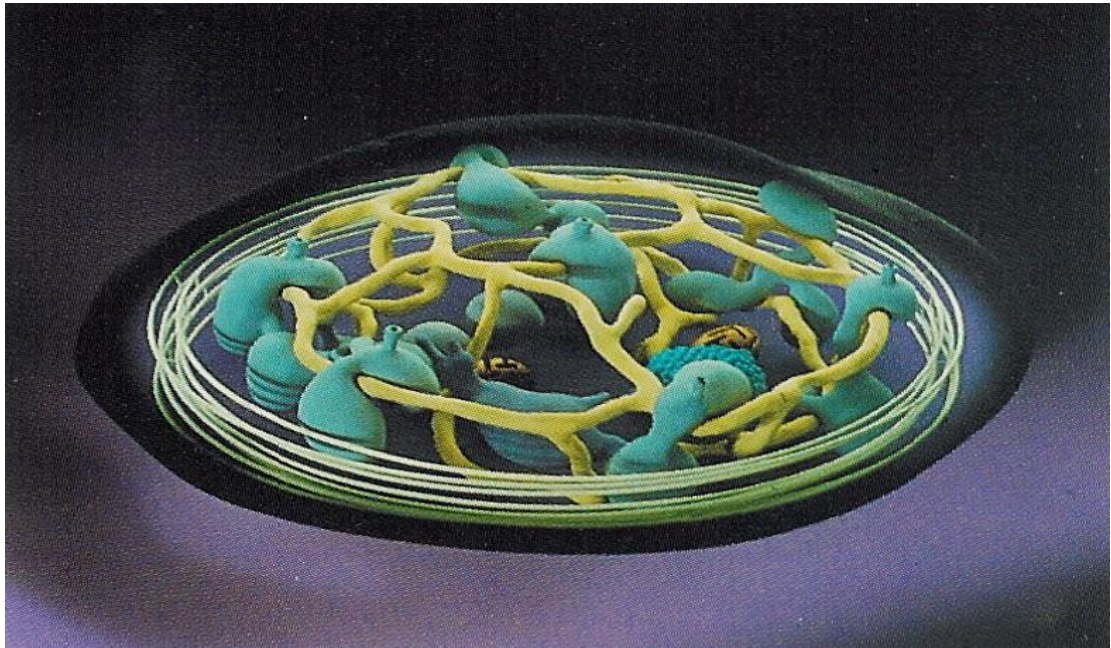
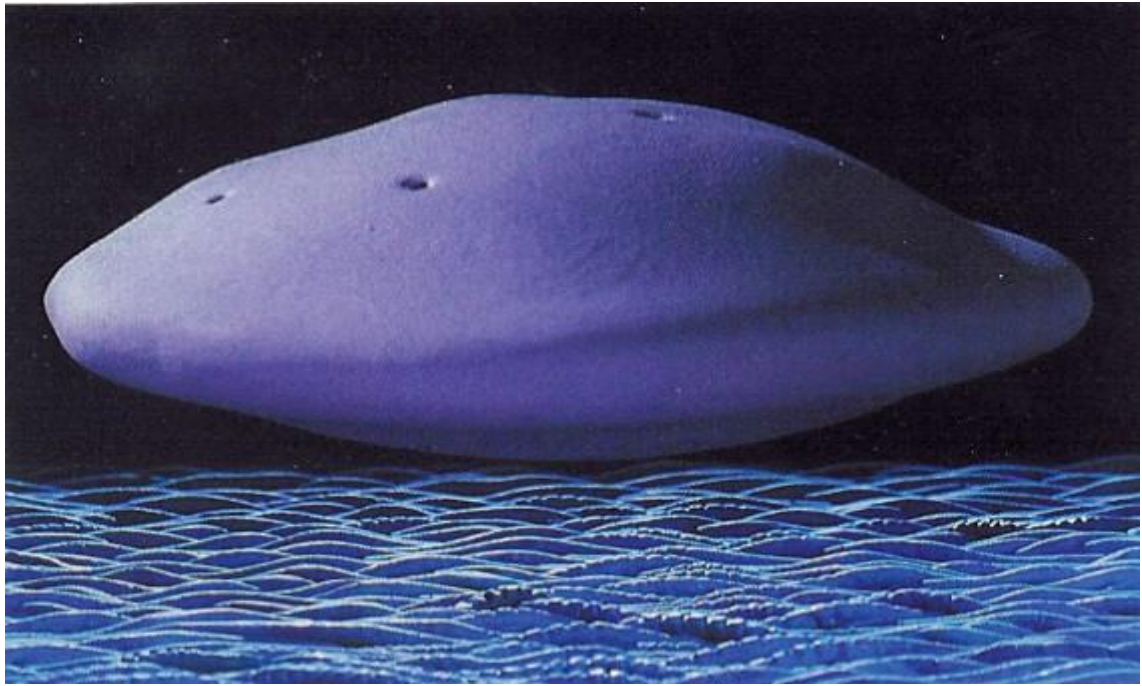
Platelets (PLT)

- small disc shaped cells
- Platelet count = $150 \times 10^3 - 300 \times 10^3 / \text{ml}$,
- life span 8-12 days
- Contain high calcium content & rich in ADP
- Active cells contain contractile protein,

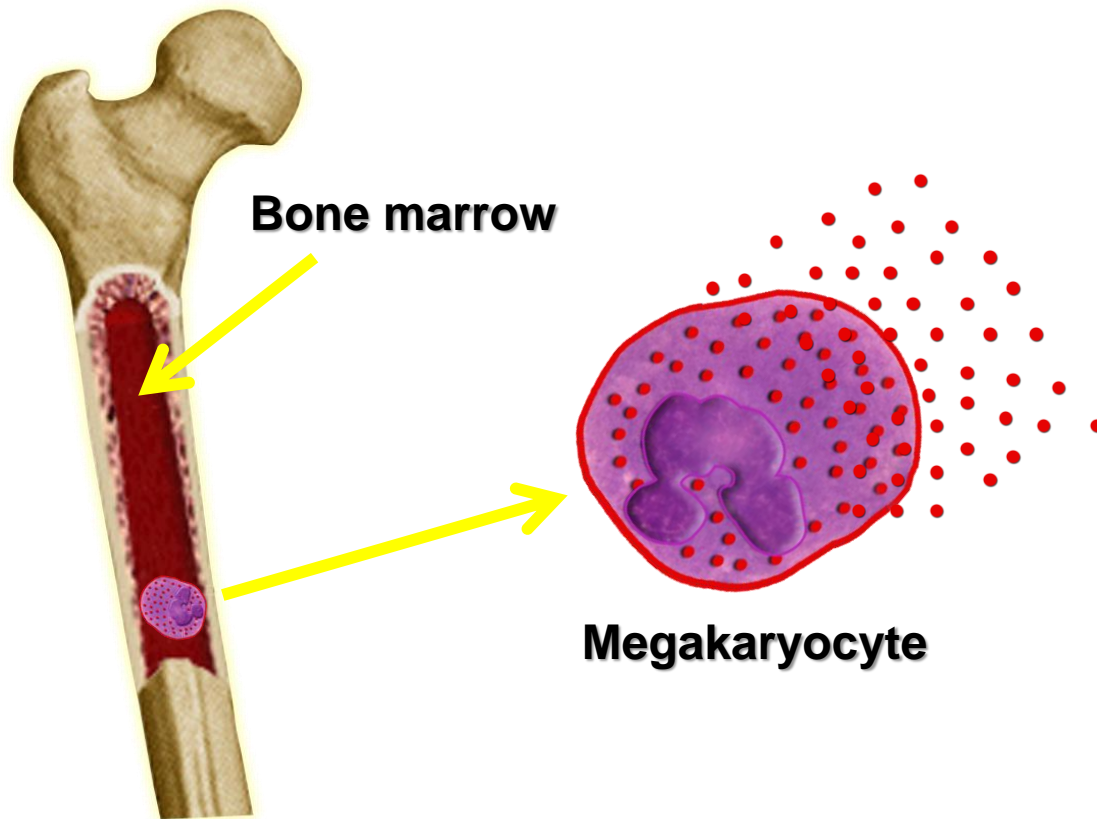


Platelets (PLT)

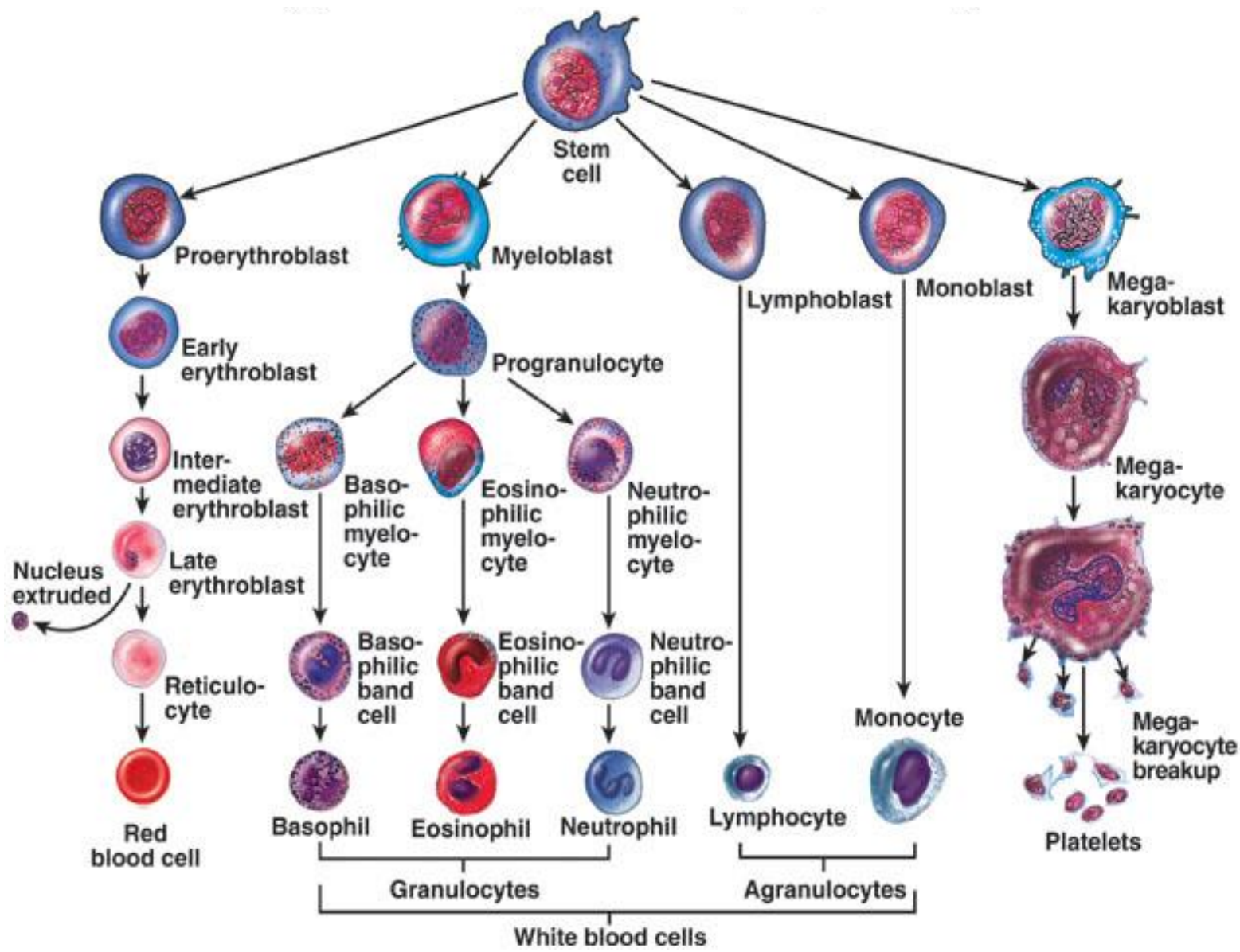




What are platelets?



- Thrombocytes are Fragments of megakaryocytes in the bone marrow
- Regulation of thrombopoiesis
By:
Thrombopoietin



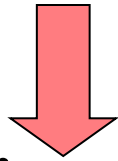
Platelets - cont.

Site of formation:

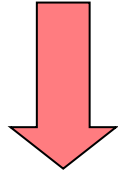
Bone marrow

Steps:

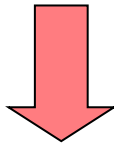
Stem cell



Megakaryoblast

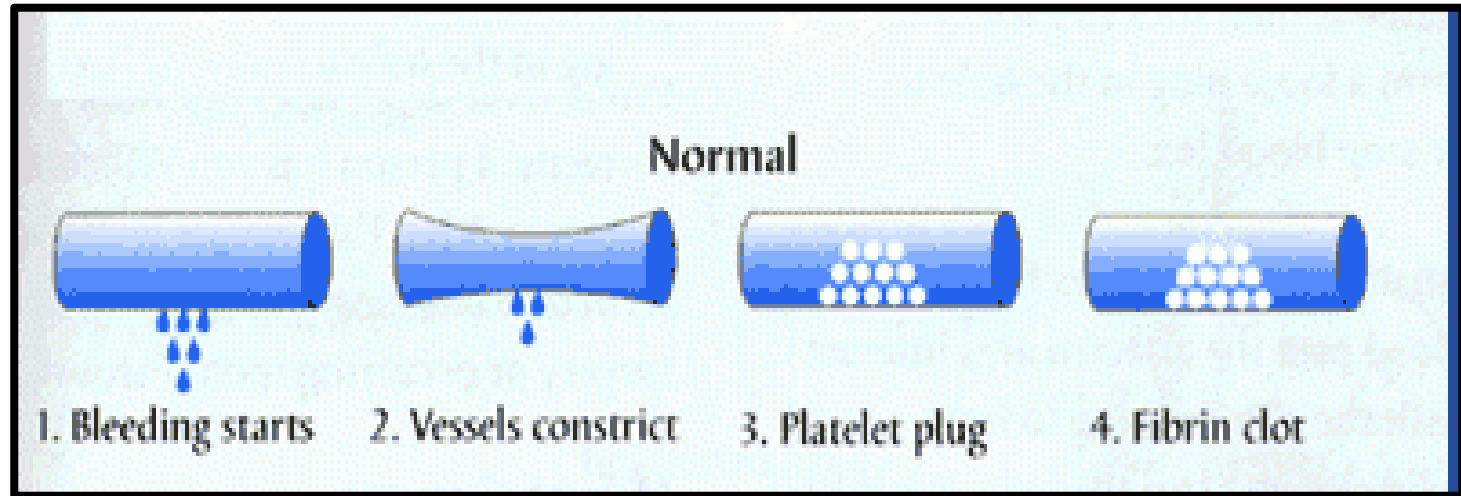


Megakaryocyte



Platelets

Platelet haemostatic plug formation



Platelet Functions

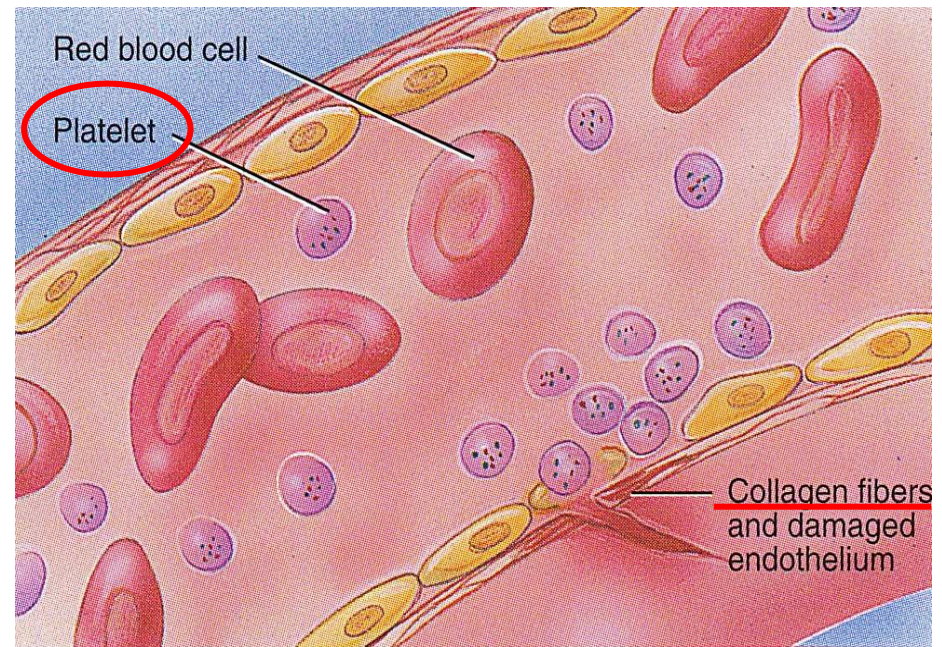
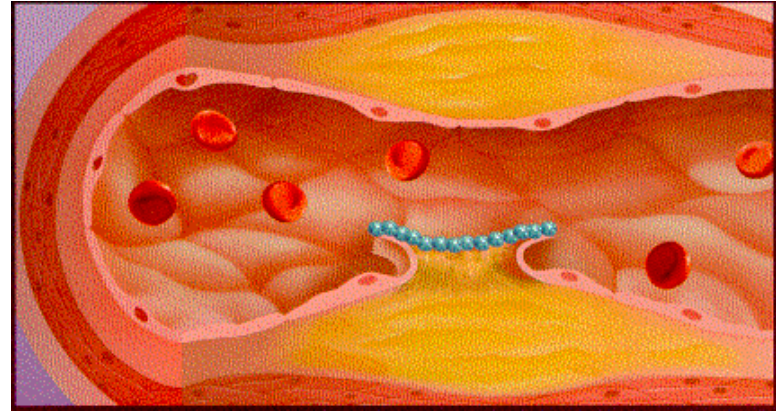
Begins with Platelet activation

Platelet Activation

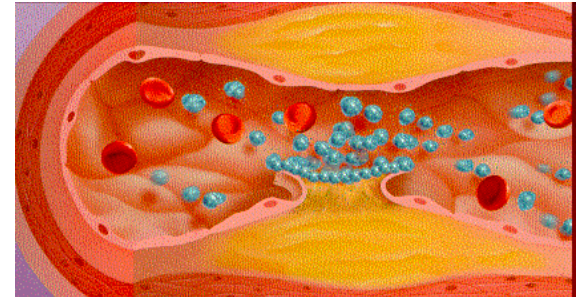
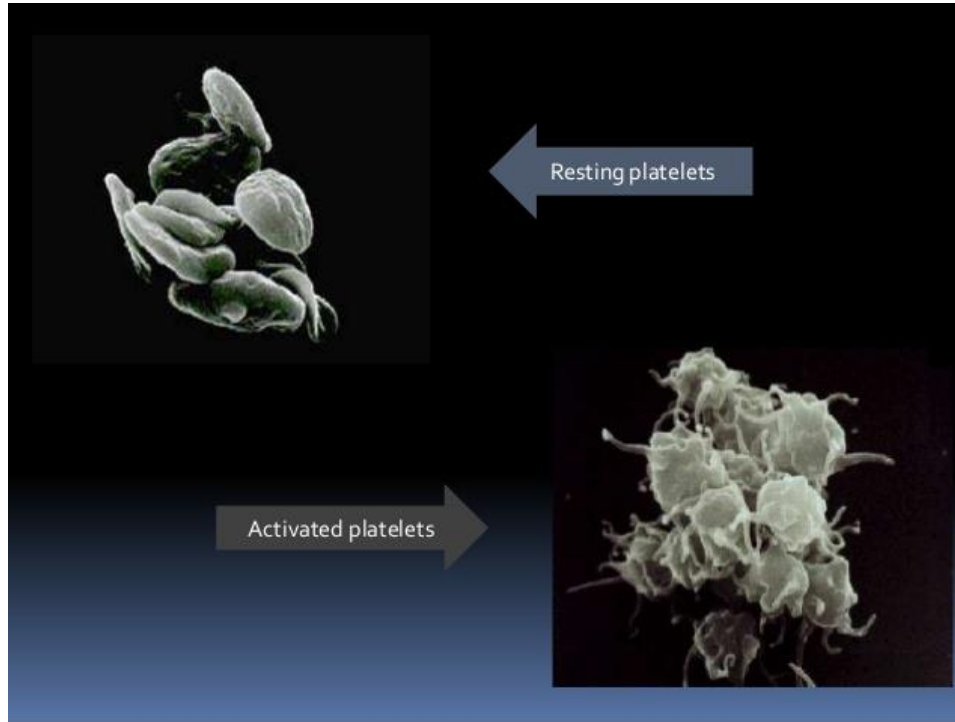
- Adhesion
- Shape change
- Aggregation
- Release
- Clot Retraction

Platelet Adhesion

- Exposed collagen attracts platelets
- Platelets stick to exposed collagen underlying damaged endothelial cells in vessel wall



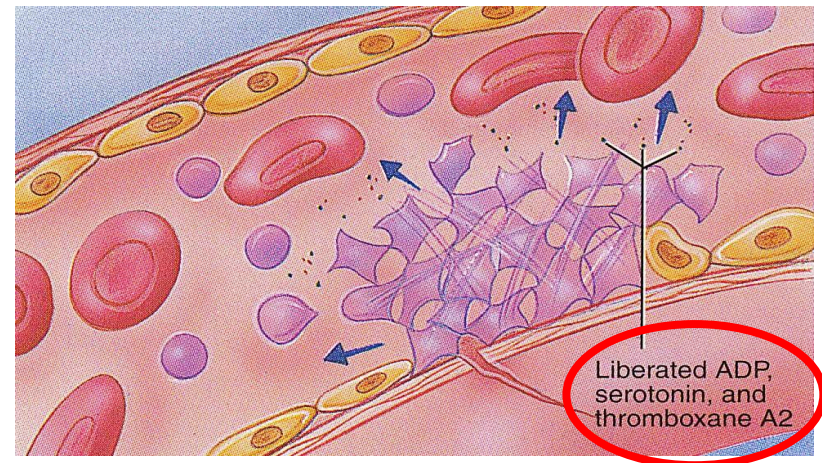
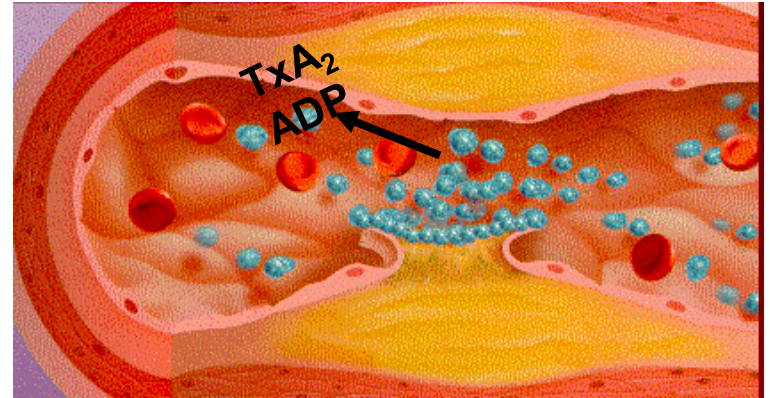
Platelet Activation



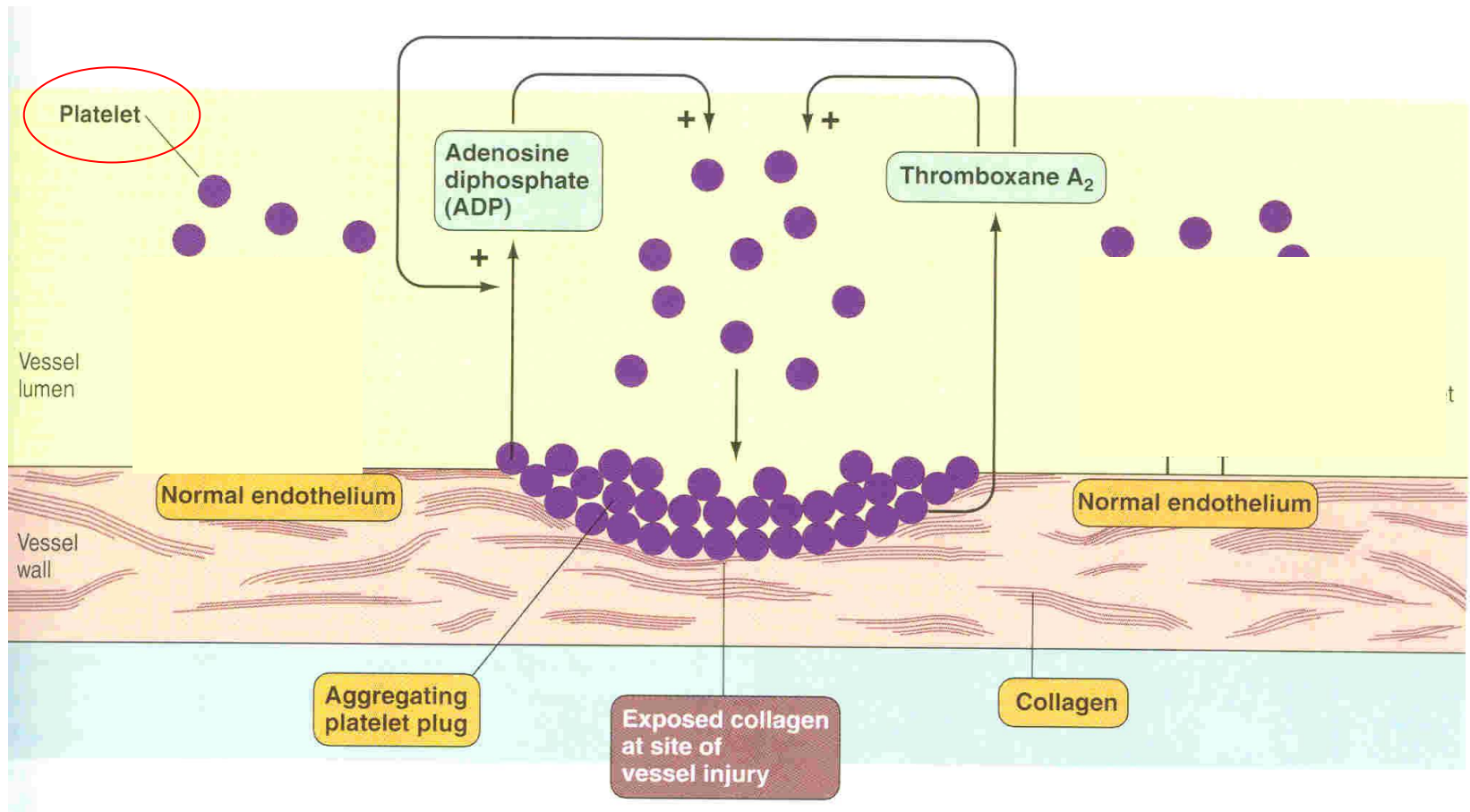
- **Platelets activated by adhesion**
- **Extend projections to make contact with each other**

Platelet Release Reaction

- Activated platelets release Serotonin, ADP & Thromboxane A2
- Serotonin & thromboxane A2 are vasoconstrictors decreasing blood flow through the injured vessel.
- ADP & Thromboxane A2 (TXA₂) → ↑ the stickiness of platelets → ↑ Platelets aggregation → plugging of the cut vessel



Platelets aggregation



Platelet Release

Secrete:

1. 5HT → vasoconstriction
2. ADP
3. Platelet phospholipid (PF3) → clot formation
4. Thromboxane A2 (TXA2) is a prostaglandin formed from arachidonic acid

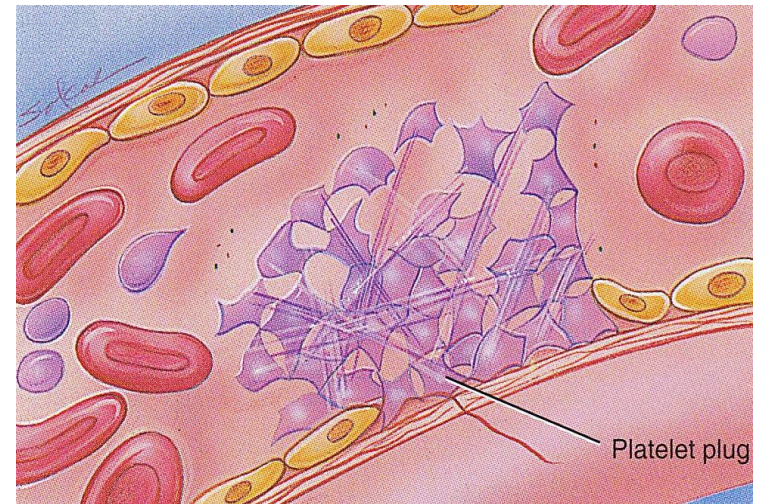
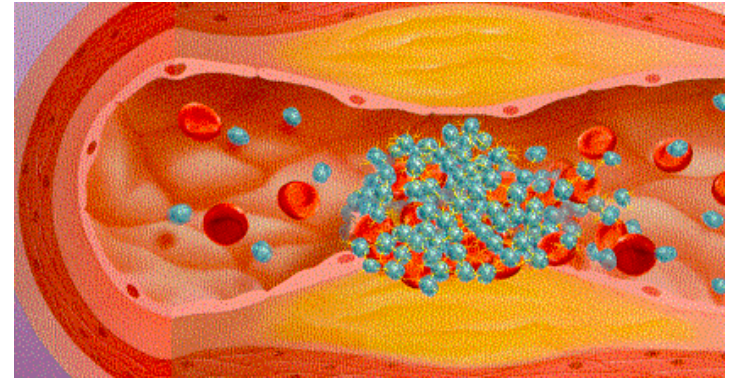
Function:

- vasoconstriction
- Platelet aggregation

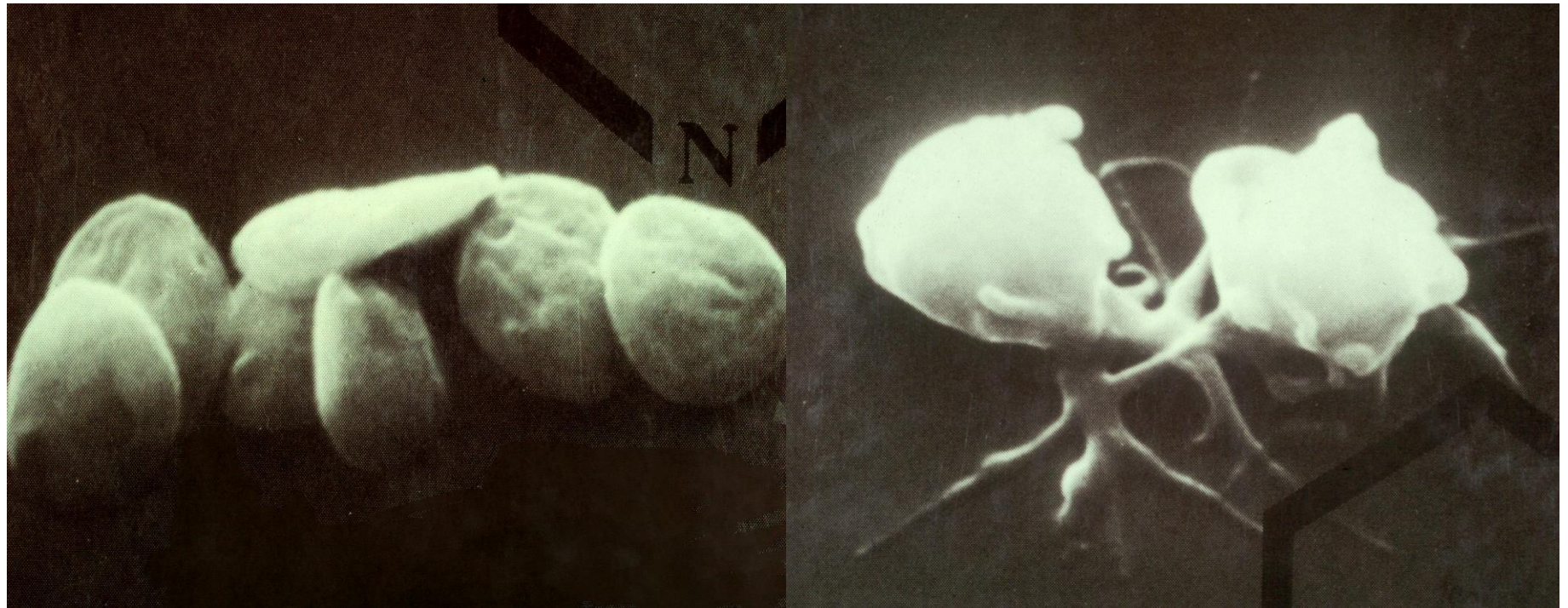
(TXA2 inhibited by aspirin)

Platelet Aggregation

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



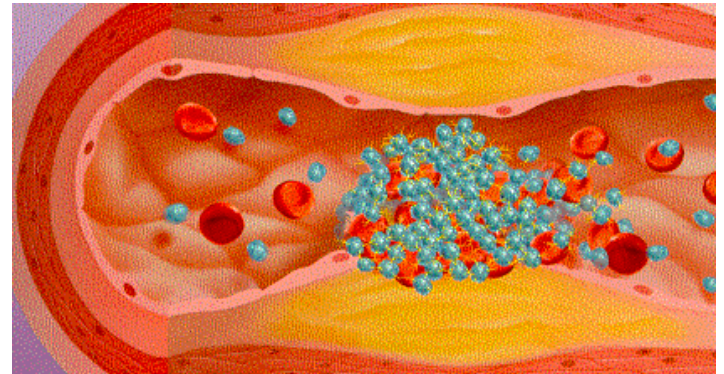
Platelet shape change and Aggregation



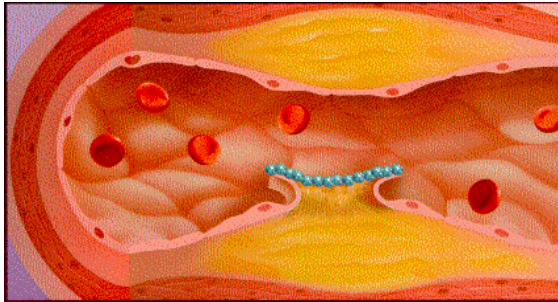
Clot Retraction

- Clot Retraction:

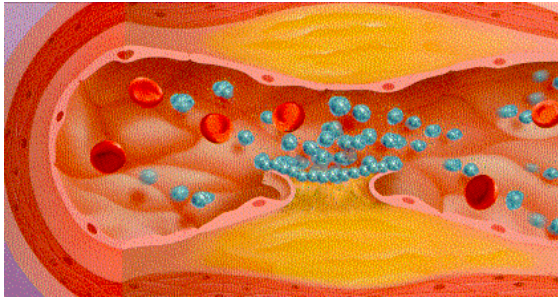
Myosin and actin filaments in platelets are stimulated to contract during aggregation further reinforcing the plug and help release of granule contents



Platelet function

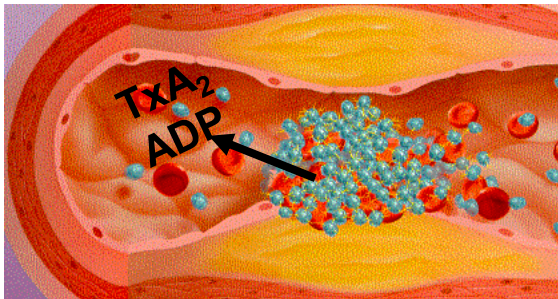


Adhesion

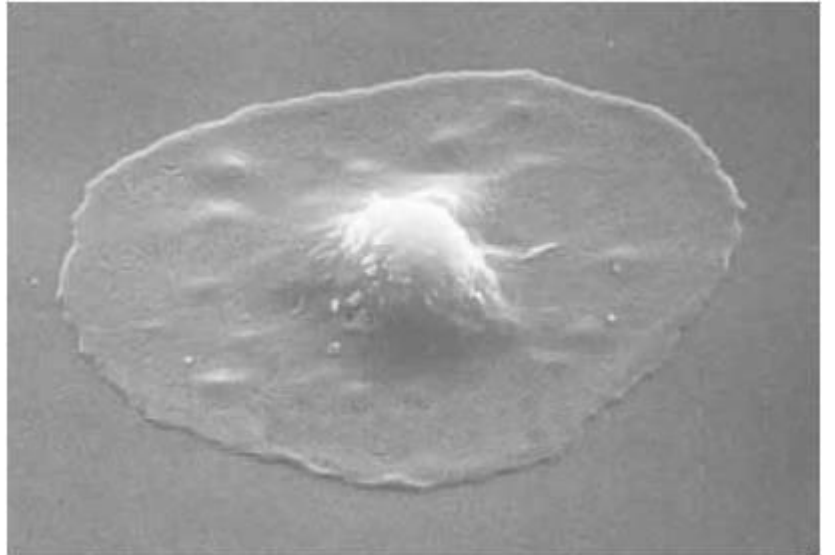
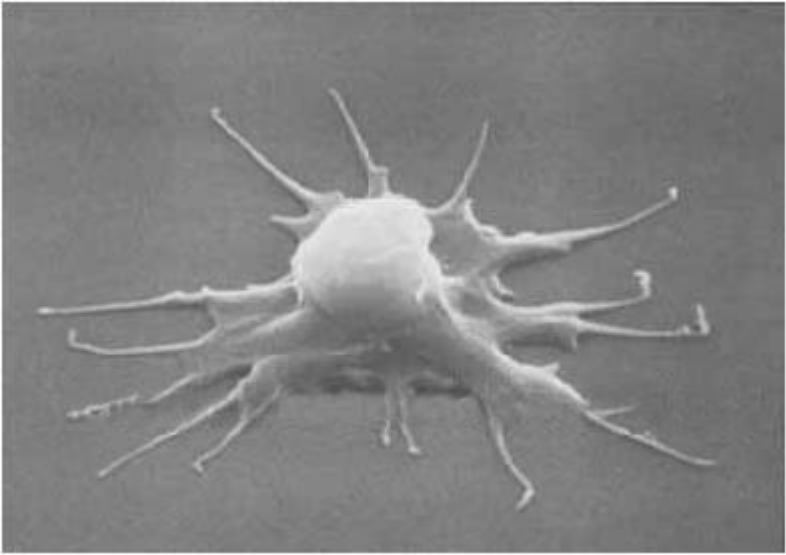
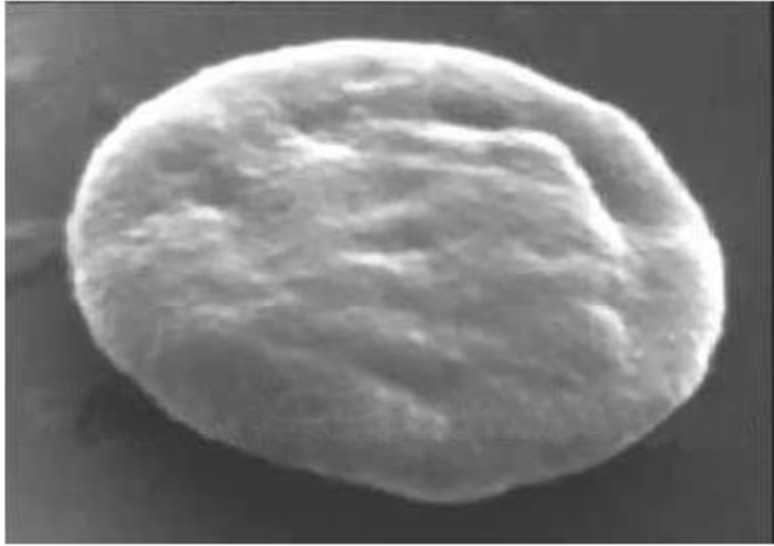


Activation

Aggregation



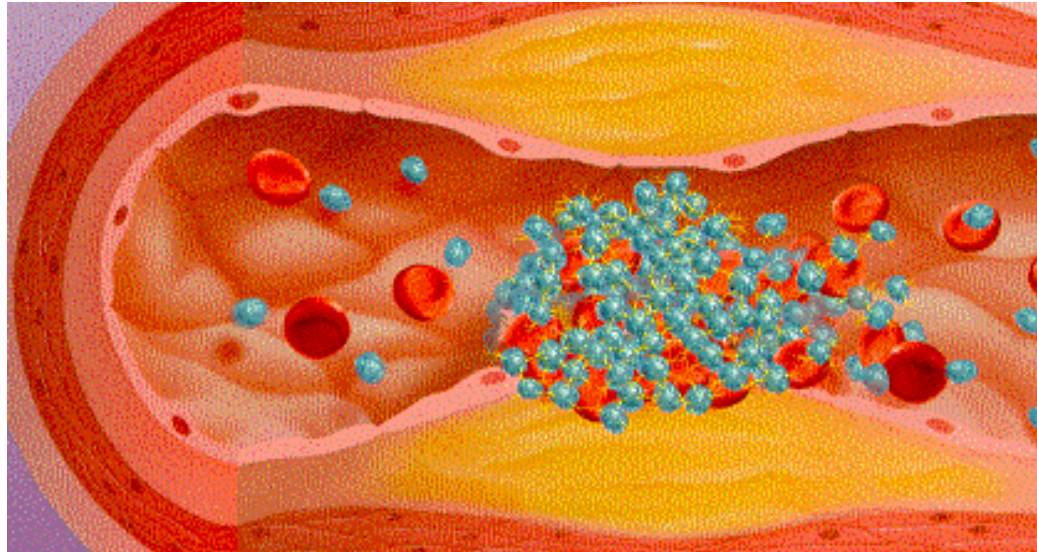
Secretion



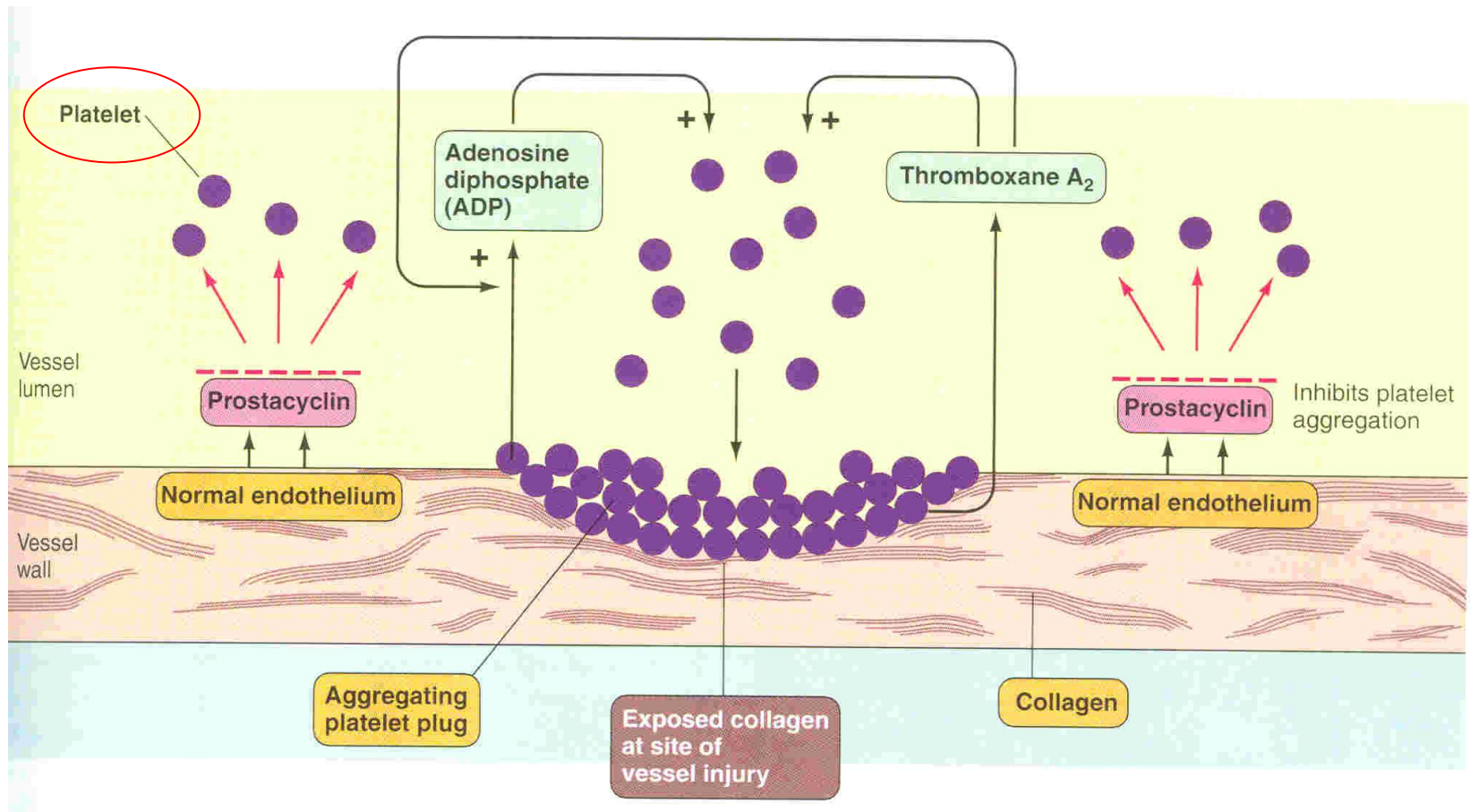
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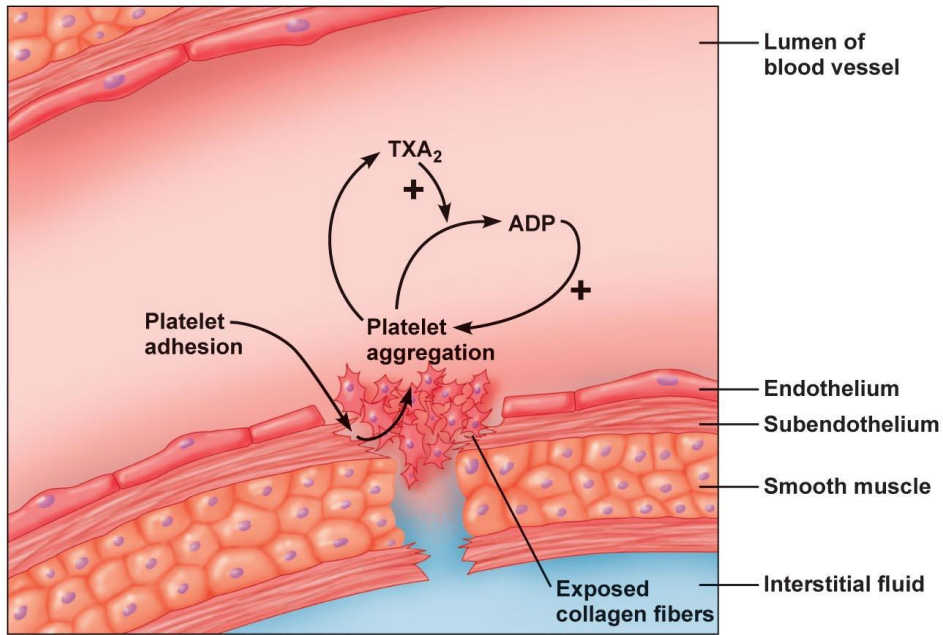


Why platelet plug is limited?



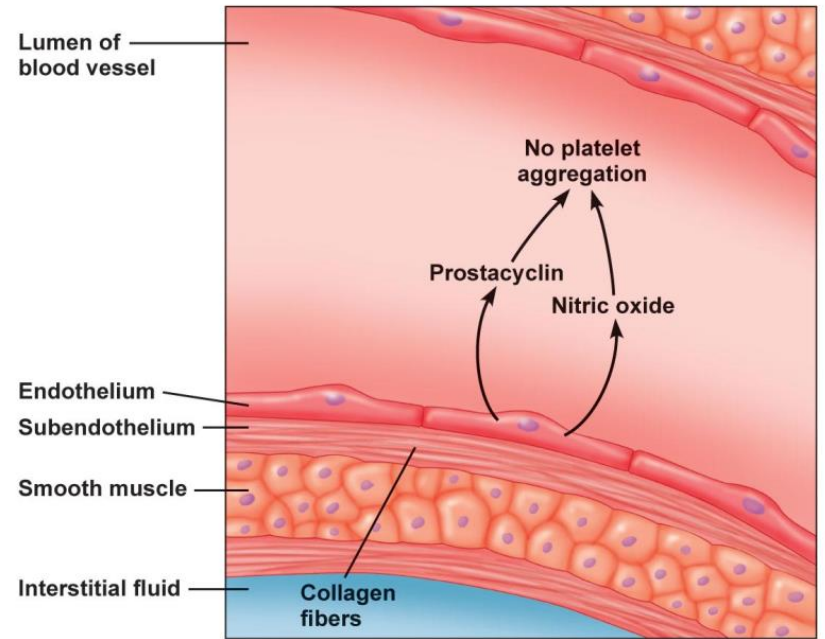
Platelets aggregation





(a) Damaged blood vessel endothelium

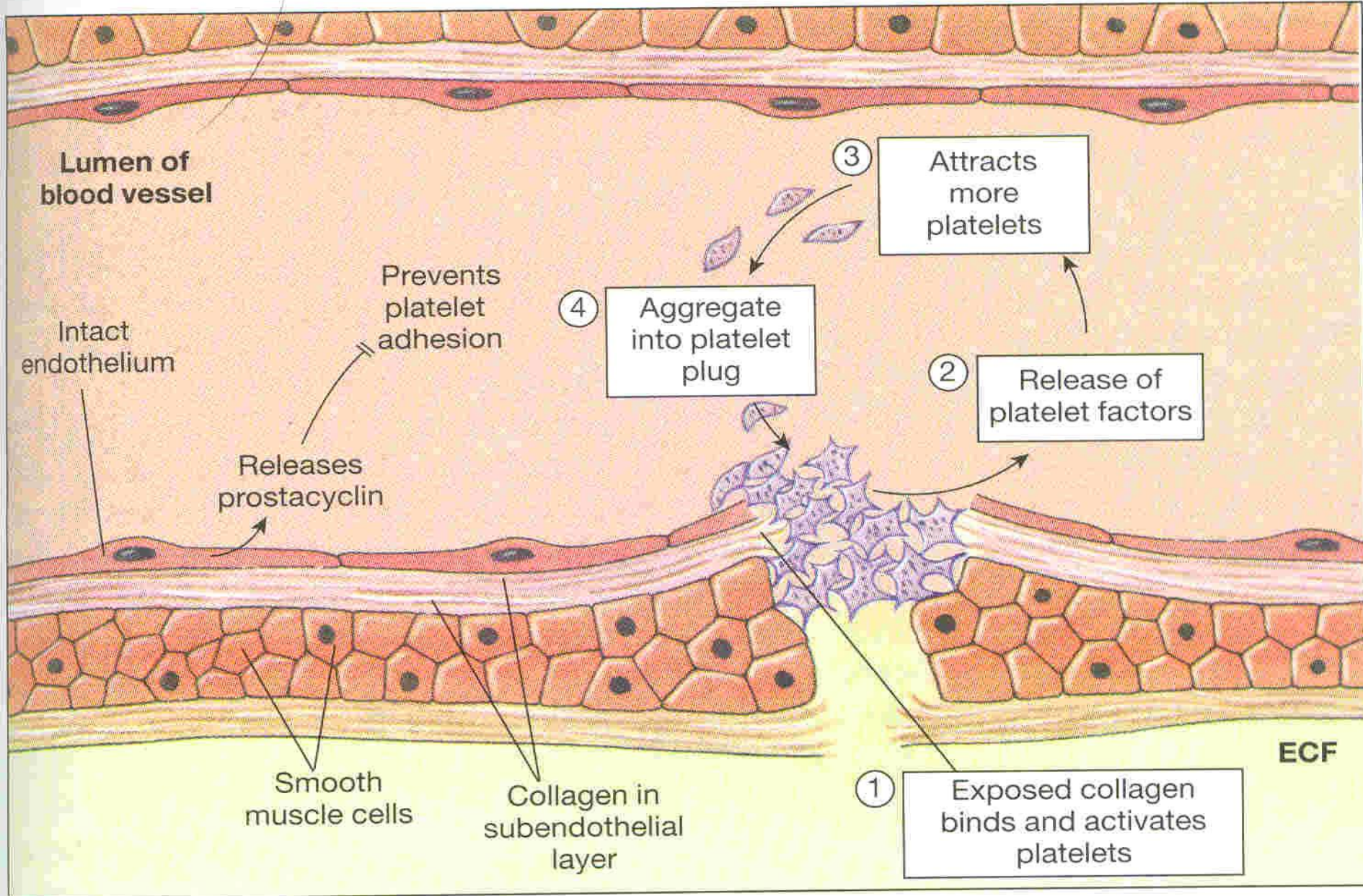
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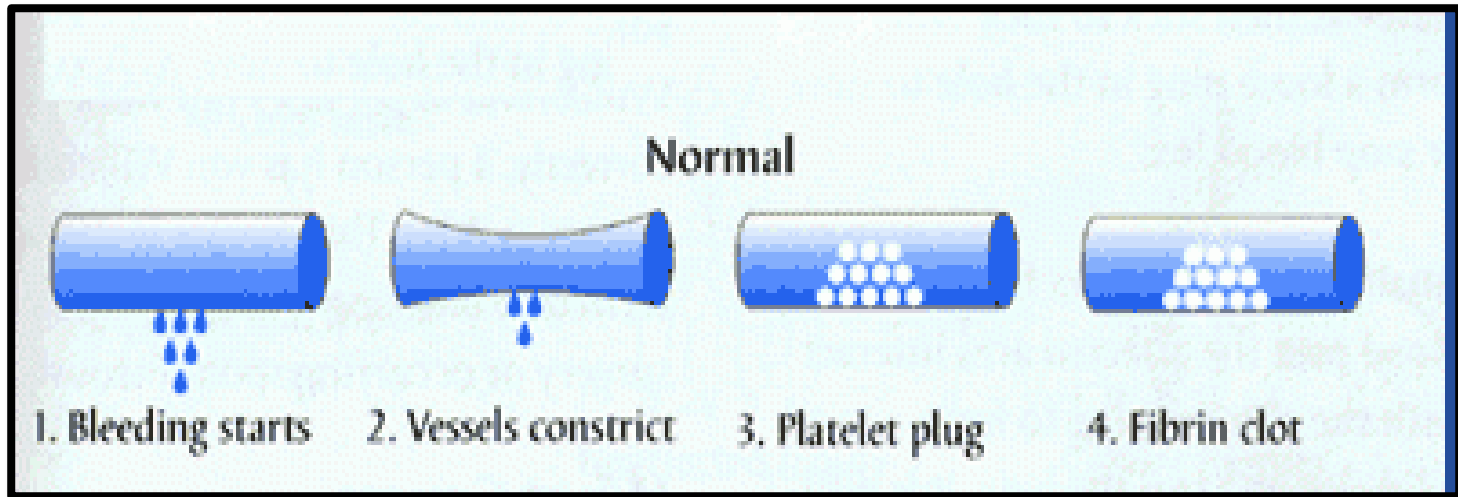


(b) Normal blood vessel endothelium

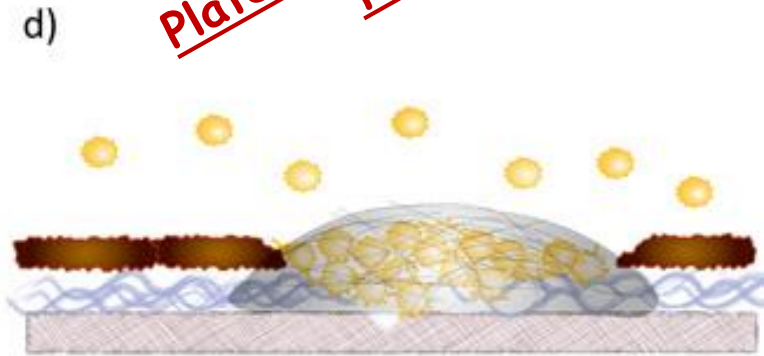
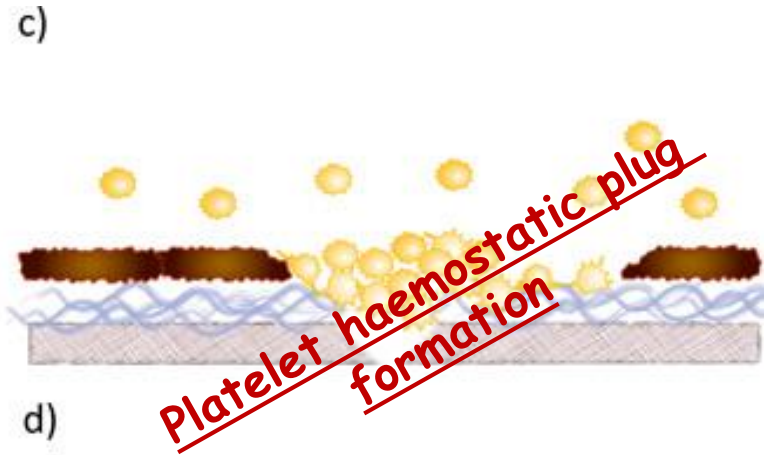
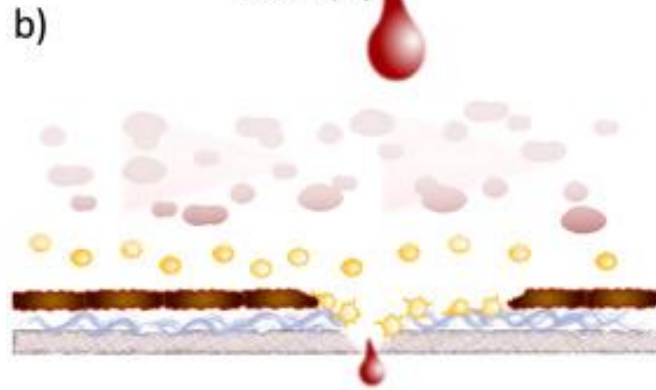
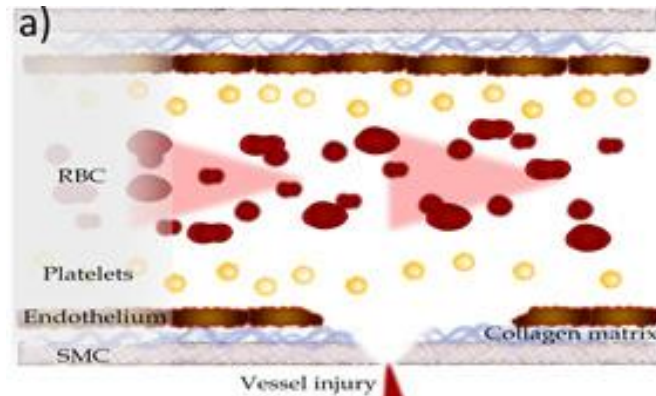
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Platelet plug formation





Platelet haemostatic plug formation

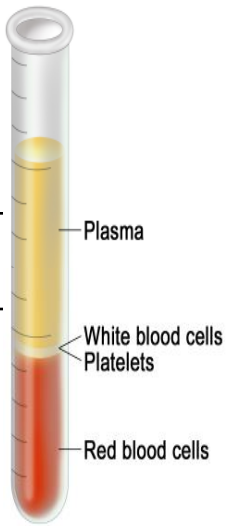


Hemostatic Mechanisms:

- **Mechanisms:**
 - Vessel wall
 - Platelet
 - **Blood coagulation**
 - Fibrinolytic system

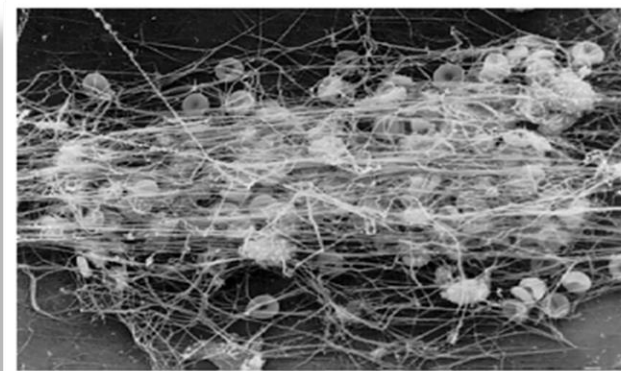
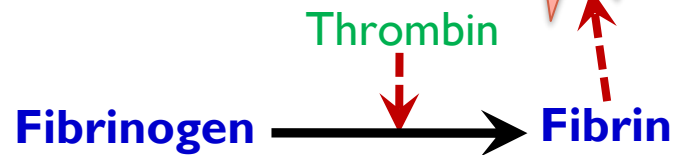
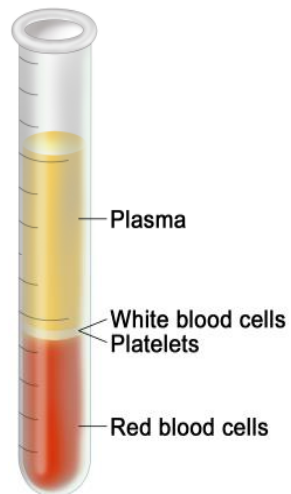
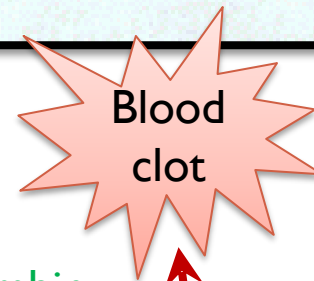
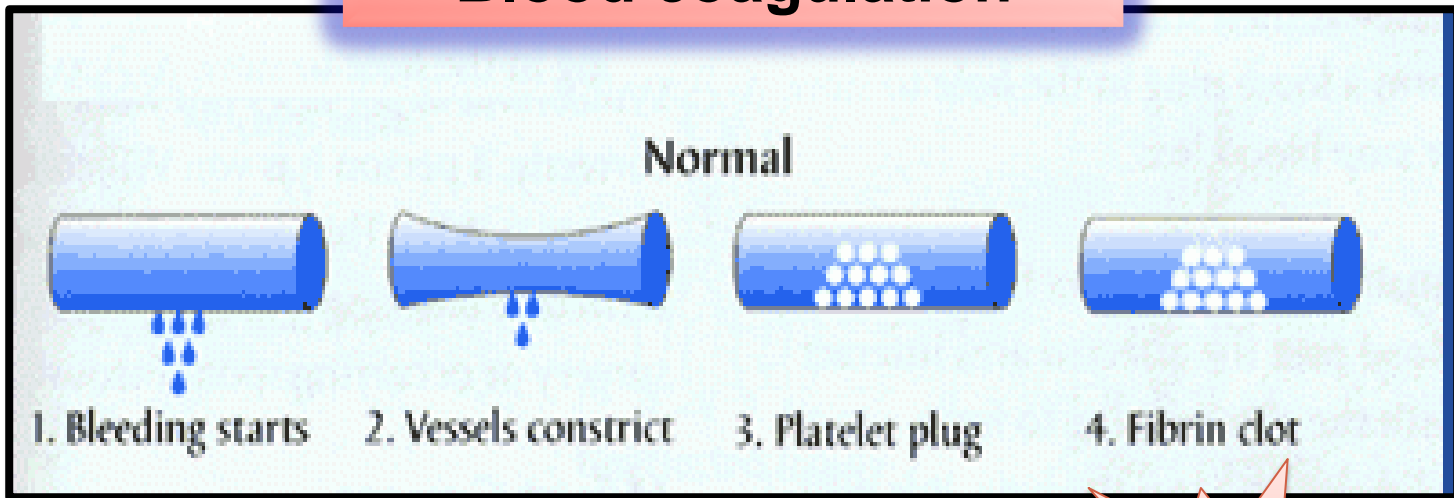
Clotting Factors

Factors	Names
I	Fibrinogen
II	Prothrombin
III	Thromboplastin
IV	Calcium
V	Labile factor
VII	Stable factor
VIII	Antihemophilic factor A
IX	Antihemophilic factor B
X	Stuart-Power factor
XI	Plasma thromboplastin antecedent (PTA)
XII	Hagman factor
XIII	Fibrin stabilizing factors



Circulate
in plasma
in inactive
state

Blood coagulation



The Intrinsic Pathway

Blood trauma
or contact
with collagen

The Extrinsic Pathway

Tissue trauma

Tissue factor (TF)

FVIIa ← FVII

Ca⁺⁺

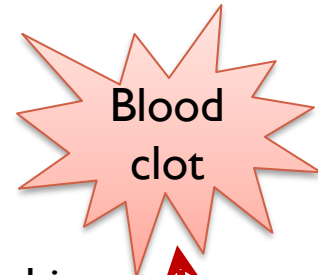
FVIII
PLTs
Ca⁺⁺

FX → FXa

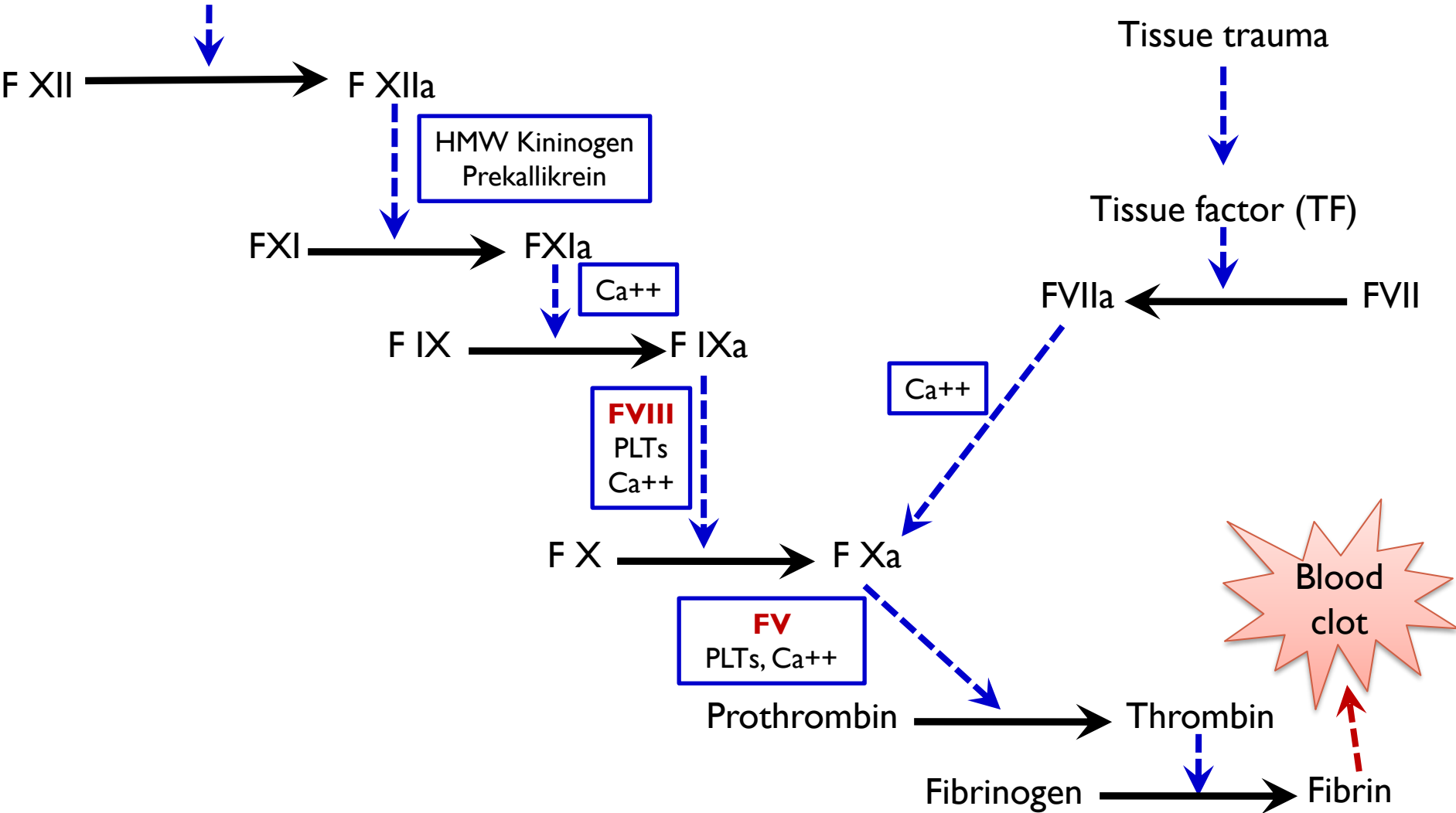
FV
PLTs, Ca⁺⁺

Prothrombin → Thrombin

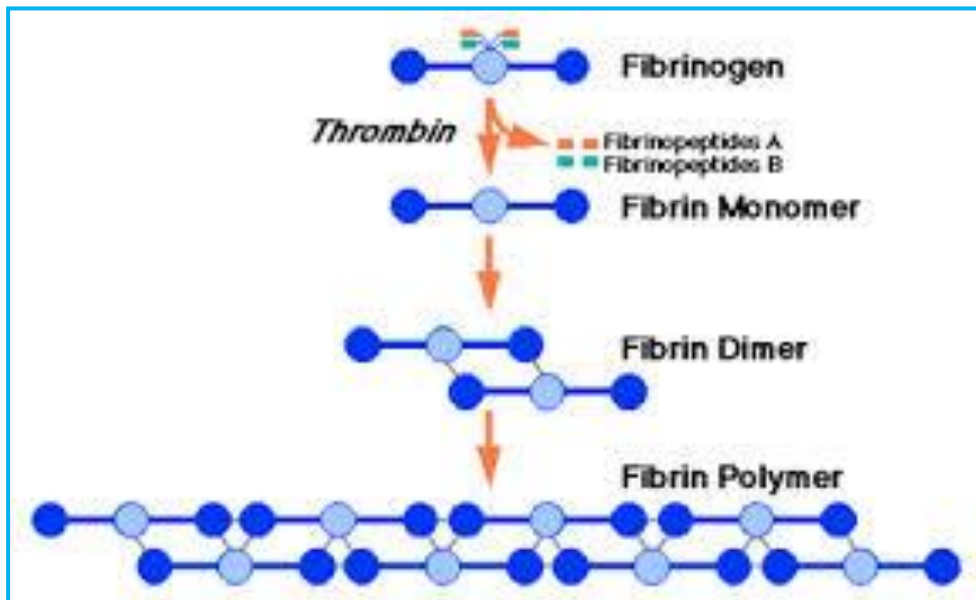
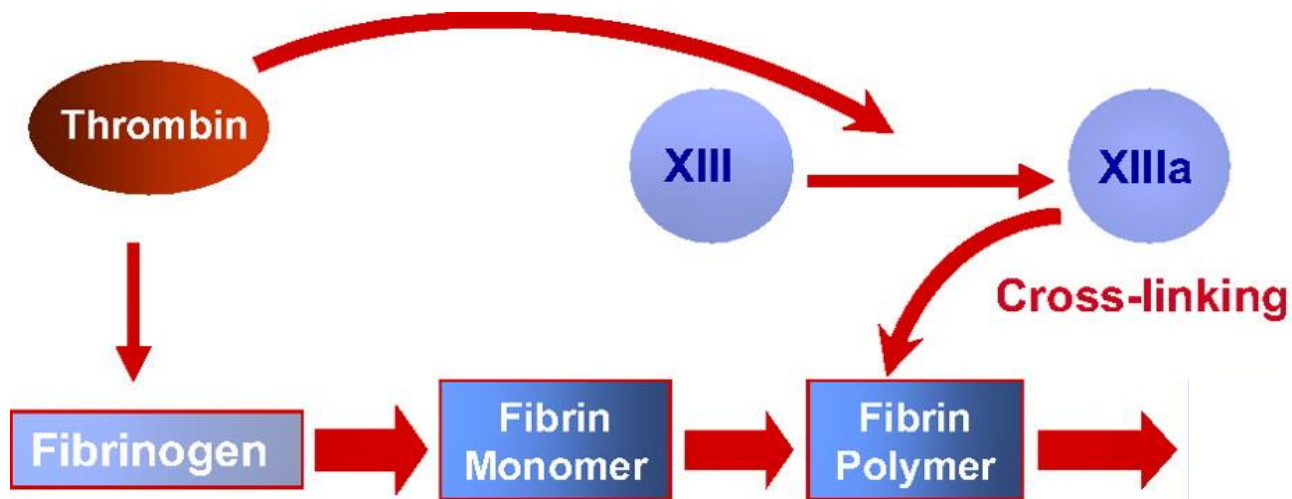
Fibrinogen → Fibrin

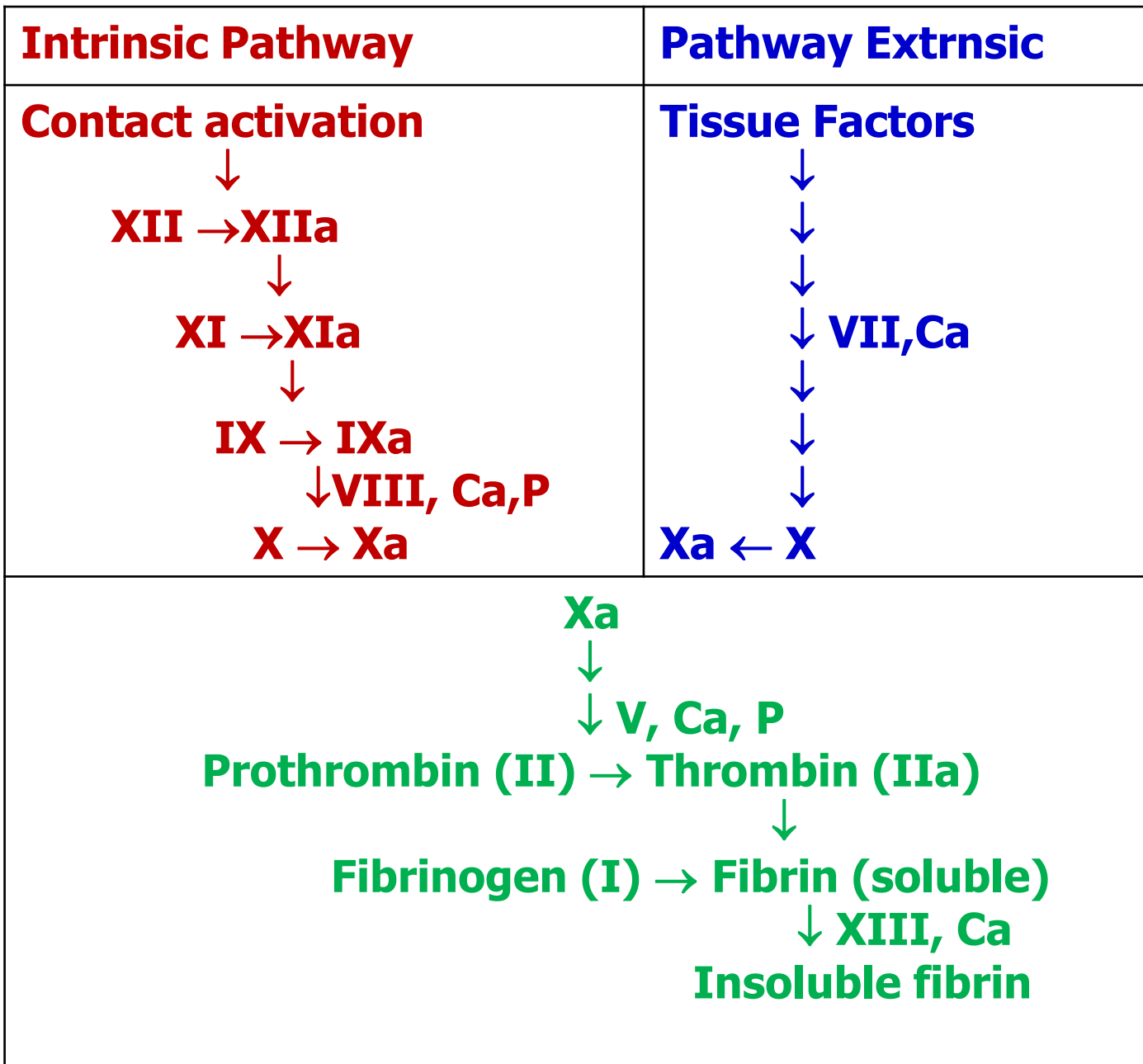


Blood
clot

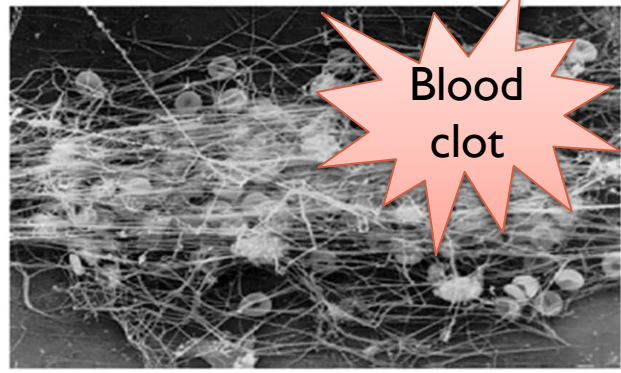
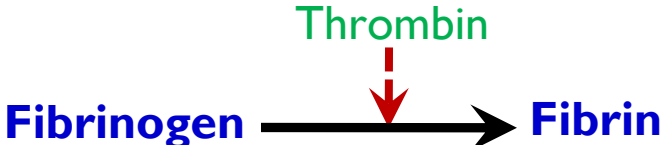
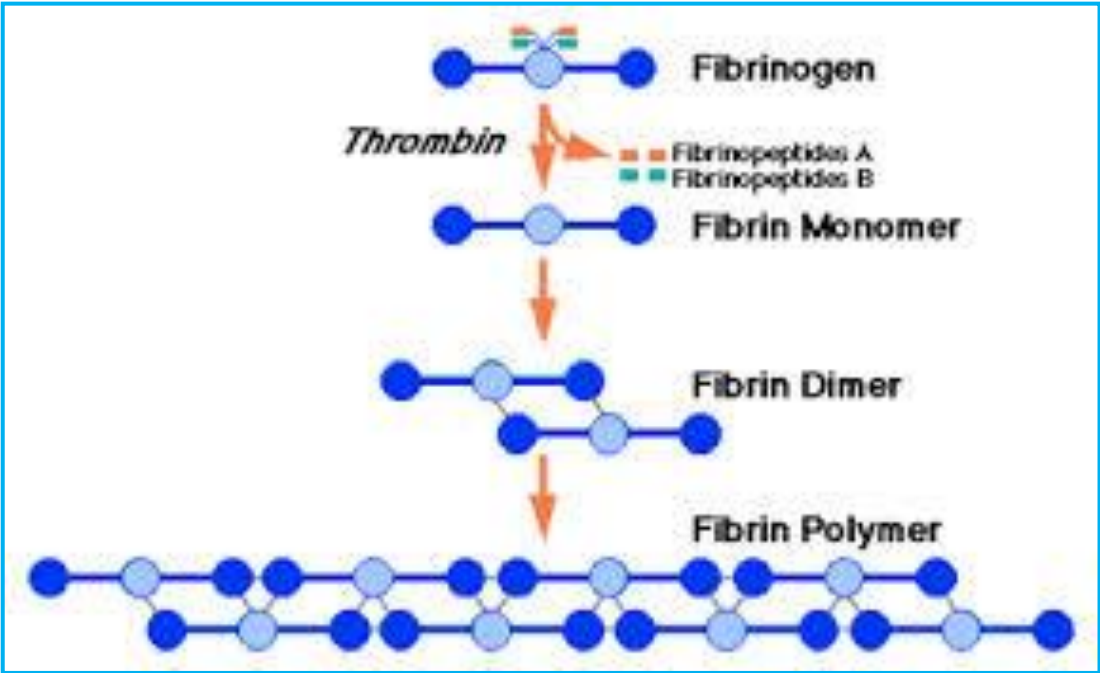


Blood coagulation





Blood coagulation

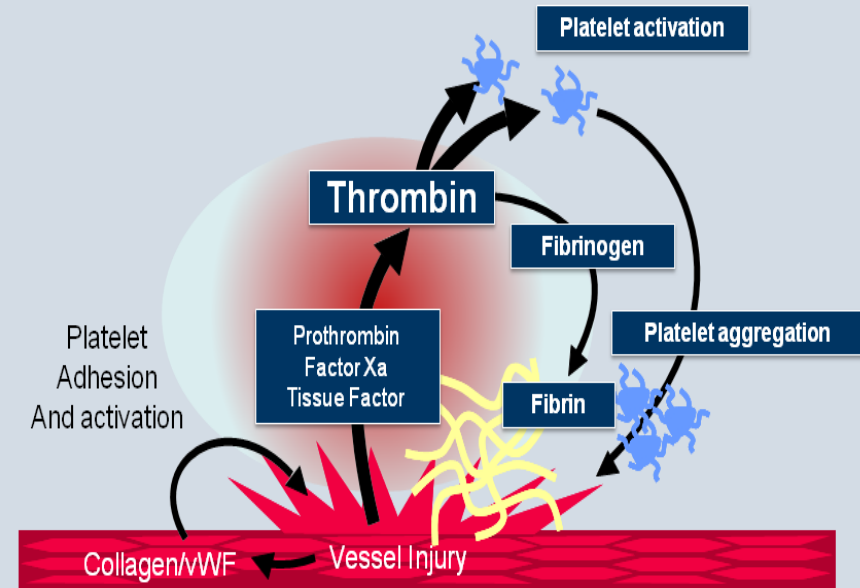


Thrombin

- Thrombin changes fibrinogen to fibrin
- Activates factor V and 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

Critical Role of Thrombin

Thrombin is the link between vascular injury, coagulation, and platelet activation





IMESHOTS

Blood coagulation

(clot formation)

- A series of biochemical reactions leading to the formation of a blood clot
- This reaction leads to the activation of thrombin enzyme from inactive form prothrombin
- Thrombin will change fibrinogen (plasma protein) to fibrin (insoluble protein)
- Prothrombin (inactive thrombin) is activated by a long intrinsic or short extrinsic pathways

Blood coagulation

Intrinsic Pathway

- The trigger is the activation of factor XII by contact with foreign surface, injured blood vessel, and glass.
- Activate factor (XIIa) will activate XI
- XIa will activate IX
- IXa + VIII + platelet phospholipid + Ca activate X
- Following this step the pathway is common for both

Blood coagulation

Extrinsic pathway

- Triggered by material released from damaged tissues (tissue thromboplastin)
- tissue thromboplastin + VII + Ca → activate X

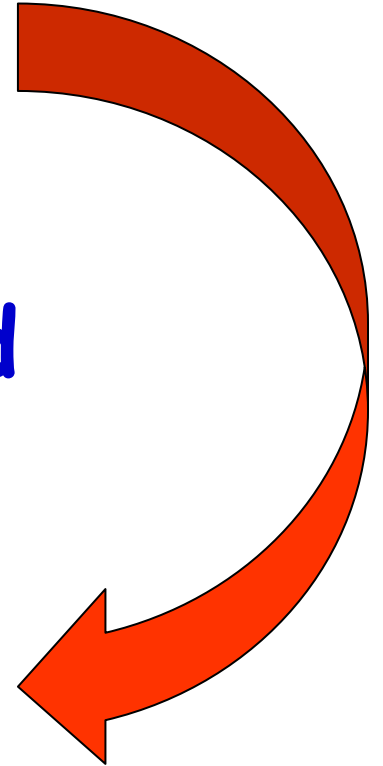
Common pathway

- Xa + V + PF3 + Ca (prothrombin activator) it is a proteolytic enzyme activate prothrombin → thrombin
- Thrombin act on fibrinogen → insoluble thread like fibrin
- Factor XIII + Ca → strong fibrin (strong clot)

Activation of Blood Coagulation

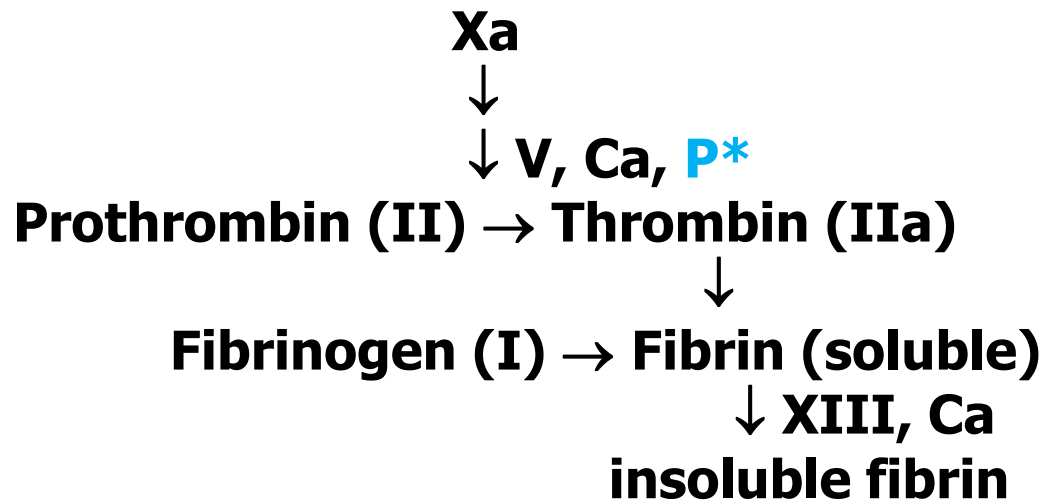
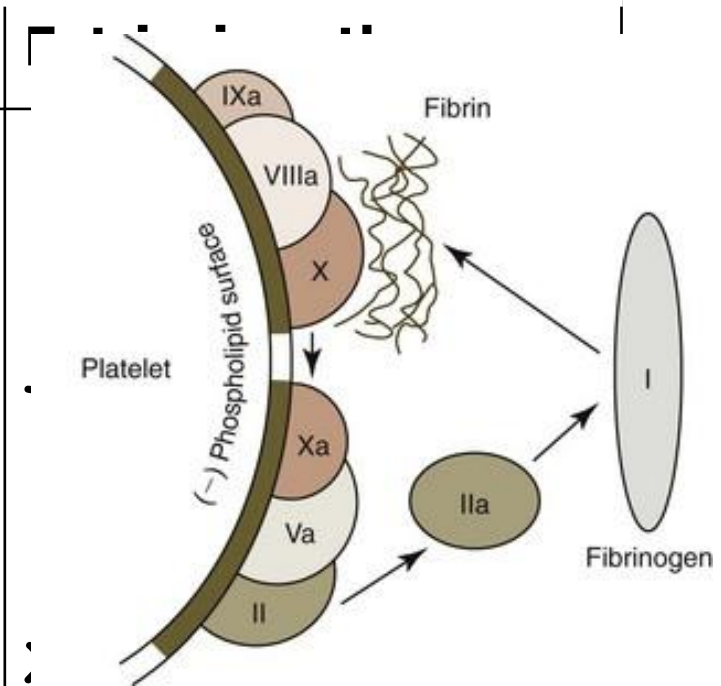
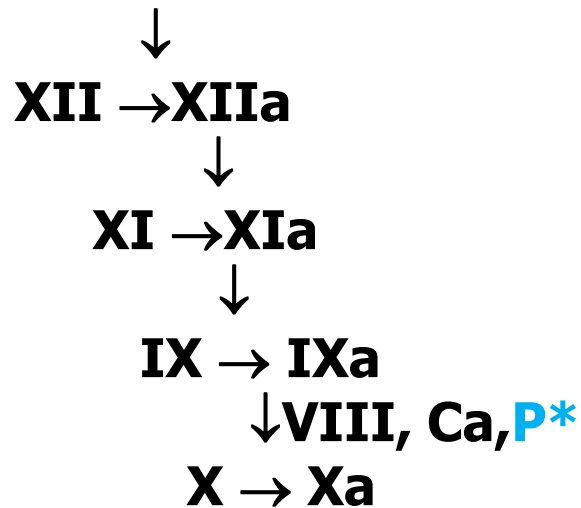
- **Intrinsic Pathway:** all clotting factors present in the blood
- **Extrinsic Pathway:** triggered by tissue factor

Common Pathway



Intrinsic Pathway

Contact activation



P* = phospholipid from platelets

The Intrinsic Pathway

Blood trauma
or contact
with collagen

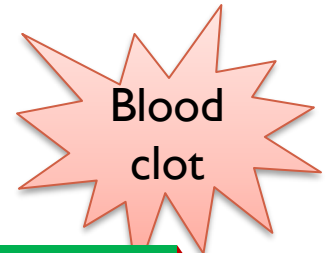
The Extrinsic Pathway

Tissue trauma

Tissue factor (TF)

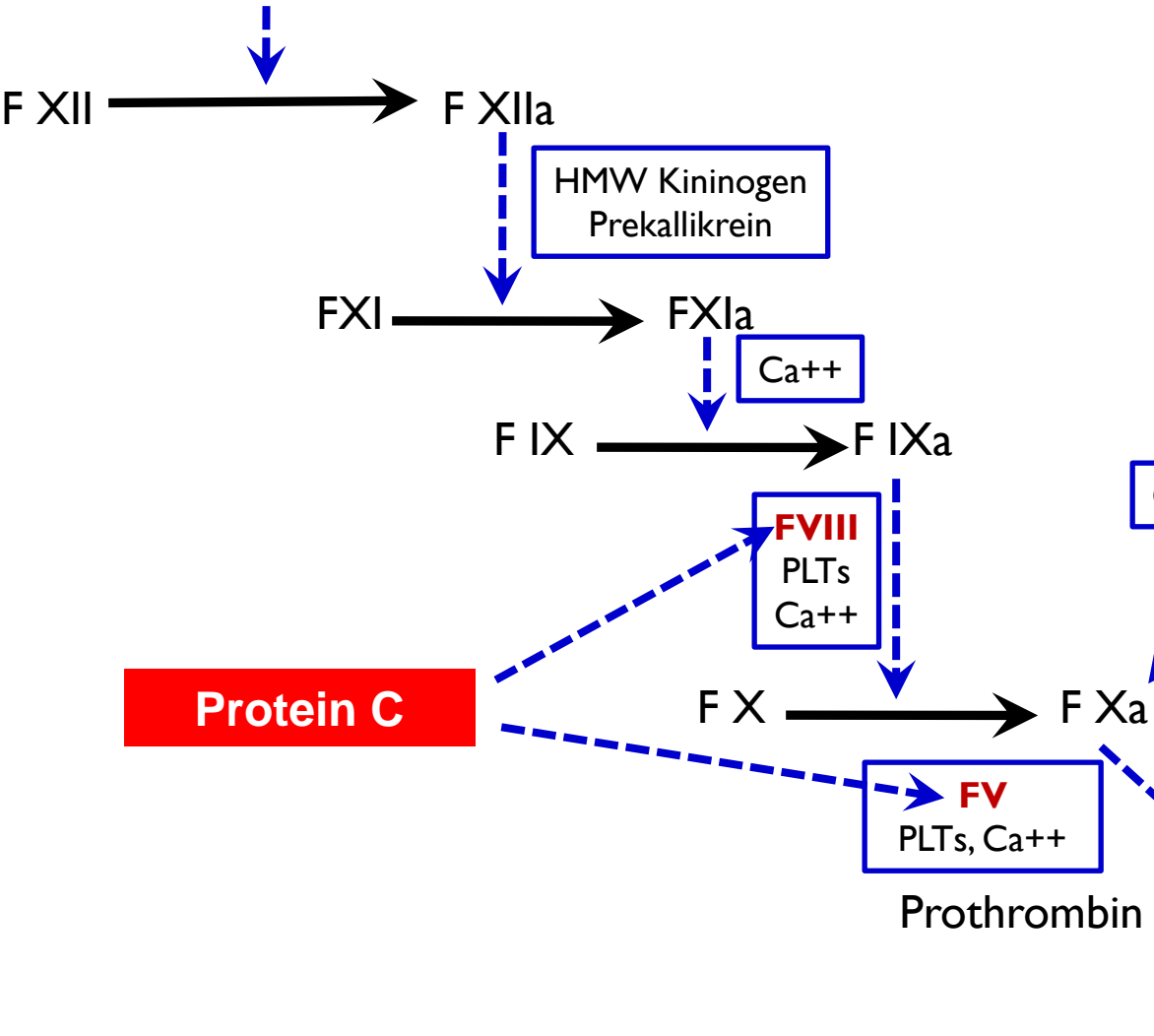
FVIIa ← FVII

Antithrombin



Antithrombin

Fibrinogen → Fibrin



Protein C

Ca⁺⁺

Ca⁺⁺

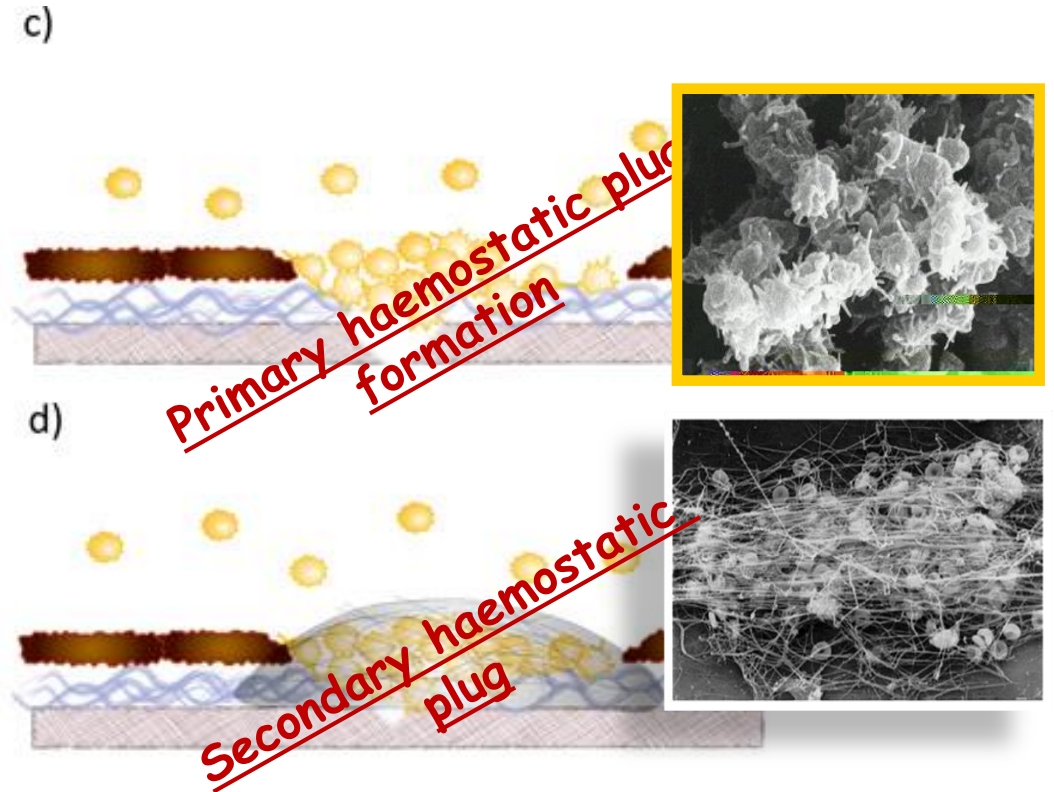
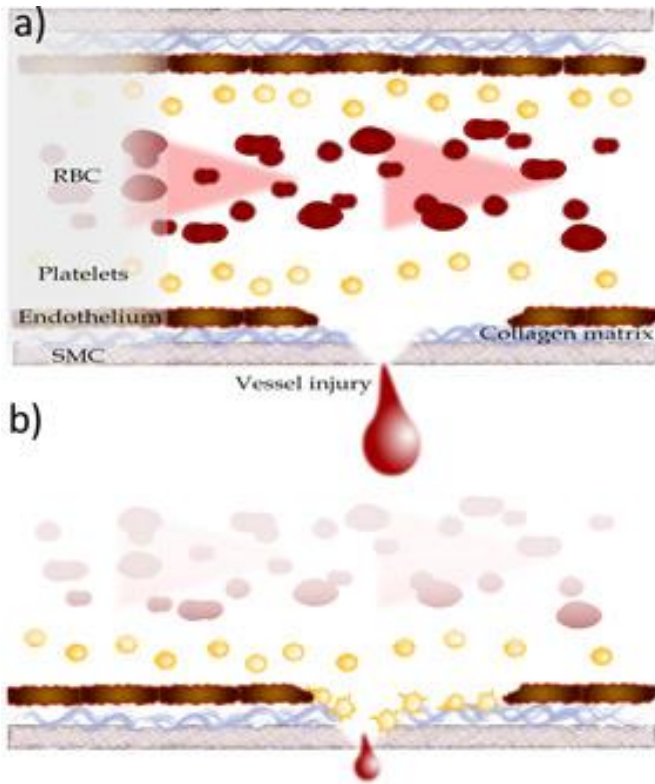
FVIII
PLTs
Ca⁺⁺

FV
PLTs, Ca⁺⁺

REGULATION OF COAGULATION

- Antithrombin:
inhibits thrombin and other enzymes
- Protein C:
degrades activated factors V and VIII
- Protein S:
cofactor for protein C
- Tissue factor pathway inhibitor (TFPI):
Inhibits the extrinsic system by inhibiting Factor VIIa
- Deficiency of any of these proteins can increase risk of thrombosis

Haemostasis



Hemostasis:

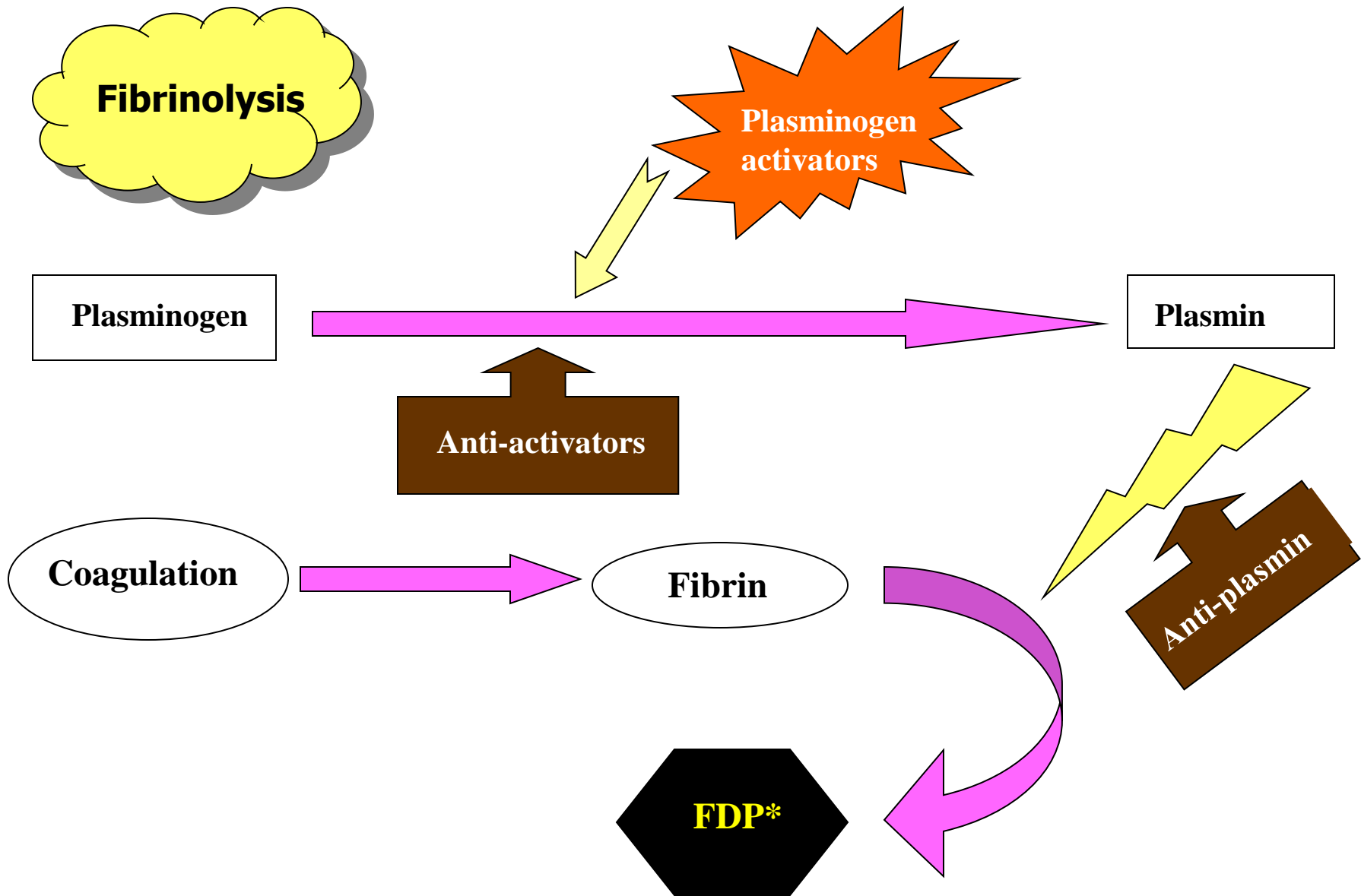
the spontaneous arrest of bleeding from ruptured blood vessels

Mechanisms:

1. Vessel wall
2. Platelet
3. Blood coagulation
4. Fibrinolytic system (Fibrinolysis)

Fibrinolysis

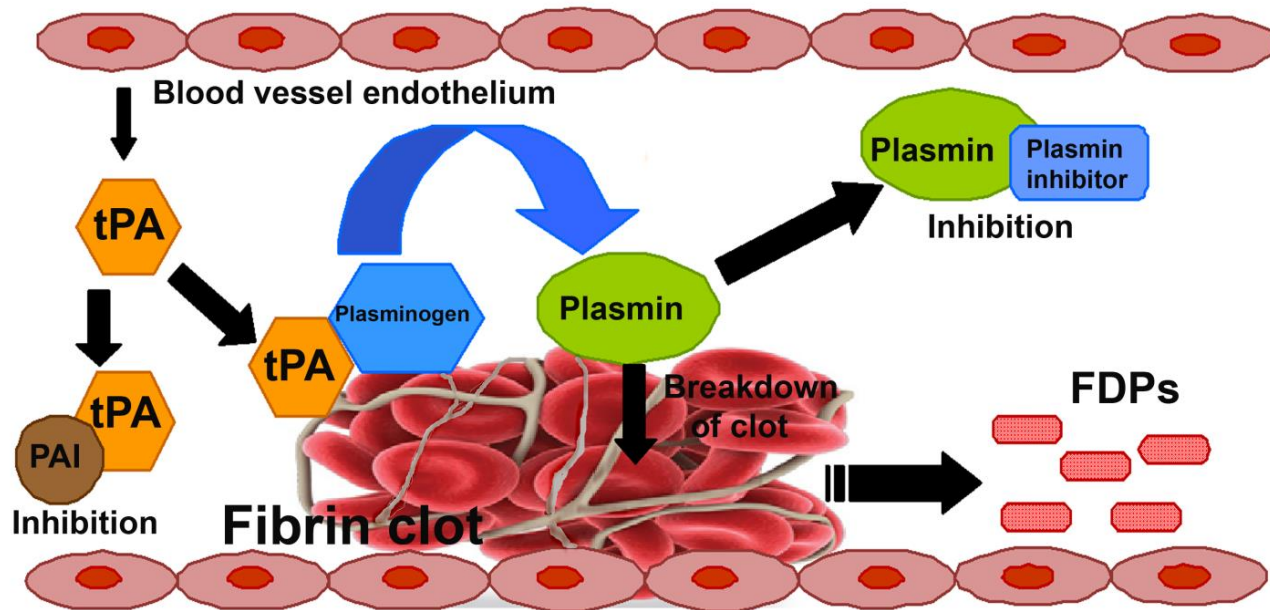
- Formed blood clot can either become fibrous or dissolve
- Fibrinolysis (dissolving) = Break down of fibrin by naturally occurring enzyme **plasmin** therefore prevent intravascular blocking



The fibrinolytic System

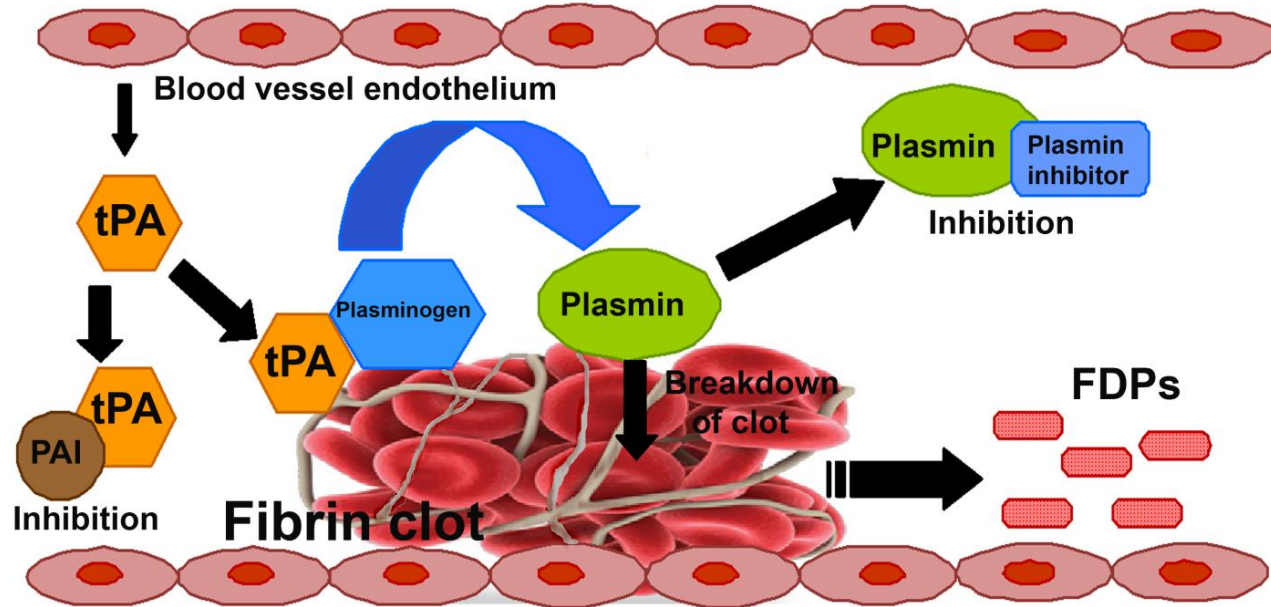
FDP*: Fibrin Degradation Products

Fibrinolysis



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

Fibrinolysis



- Plasmin is controlled by:
 - Plasminogen Activator Inhibitor (PAI)
 - Antiplasmin from the liver
- Uses:
 - Tissue Plasminogen Activator (t-PA) used to activate plasminogen to dissolve coronary clots

Haemostatic Mechanisms:

- Vessel wall
- Platelet
- Blood coagulation
- Fibrinolytic system

Bleeding disorders

Normal

1) Bleeding starts



2) Vessels constrict



3) Platelet plug



4) Fibrin clot



Bleeding Disorder

1) Bleeding starts



2) Vessels constrict



3) Incomplete platelet plug,
continued bleeding



4) Incomplete and/or delayed
formation of fibrin clot,
continued bleeding



- Bleeding can result from:

- Platelet defects: deficiency in number (thrombocytopenia) or defect in function.

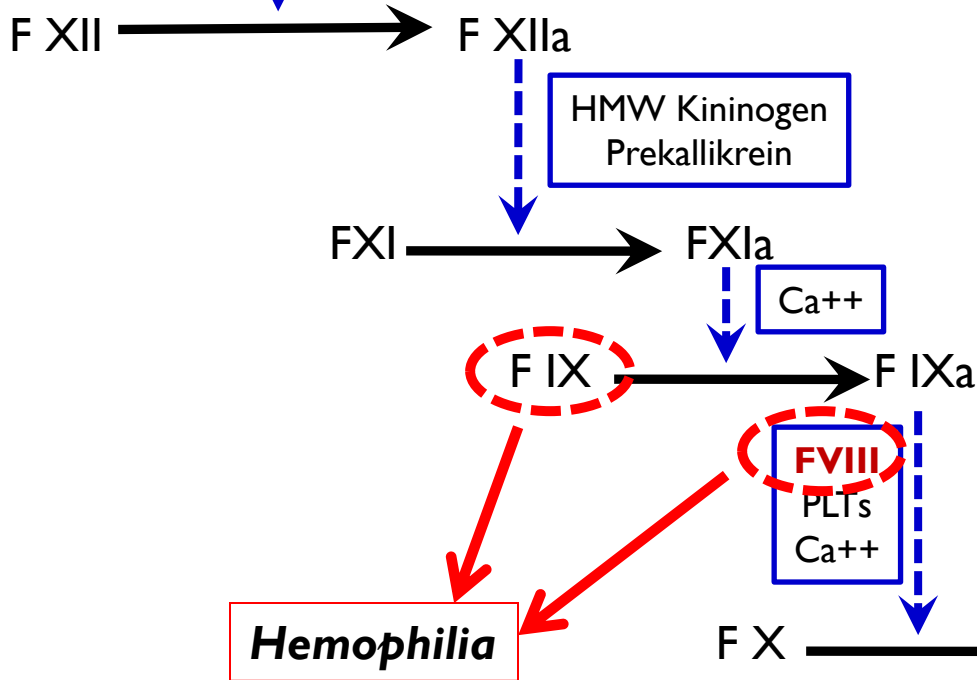
- Coagulation factors defect:

Deficiency in coagulation factors (e.g. hemophilia).

- Vitamin K deficiency.

The Intrinsic Pathway

Blood trauma
or contact
with collagen

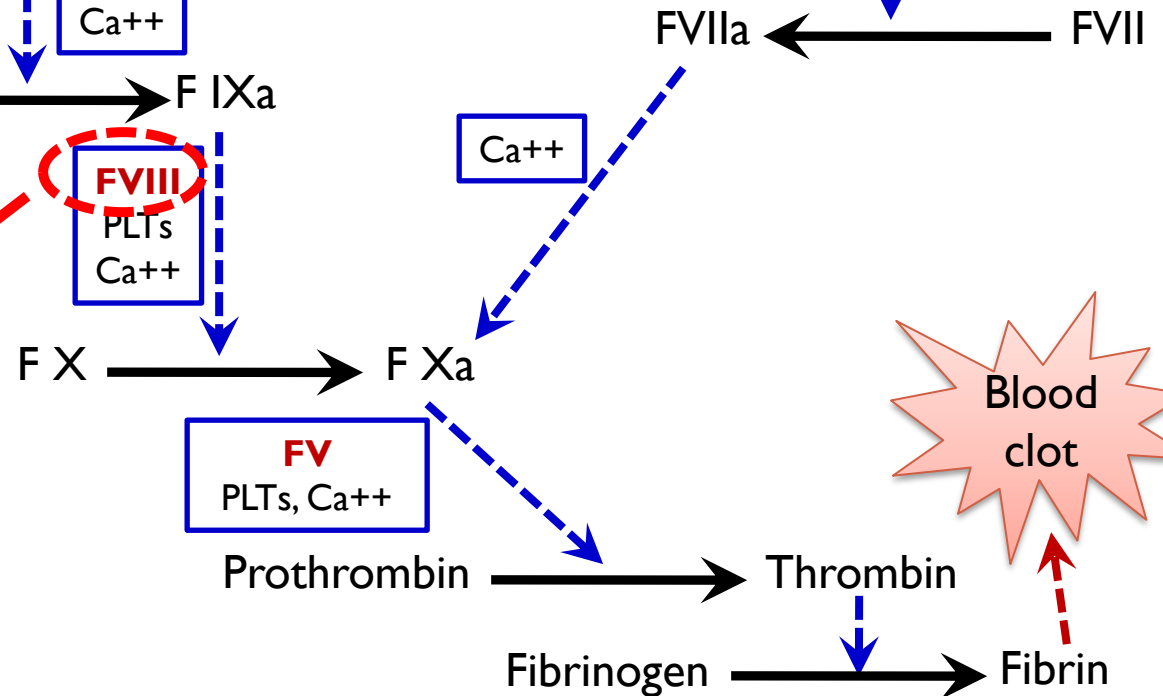


The Extrinsic Pathway

Tissue trauma

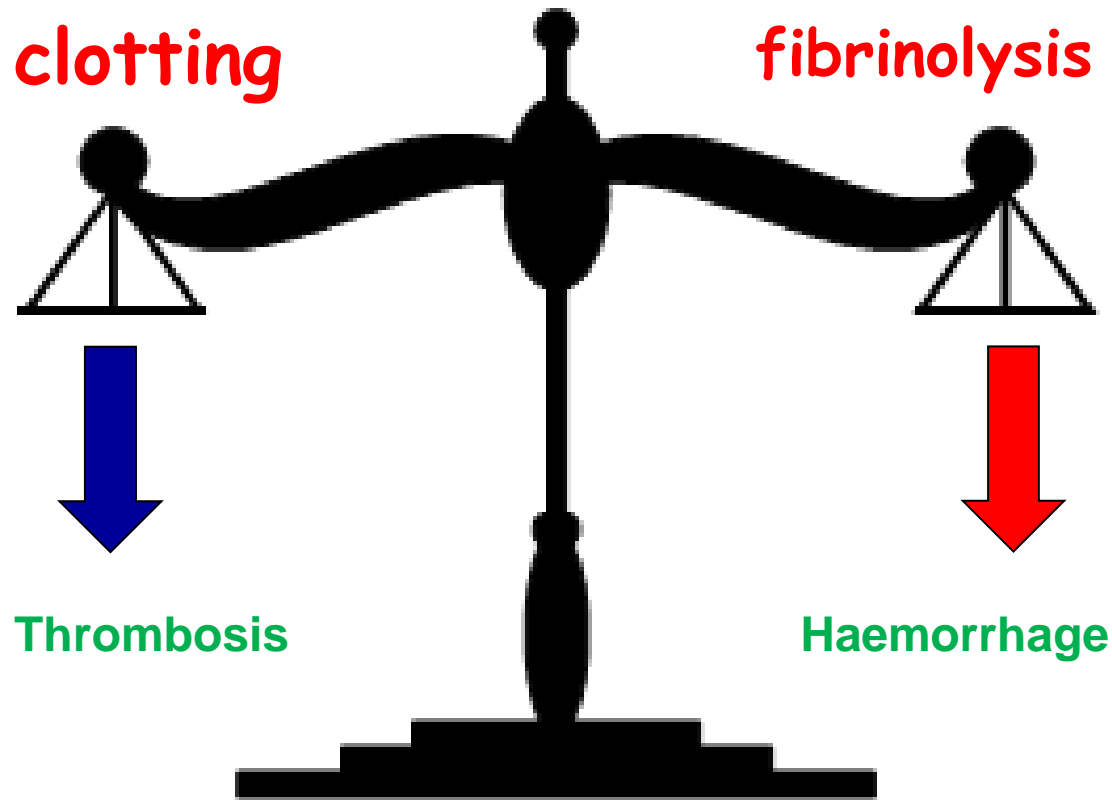


Tissue factor (TF)



Bleeding disorders

- Hemophilia:
 - ↑ bleeding tendency.
 - X-linked disease.
 - Affects males.
 - 85% due to FVIII deficiency (hemophilia A), and 15% due to FIX deficiency (hemophilia B).
- Vitamin K deficiency & liver disease:
 - Almost all coagulation factors are synthesized in the liver.
 - Prothrombin, FVII, FIX, & FX require vitamin K for their synthesis.

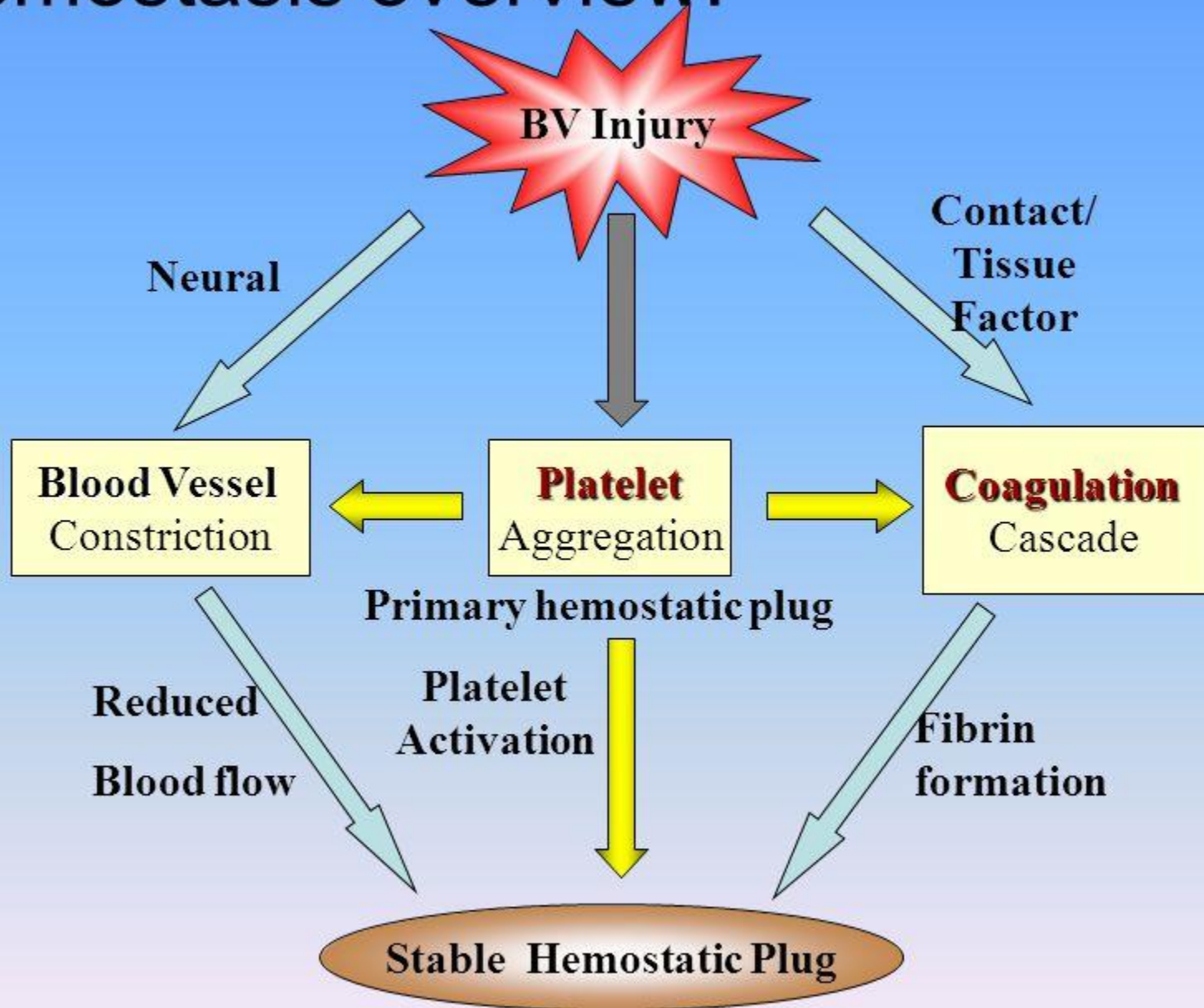


There is balance between clotting and fibrinolysis

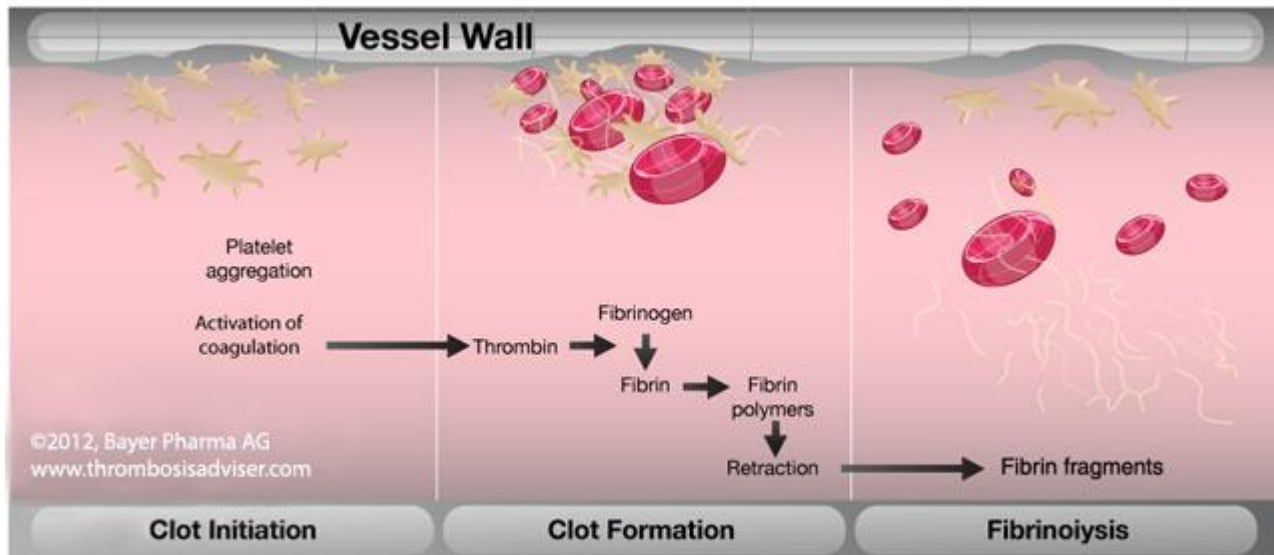
Excess clotting → blocking of Blood Vessels

Excess fibrinolysis → tendency for bleeding

Haemostasis overview:



Haemostatic Mechanisms





THANK YOU