بسم الله الرحمن الرحيم

Hemostasis

Dr. Abeer Al-Ghumlas

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 .

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

Hemostasis:

the spontaneous arrest of bleeding from ruptured blood vessels

Mechanisms:

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

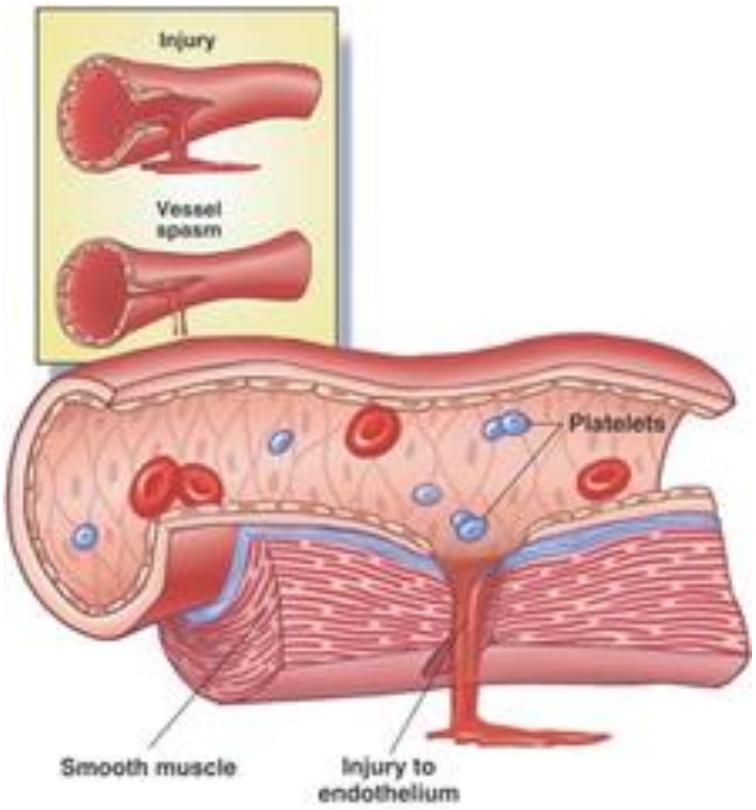
Hemostatic Mechanisms- cont

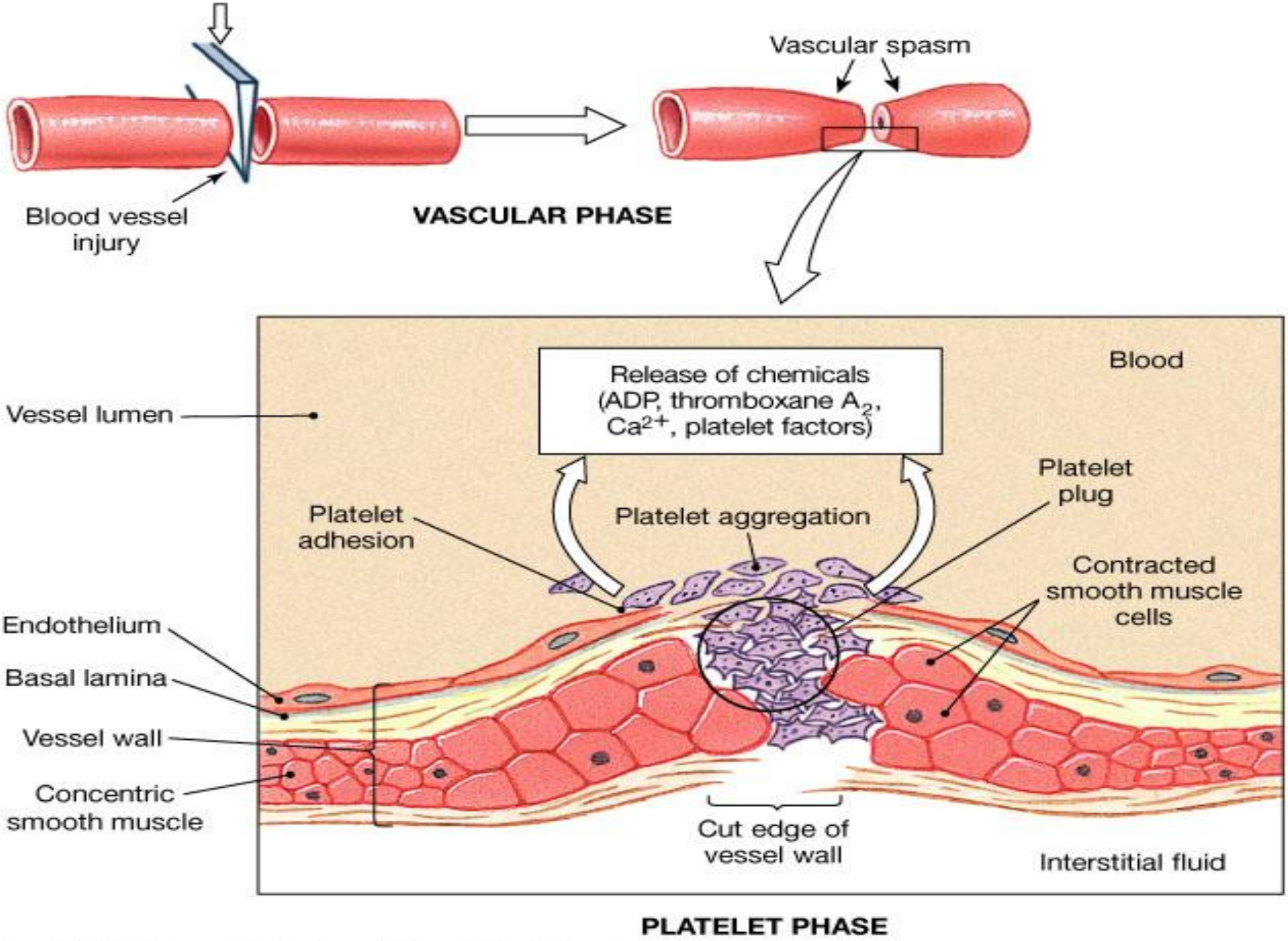
1. Vessel wall

- Immediately After injury a localized

Vasoconstriction

- Mechanism:
  - Systemic release of adrenaline
  - Nervous factors
  - local release of thromboxane A2 & 5HT by platelets



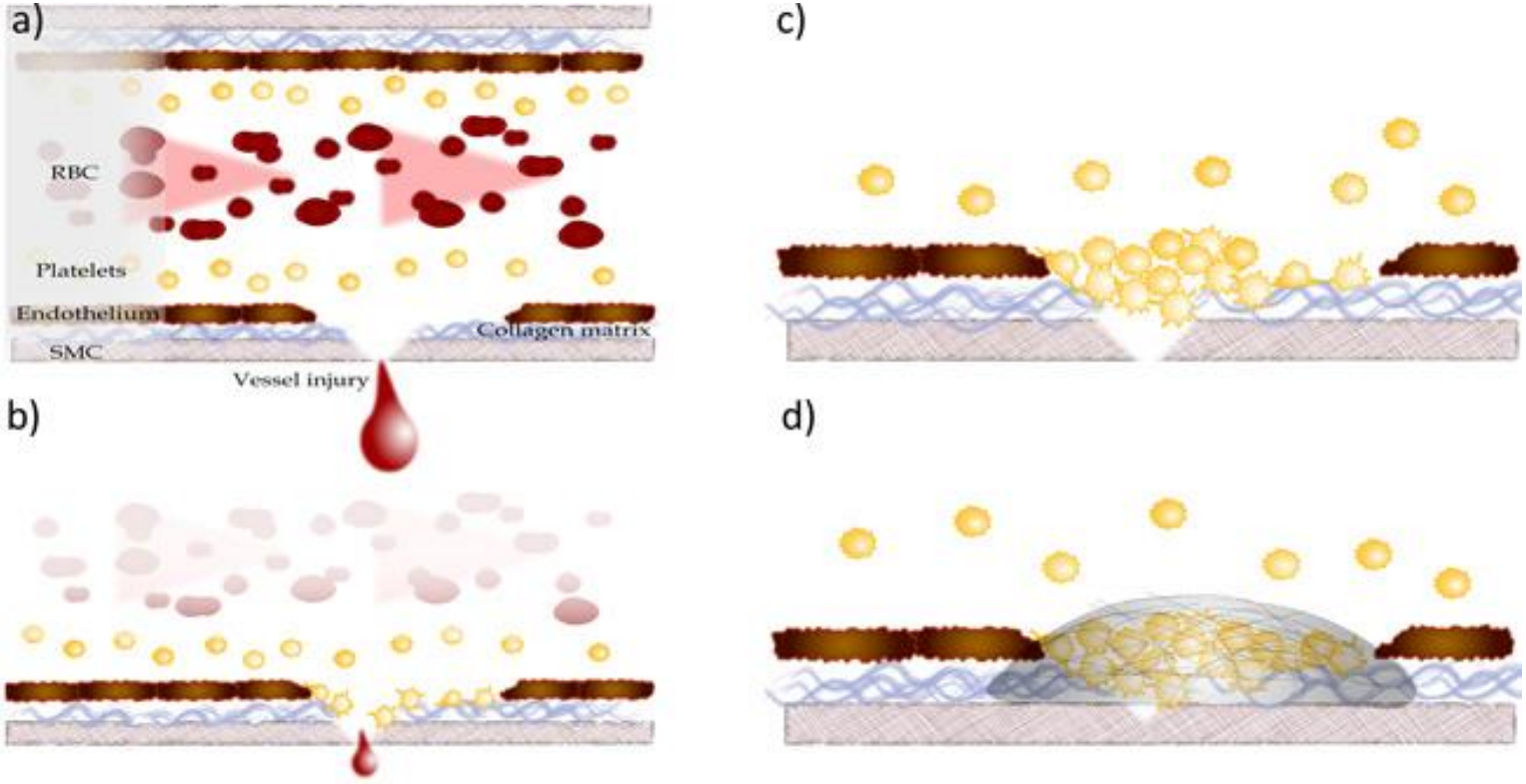


PLATELET PHASE

Hemostatic Mechanisms:

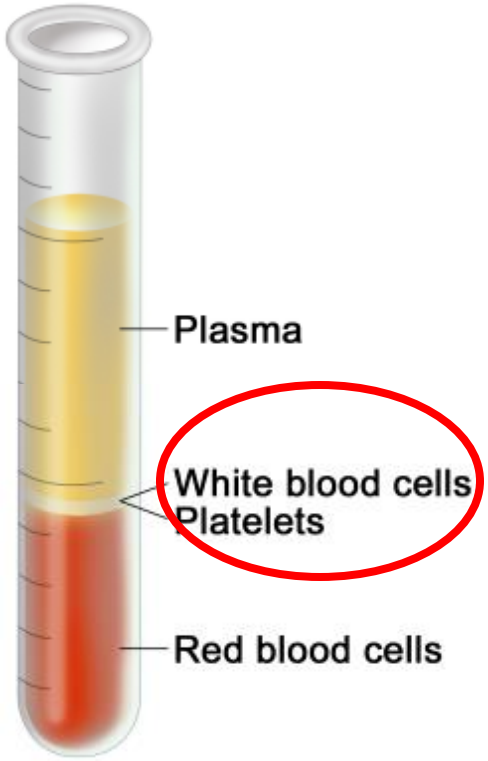
- Mechanisms:
  - Vessel wall
  - Platelet
  - Blood coagulation
  - Fibrinolytic system

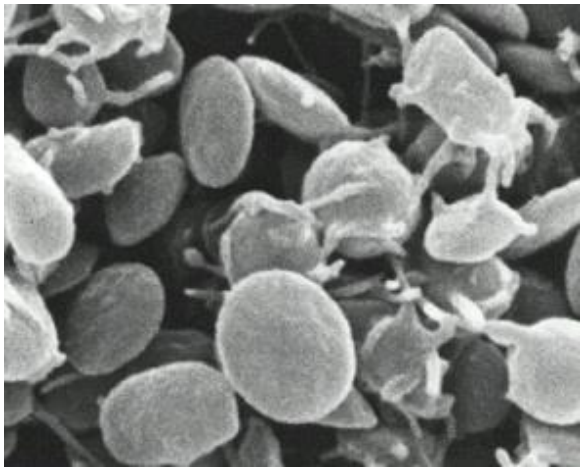
Platelet haemostatic plug formation



Platelets (PLT)

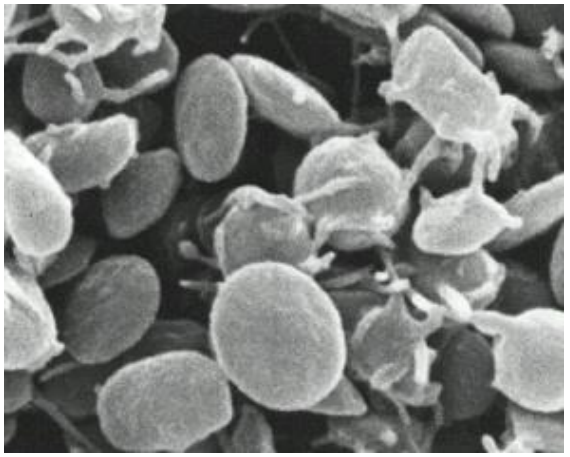
Thrombocytes

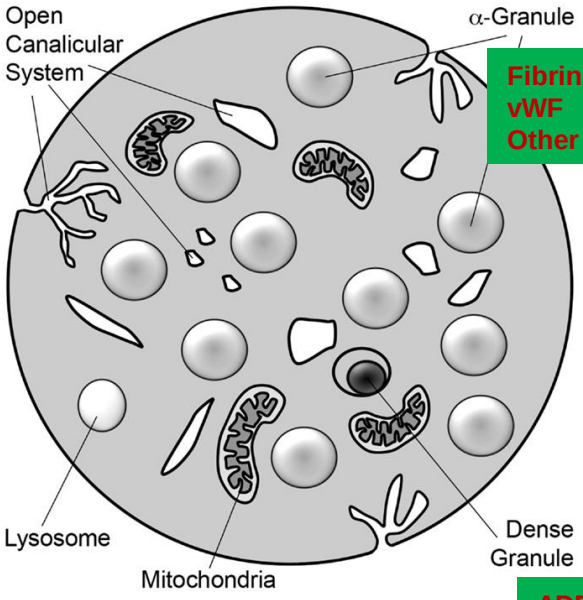


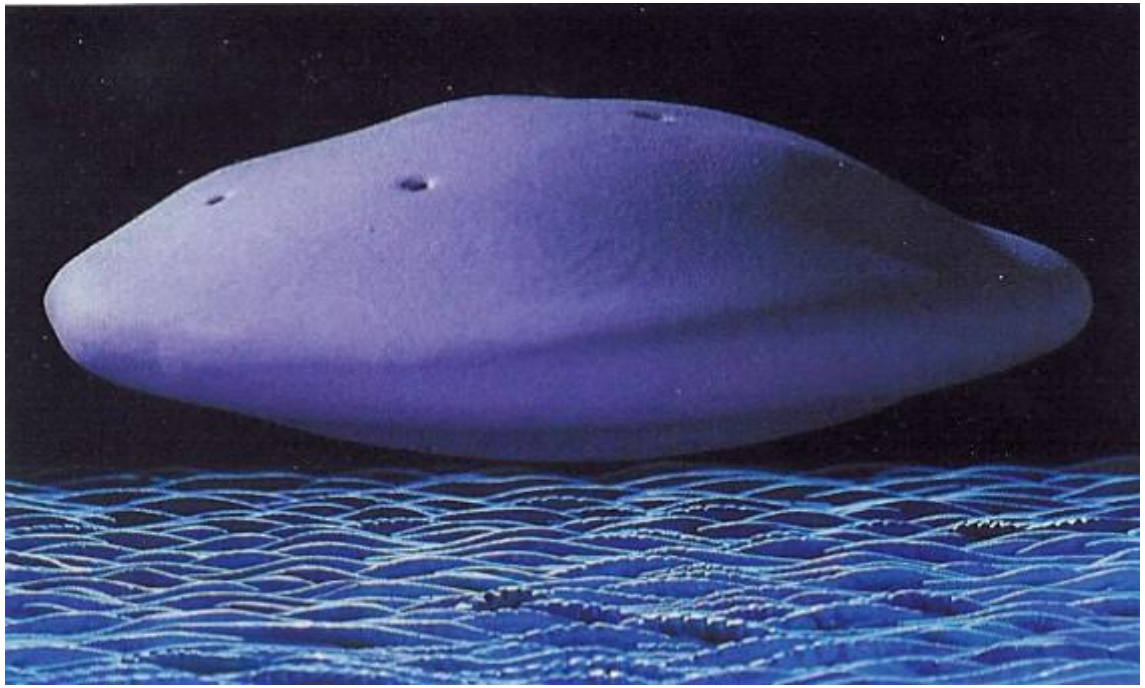


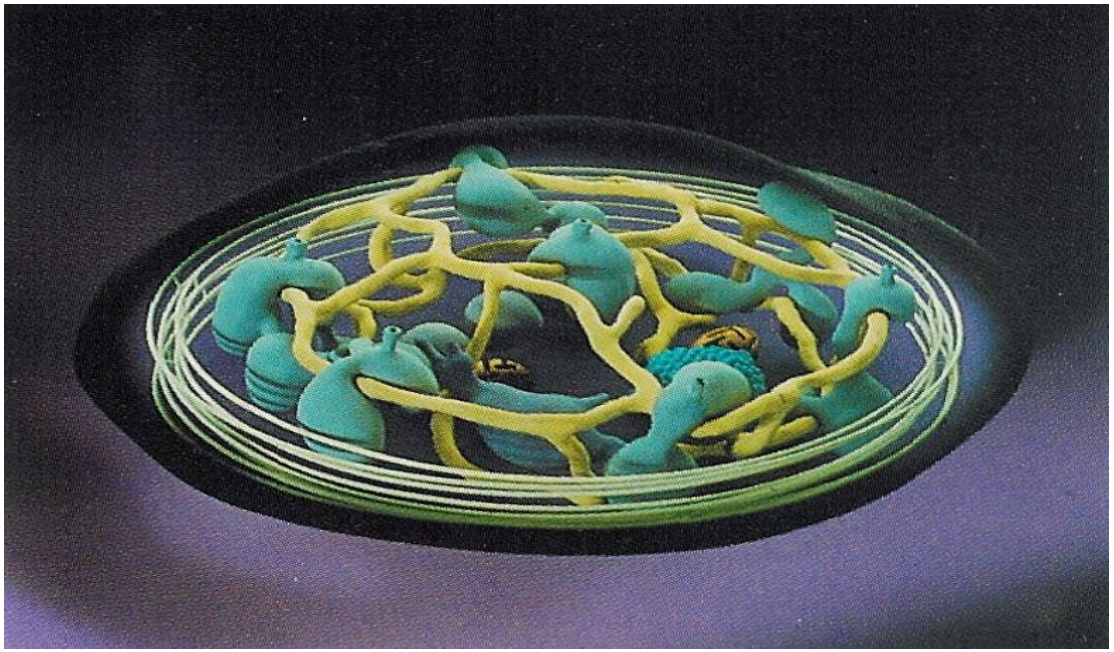
Platelets - cont

- small disc shaped cells
- Platelet count = $150x10^3$-$300x10^3$/ml,
- life span 8-12 days
- Contain high calcium content & rich in ADP
- Active cells contain contractile protein,

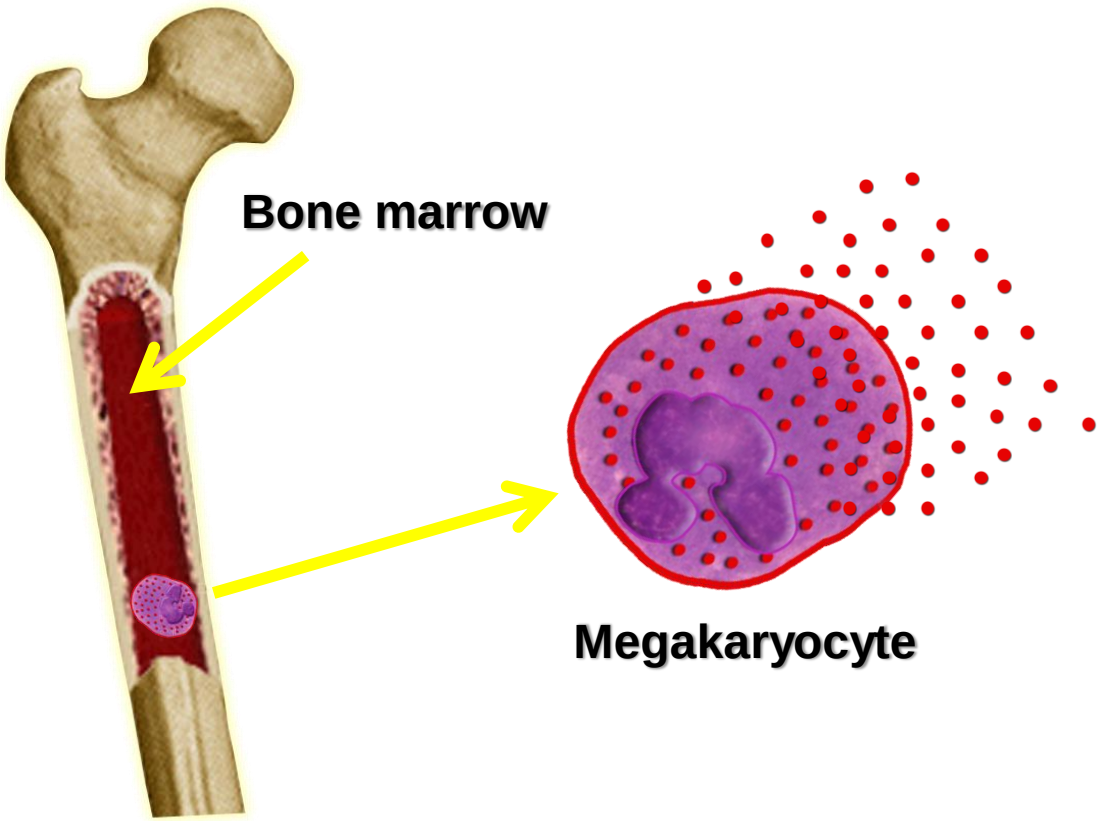








platelets



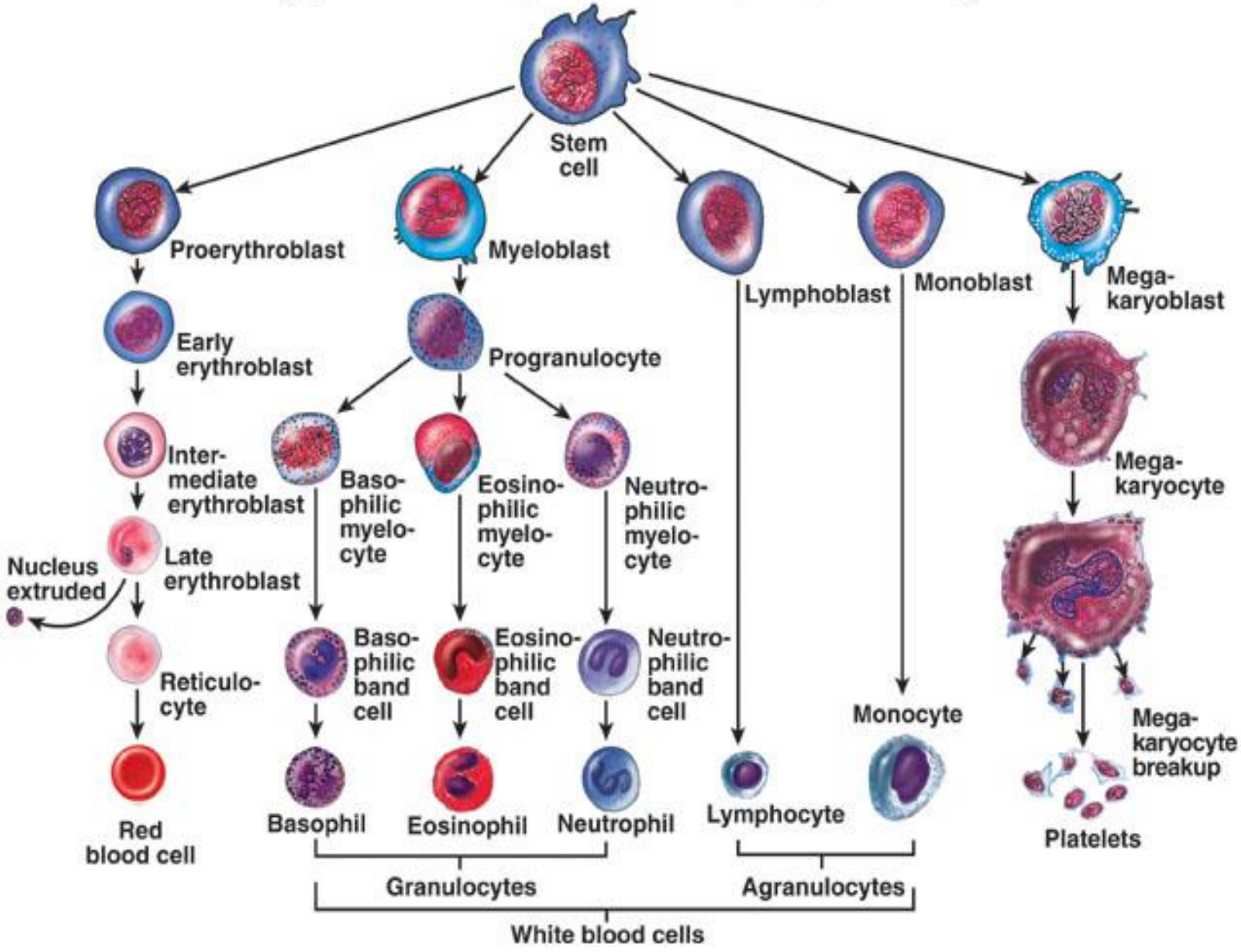
- Thrombocytes are

Fragments of megakaryocytes in the bone marrow

- Regulation of thrombopoiesis

By:

Thrombombopoietin

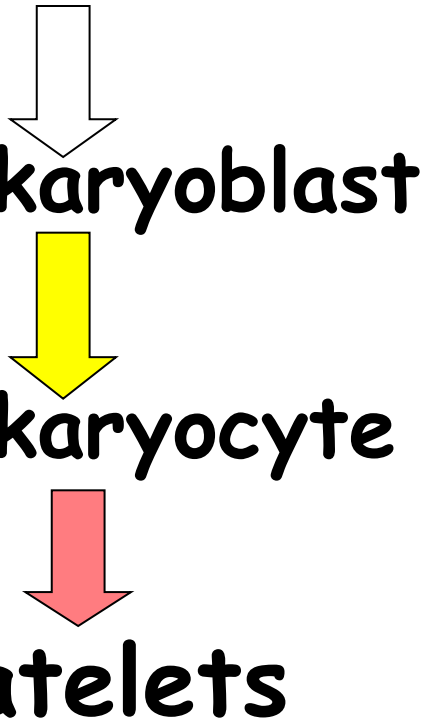

Stem cell
Proerythroblast
Myeloblast
Lymphoblast
Monoblast
Mega-karyoblast
Early erythroblast
Progranulocyte
Inter-mediate erythroblast
Baso-philic myelo-cyte
Eosino-philic myelo-cyte
Neutro-philic myelo-cyte
Mega-karyocyte
Nucleus extruded
Late erythroblast
Reticulo-cyte
Baso-philic band cell
Eosino-philic band cell
Neutro-philic band cell
Monocyte
Mega-karyocyte breakup
Red blood cell
Basophil
Eosinophil
Neutrophil
Lymphocyte
Platelets
Granulocytes
Agranulocytes
White blood cells

Platelets – cont.

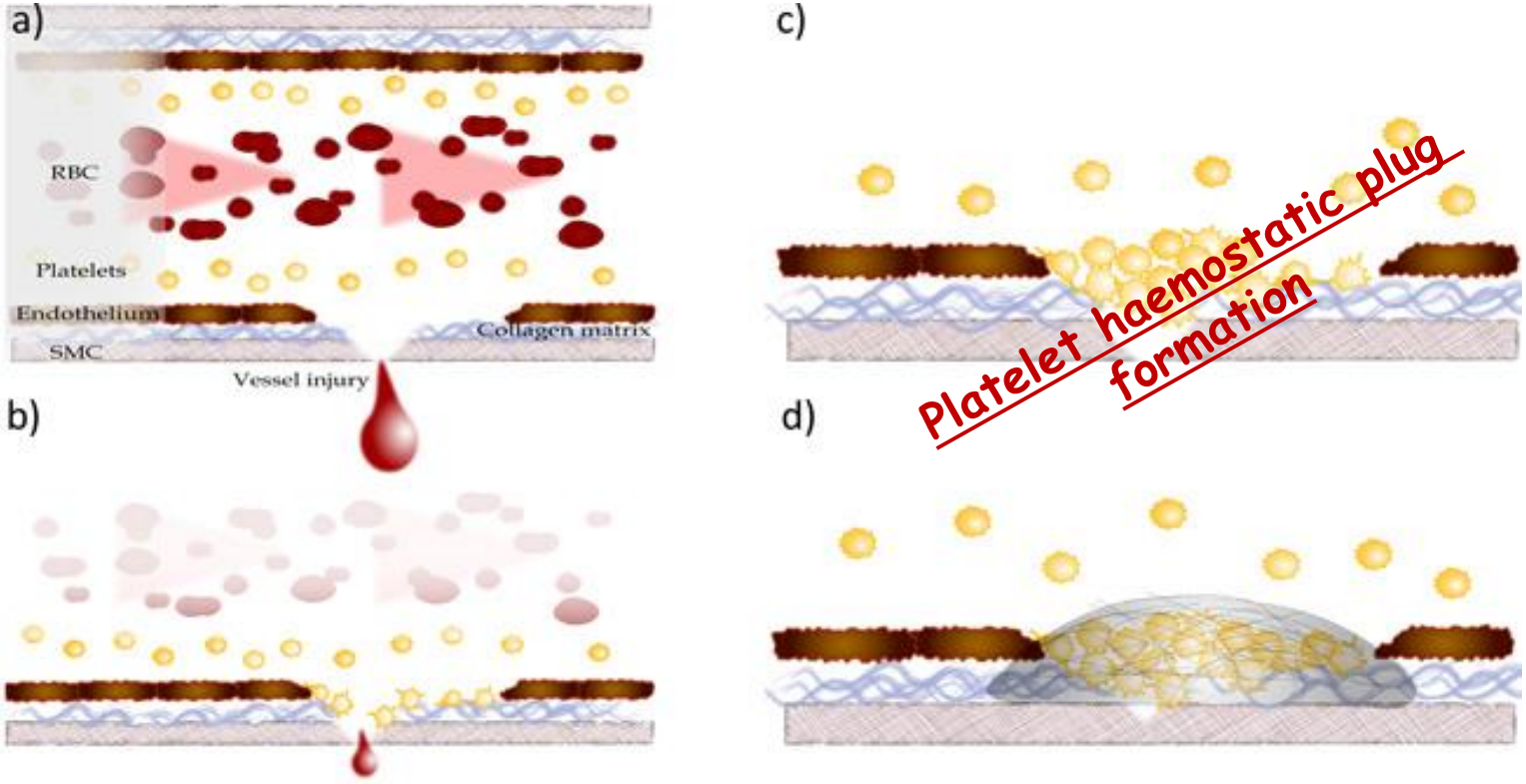
Site of formation:

Bone marrow

Steps: Stem cell



Platelet haemostatic plug formation

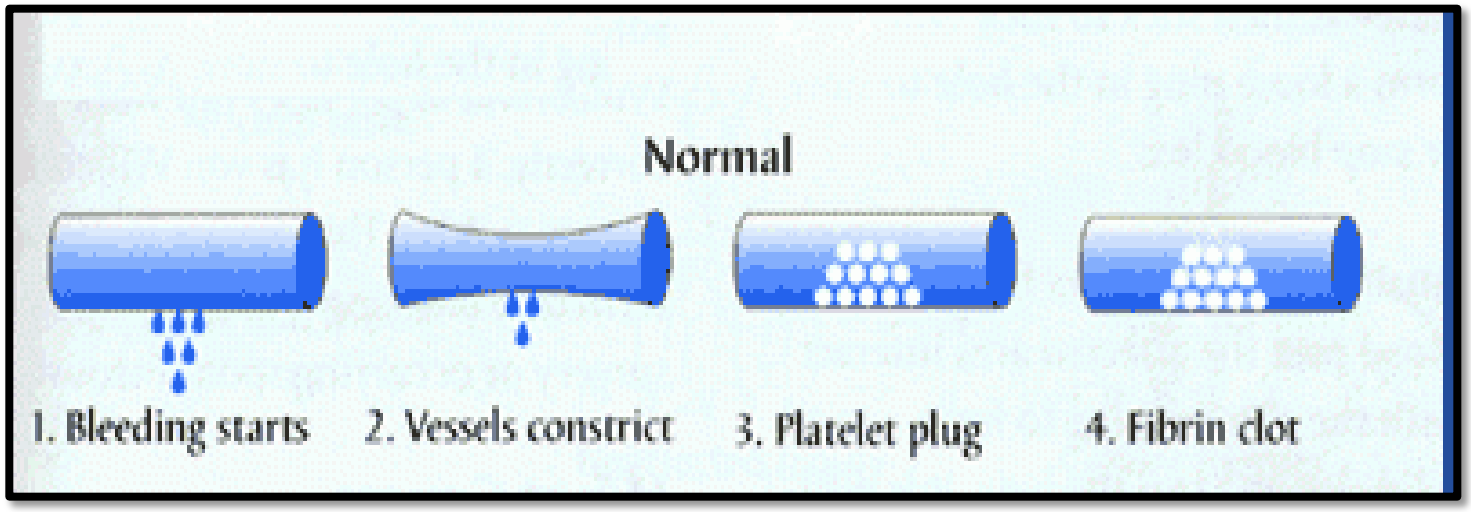


Platelet Functions

Begins with Platelet activation

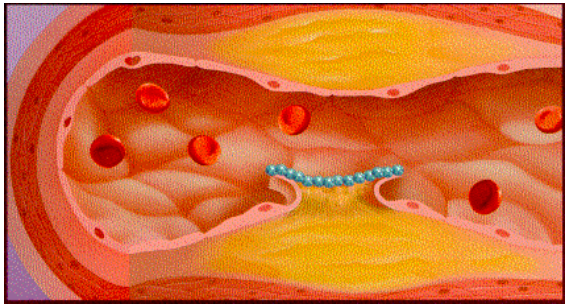
Platelet Activation

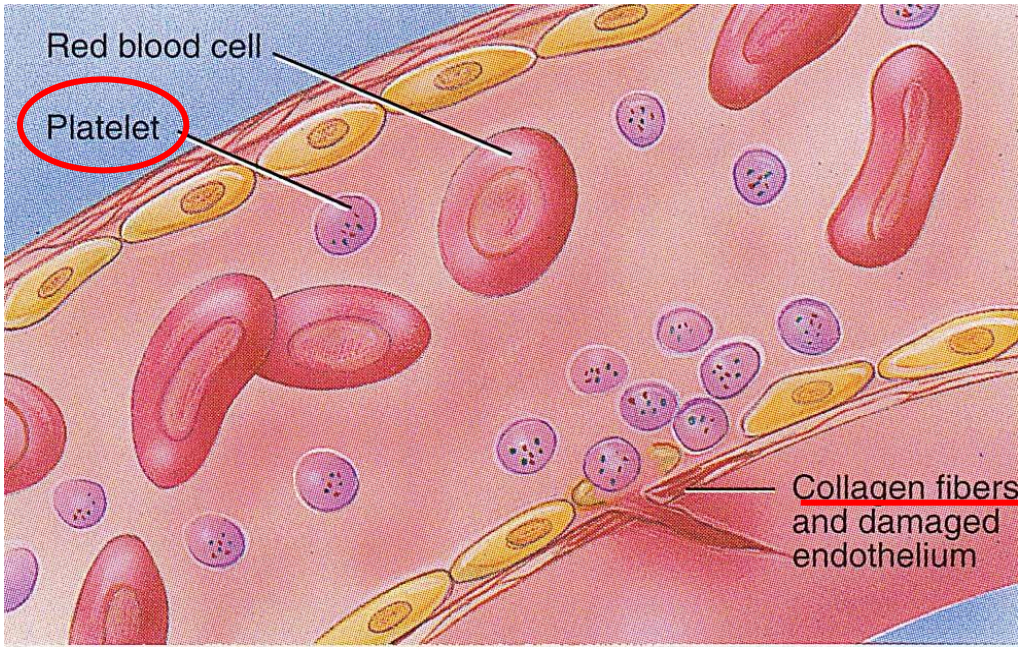
- Adhesion
- Shape change
- Aggregation
- Release
- Clot Retraction

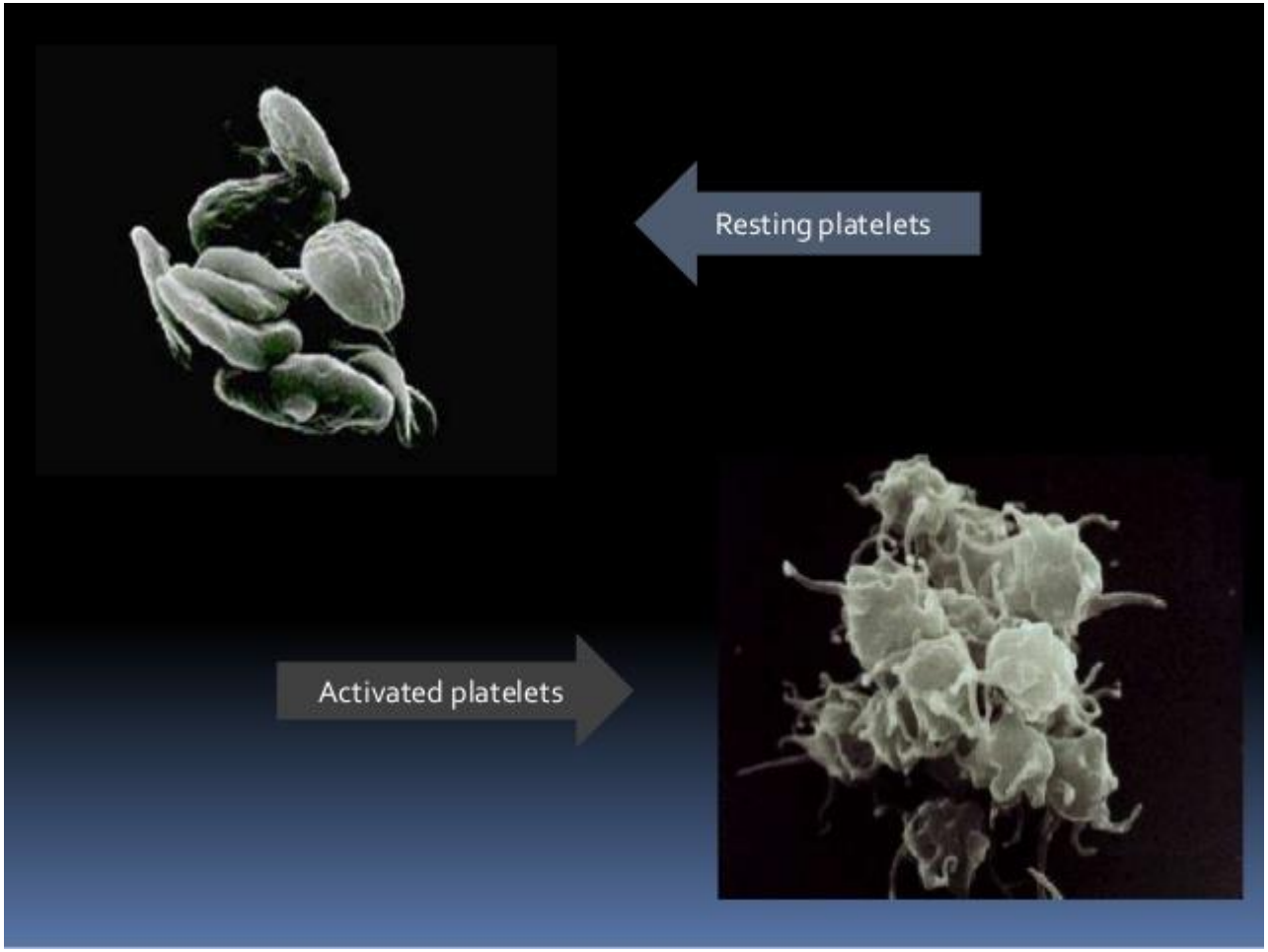

Normal
1. Bleeding starts
2. Vessels constrict
3. Platelet plug
4. Fibrin clot

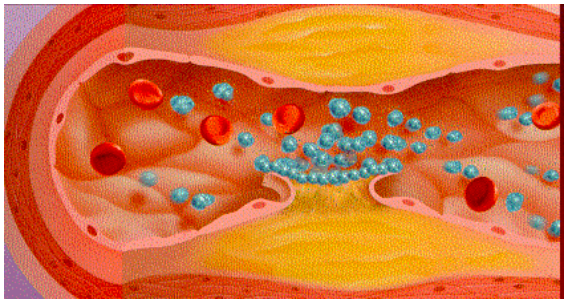
Platelet Adhesion

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





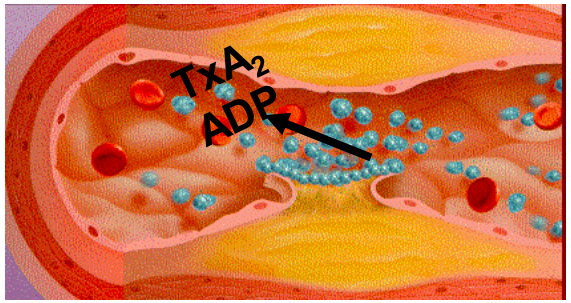




- **Platelets activated by adhesion**
- **Extend projections to make contact with each other**

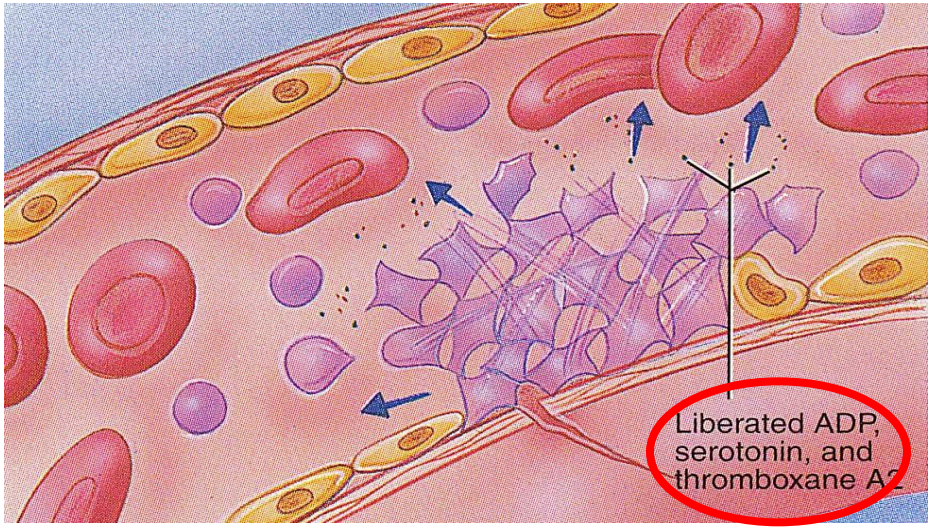
Platelet Release Reaction

- 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**



Activated Platelets

Secrete:

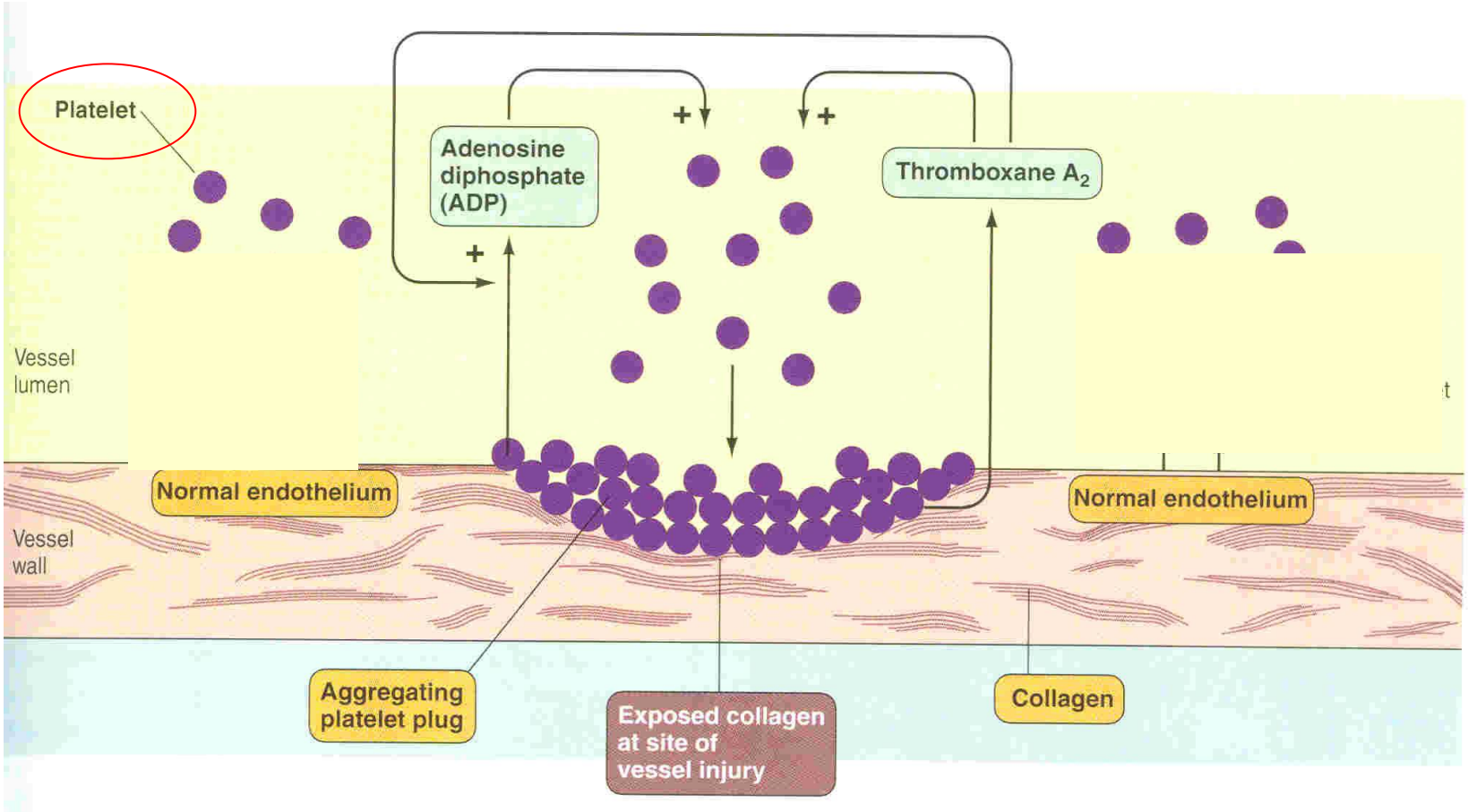
1. 5HT → vasoconstriction
2. ADP
3. Platelet phospholipid (PF3) → clot formation
4. Thromboxane A2 (TXA2) is a prostaglandin formed from arachidonic acid

   Function:

   - vasoconstriction
   - Platelet aggregation

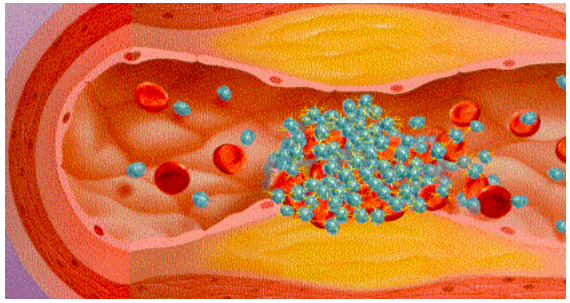
   (TXA2 inhibited by aspirin)

Platelets aggregation

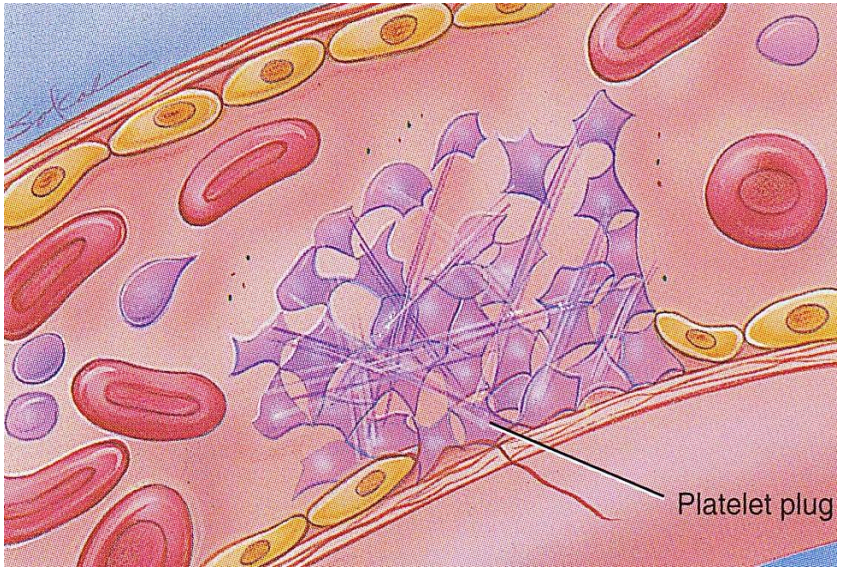


Platelet Aggregation

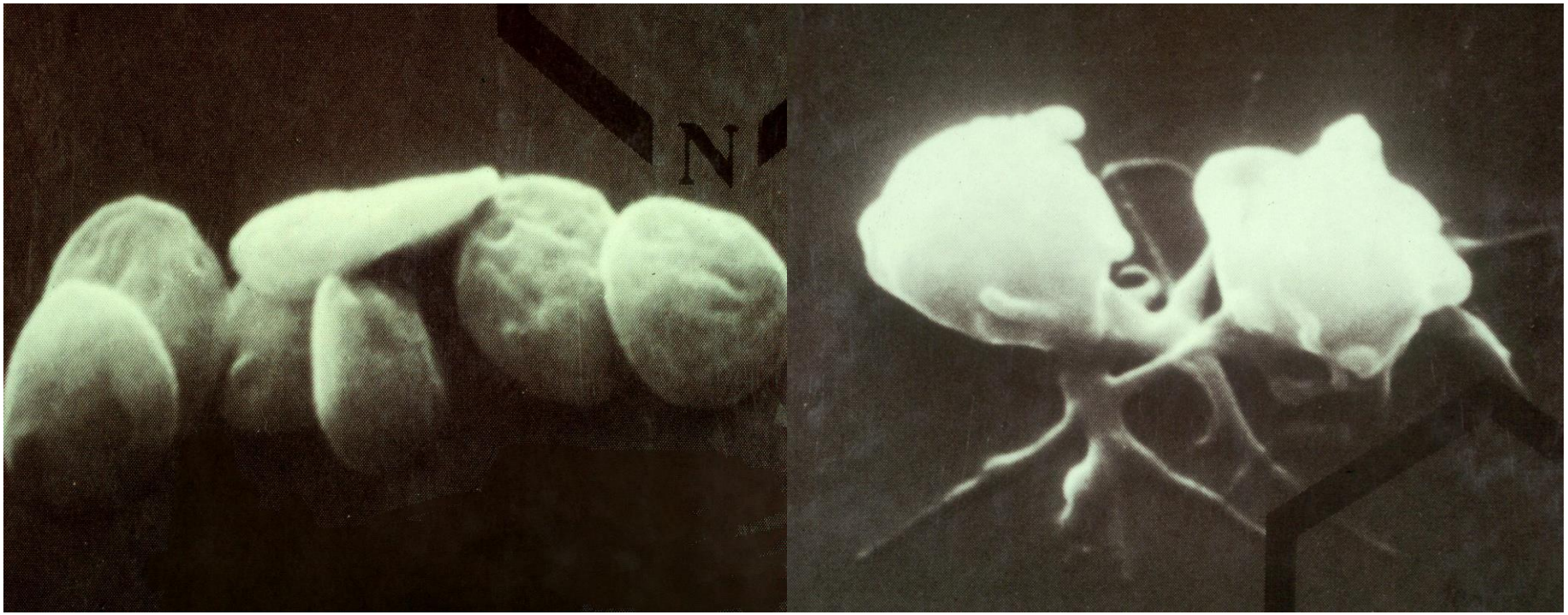
- **Activated platelets stick together and activate new platelets to form a mass called a platelet plug**



- **Plug reinforced by fibrin threads formed during clotting process**



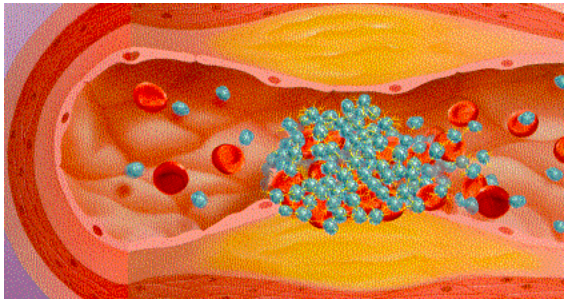
Platelet shape change and Aggregation

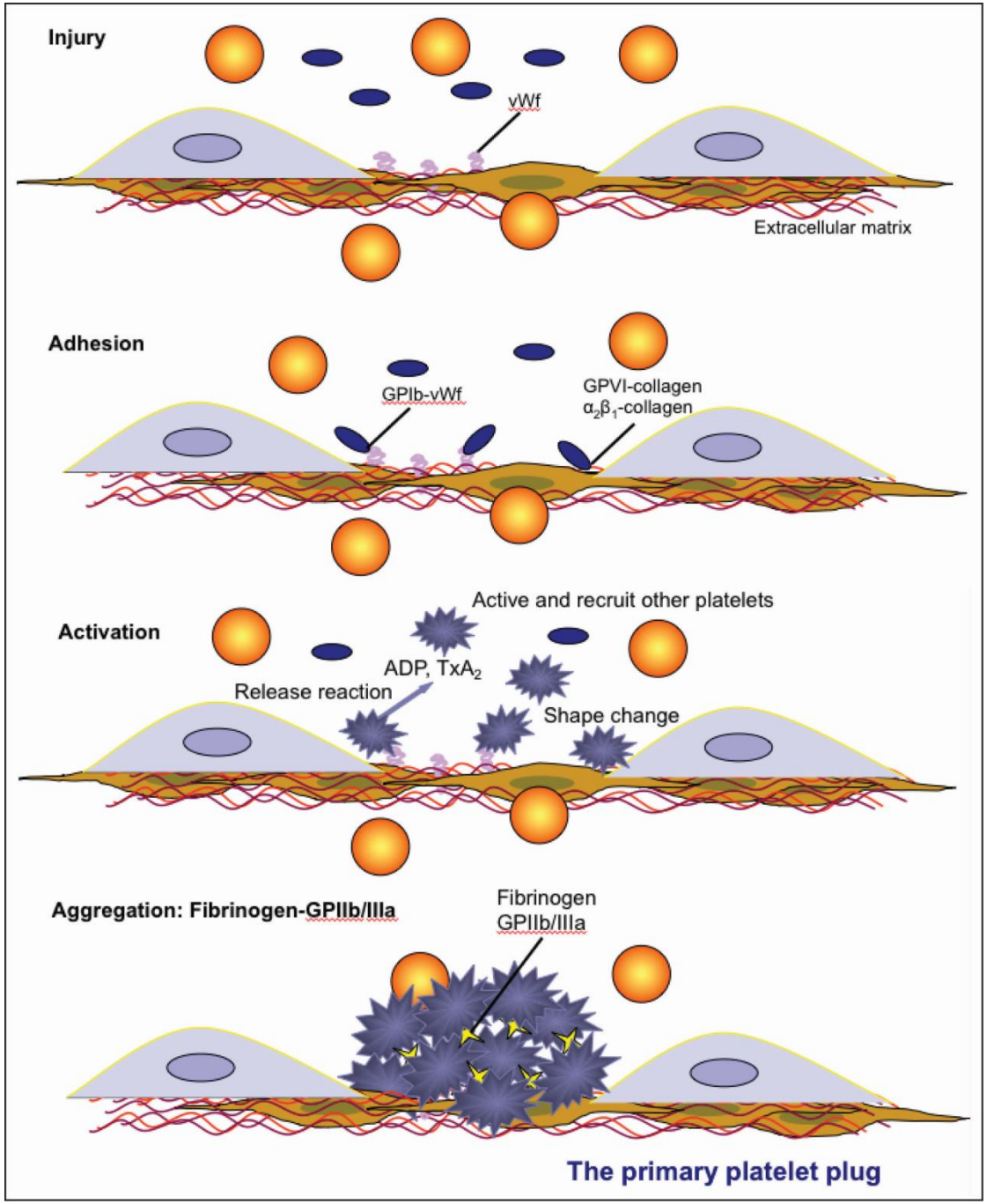


Platelet Activation

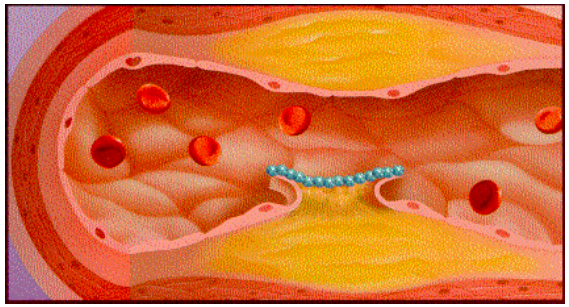
- **Clot Retraction:**

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

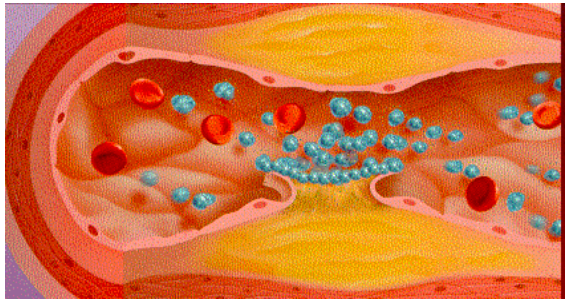



Injury
vWf
Extracellular matrix
Adhesion
GPIb-vWf
GPVI-collagen
$\alpha_2\beta_1$-collagen
Activation
Active and recruit other platelets
ADP, TxA_2
Release reaction
Shape change
Aggregation: Fibrinogen-GPIIb/IIIa
Fibrinogen
GPIIb/IIIa
The primary platelet plug

Platelet function

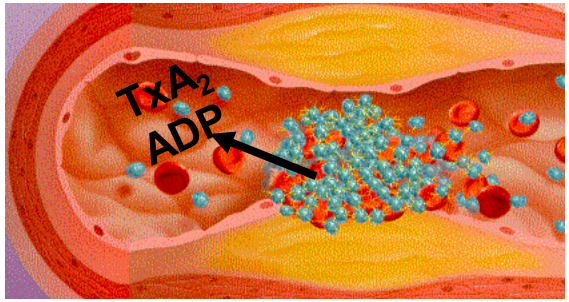


Adhesion

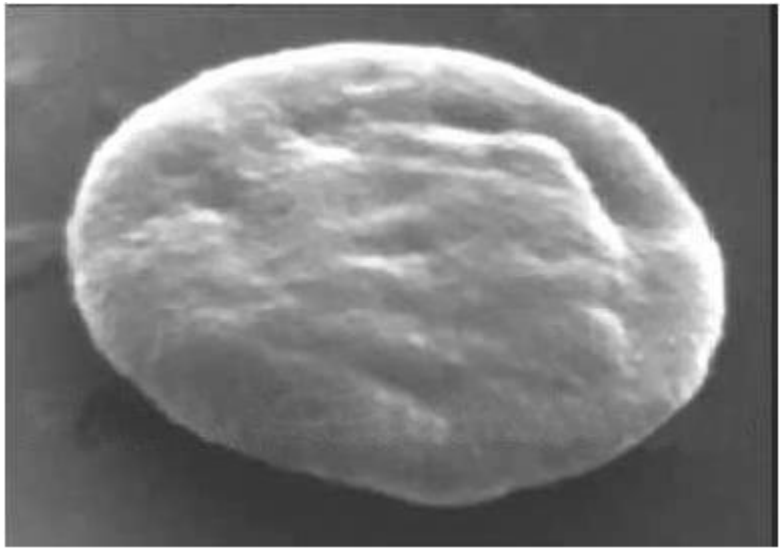


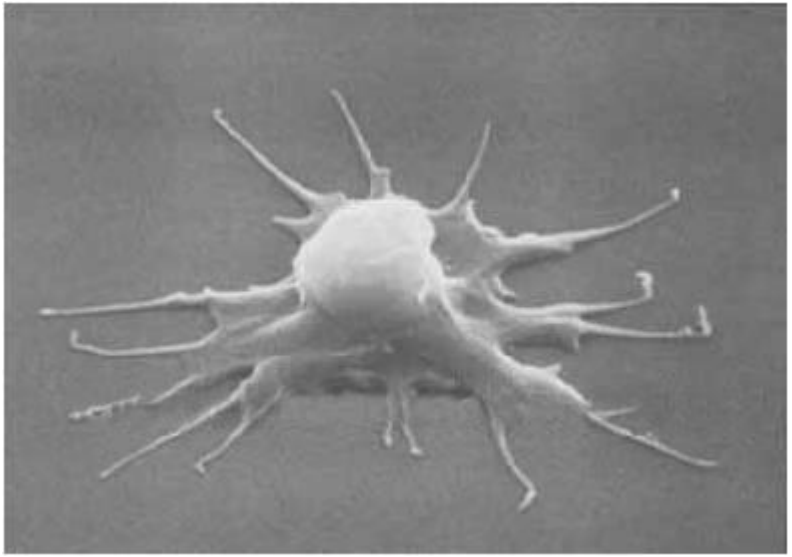
Activation

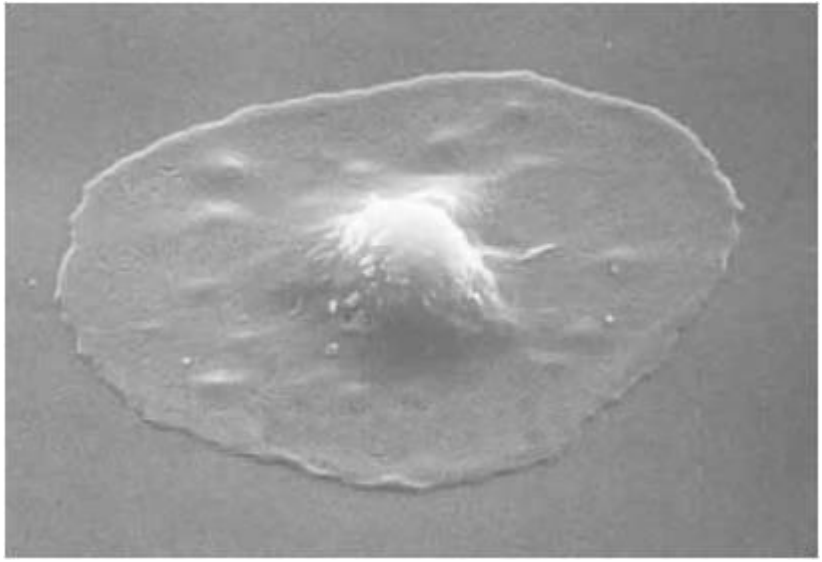
Aggregation

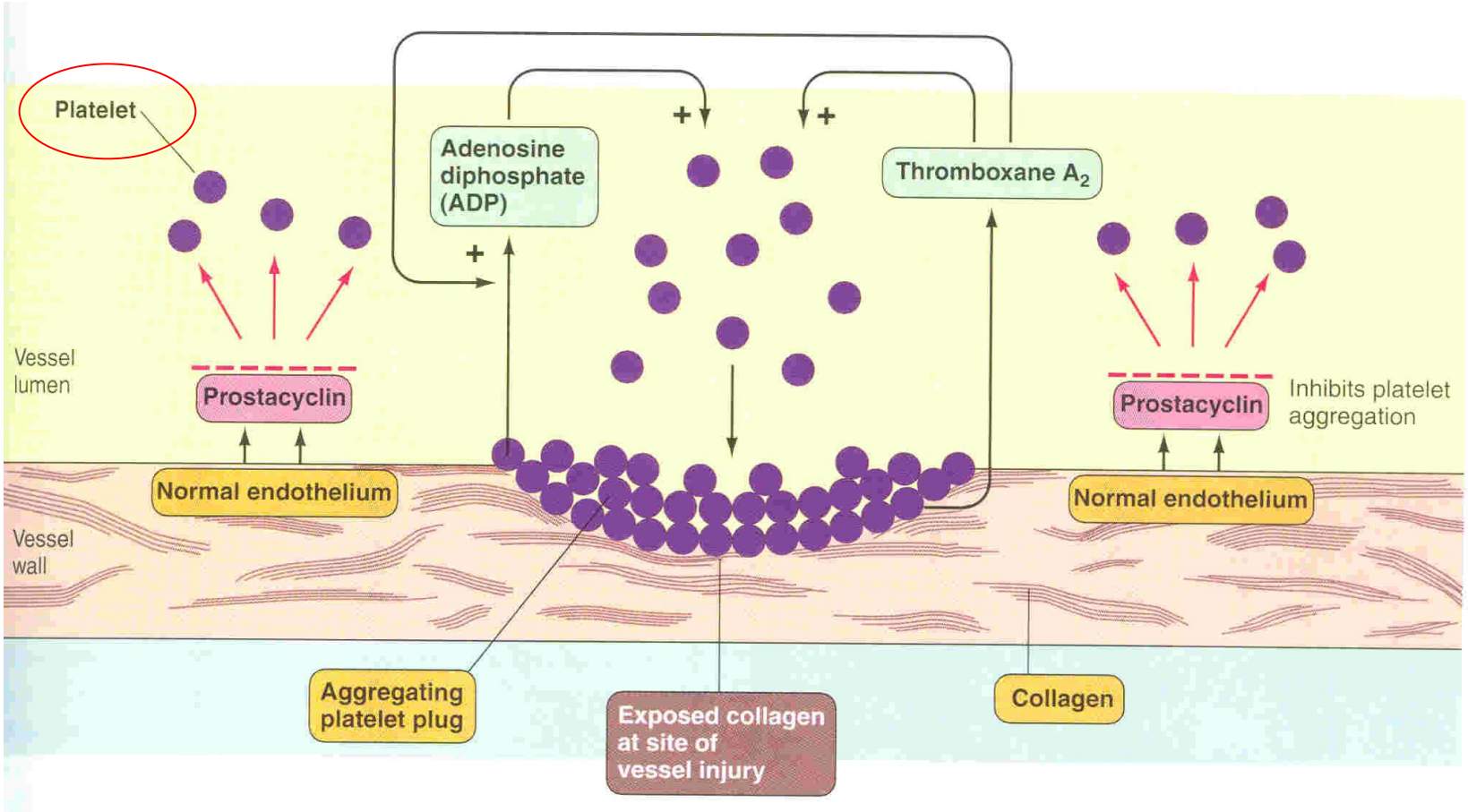


Secretion

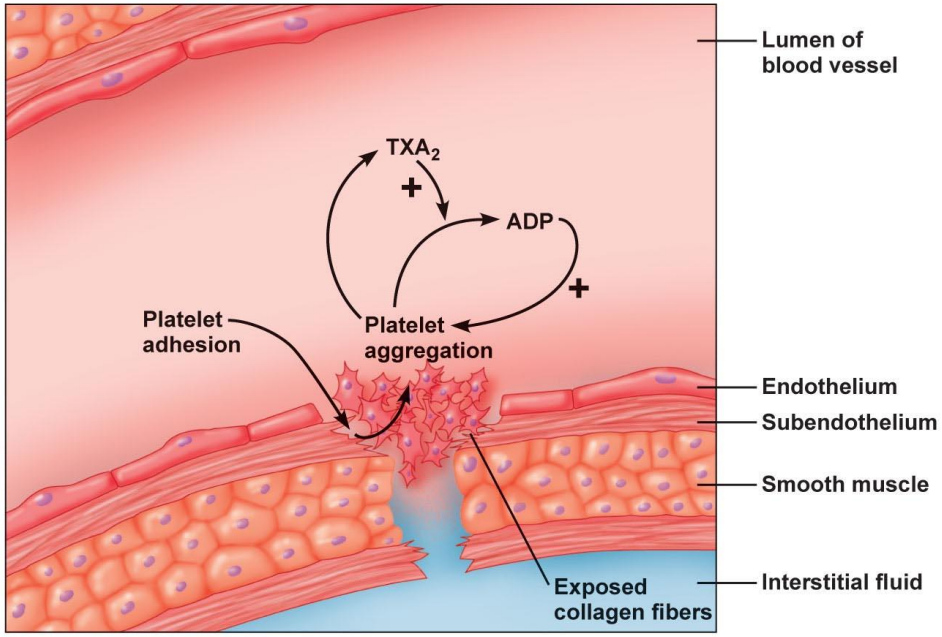




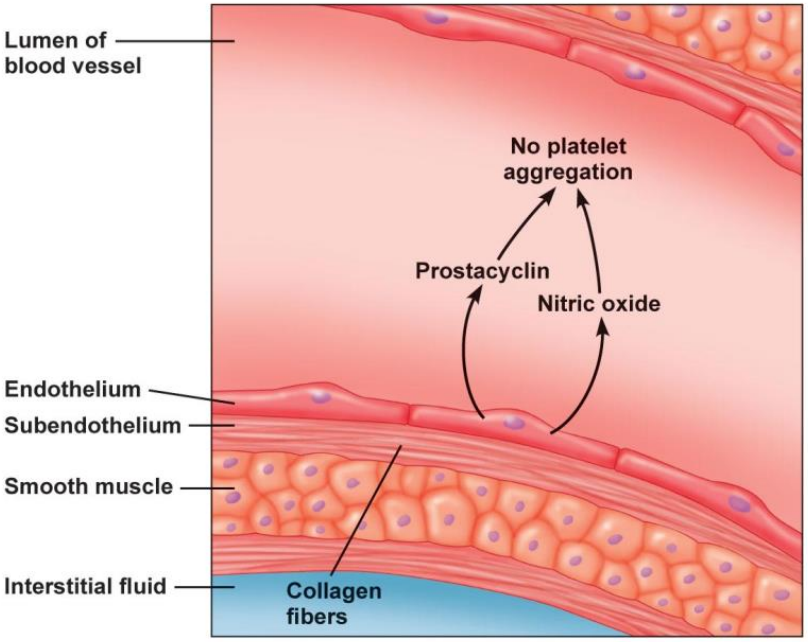




- **Intact endothelium secret prostacyclin and NO which inhibit aggregation**

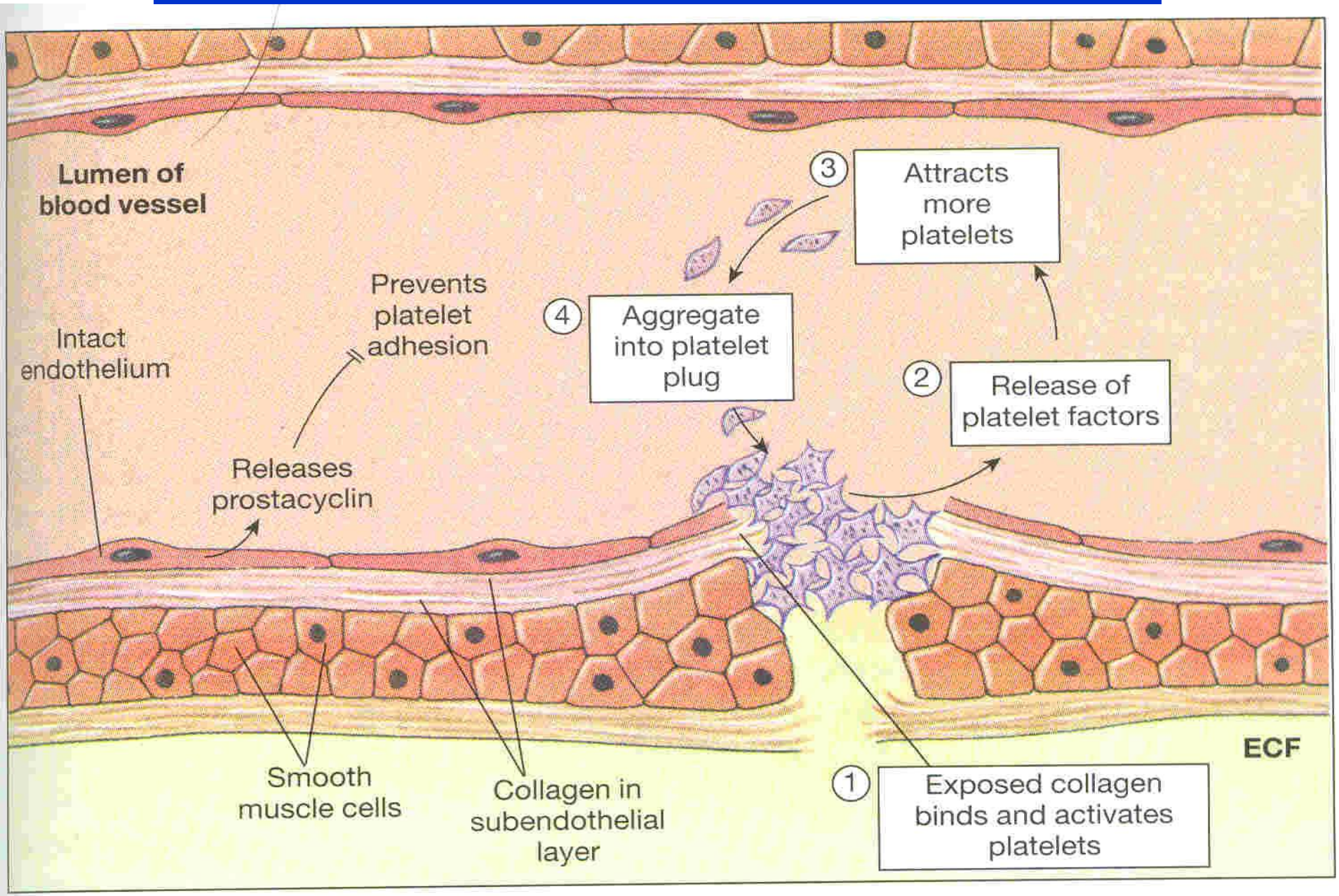


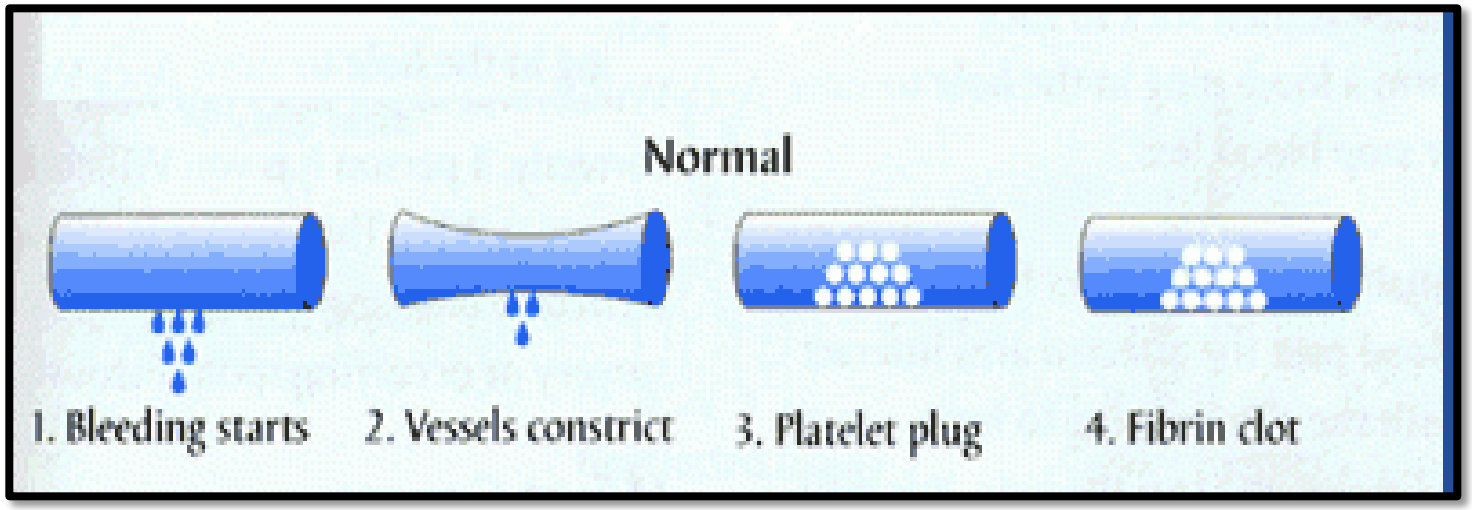
(a) Damaged blood vessel endothelium



(b) Normal blood vessel endothelium

Platelet plug formation




Normal
1. Bleeding starts
2. Vessels constrict
3. Platelet plug
4. Fibrin clot

Memostatic Mechanisms:

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

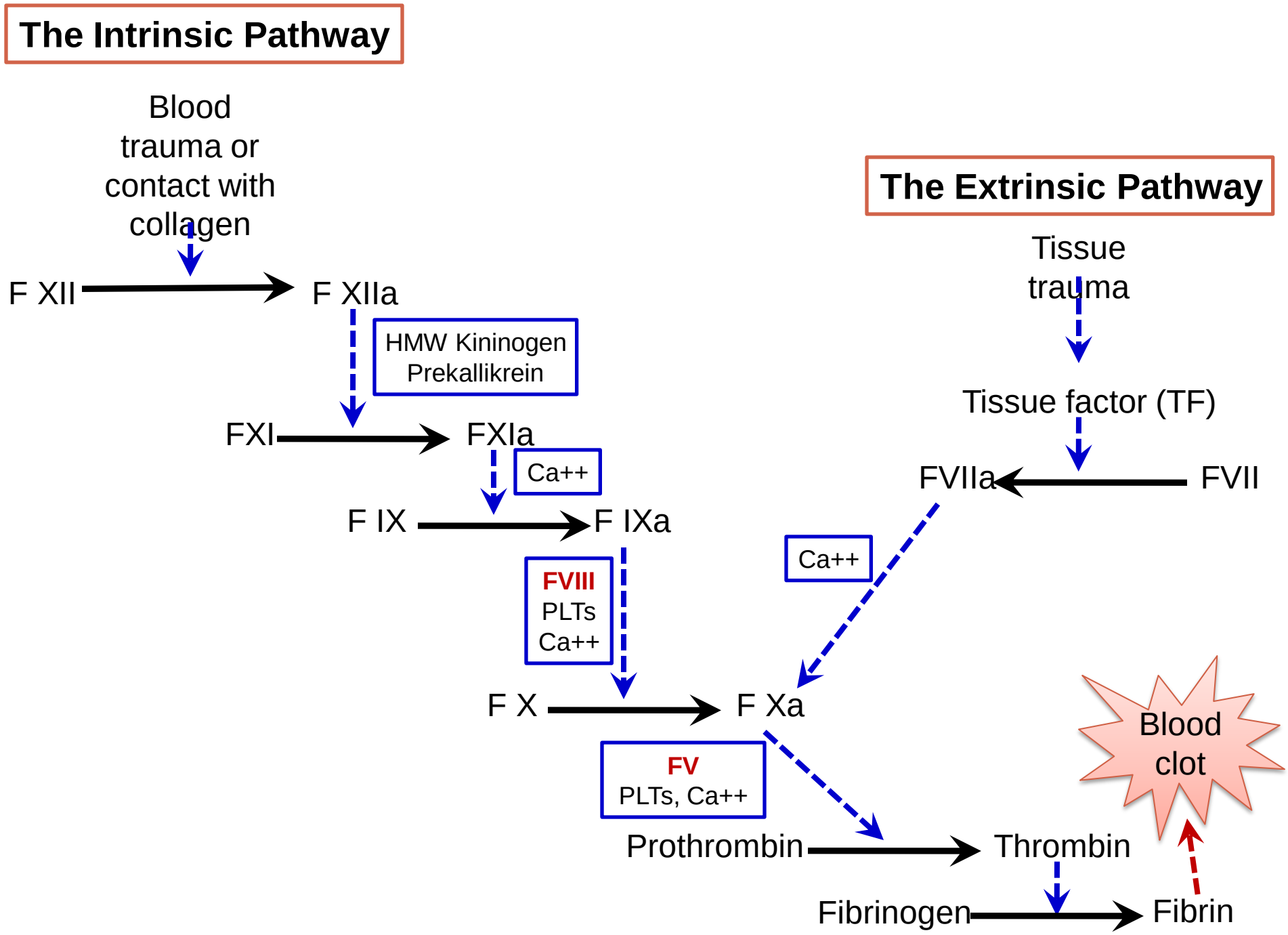
Clotting Factors

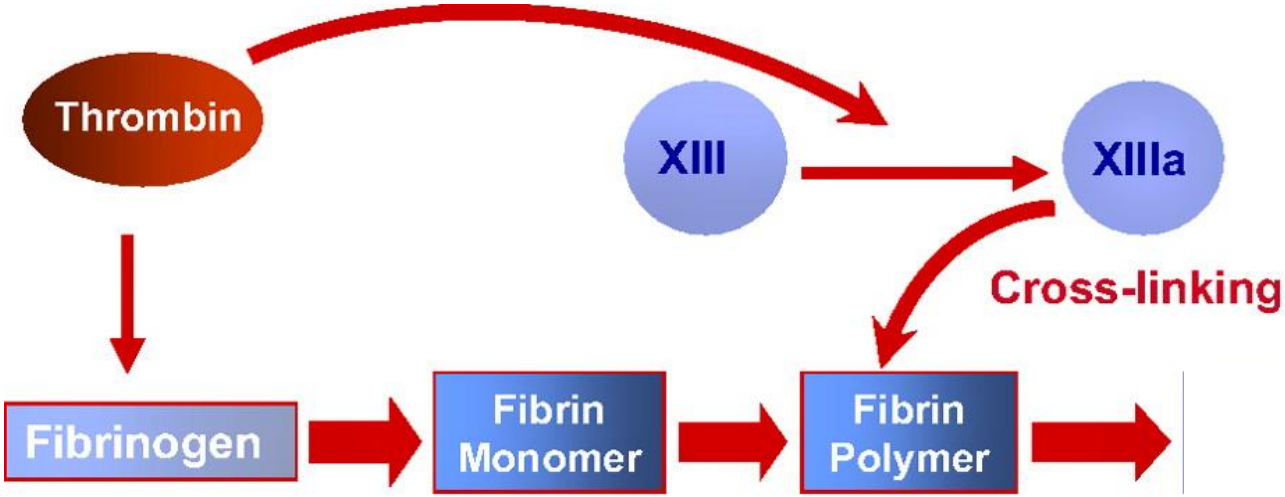
Circulate in plasma in inactive sate

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 stablizing factors

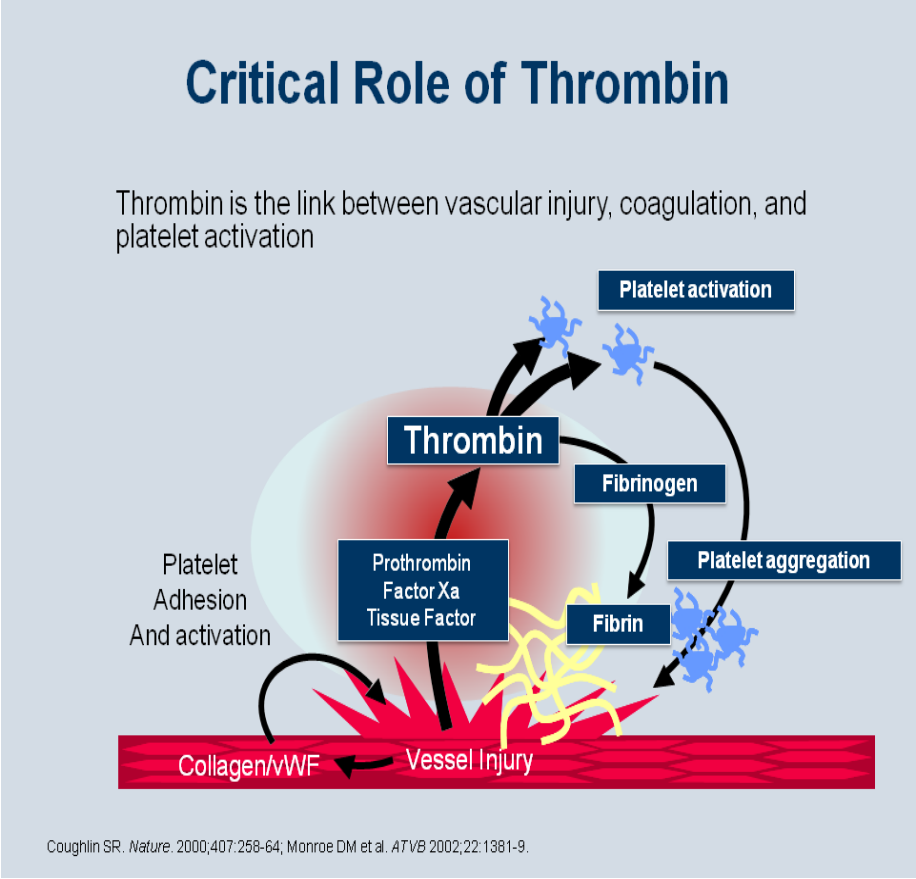
Blood coagulation
(clot formation)

- 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


The Intrinsic Pathway
Blood trauma or contact with collagen
F XII
F XIIa
HMW Kininogen Prekallikrein
FXI
FXIa
Ca++
F IX
F IXa
FVIII PLTs Ca++
F X
F Xa
The Extrinsic Pathway
Tissue trauma
Tissue factor (TF)
FVIIa
FVII
Ca++
FV PLTs, Ca++
Prothrombin
Thrombin
Fibrinogen
Fibrin
Blood clot


Thrombin
XIII
XIIIa
Cross-linking
Fibrinogen
Fibrin Monomer
Fibrin Polymer

Thrombin



- Thrombin changes fibrinogen to fibrin
- Activates factor V
- Thrombin is essential in platelet morphological changes to form primary plug
- Thrombin stimulates platelets to release ADP & thromboxane A2; both stimulate further platelets aggregation

Intrinsic Pathway	Pathway Extrnsic
Contact activation ↓ XII →XIIa ↓ XI →XIa ↓ IX → IXa ↓VIII, Ca,P X → Xa	Tissue Factors ↓ ↓ ↓ ↓ VII,Ca ↓ ↓ ↓ Xa ← X

Xa
↓
↓ V, Ca, P
Prothrombin (II) → Thrombin (IIa)
↓
Fibrinogen (I) → Fibrin (soluble)
↓ XIII, Ca
Insoluble fibrin

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
- Xla will activate IX
- IXa + VIII + platelet phospholipid + Ca activate X
- Following this step the pathway is common for both

Extrinsic pathway

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

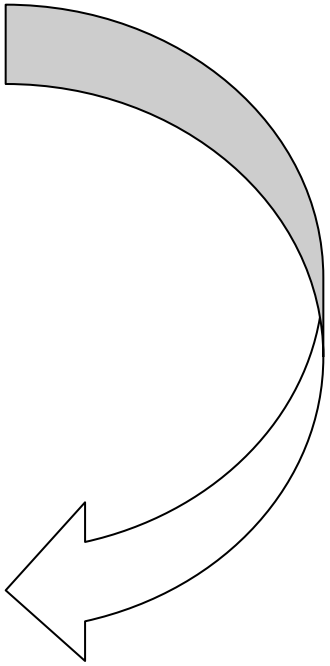
Common pathway

- 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 Blood Coagulation

- **Intrinsic Pathway:** all clotting factors present in the blood

- **Extrinsic Pathway: triggered by tissue factor**



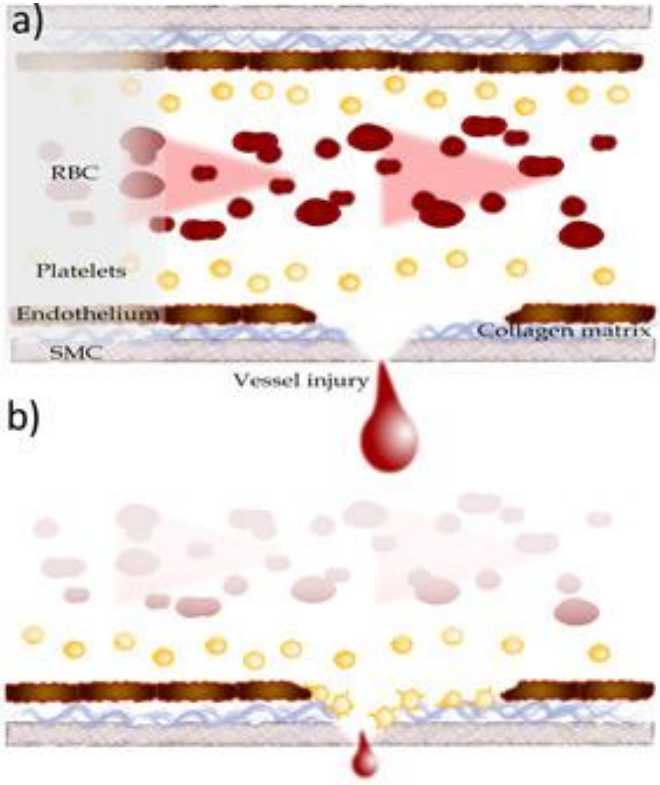
Common Pathway

Intrinsic Pathway	Extrinsic pathway
Contact activation ↓ XII → XIIa ↓ XI → XIa ↓ IX → IXa ↓VIII, Ca,P* X → Xa	Tissue factor ↓ ↓ VII,Ca ↓ Xa ← X

Xa
↓
↓ V, Ca, P*
Prothrombin (II) → Thrombin (IIa)
↓
Fibrinogen (I) → Fibrin (soluble)
↓ XIII, Ca
insoluble fibrin

P* = phospholipid from platelets

Platelet haemostatic plug formation



Hemostasis:

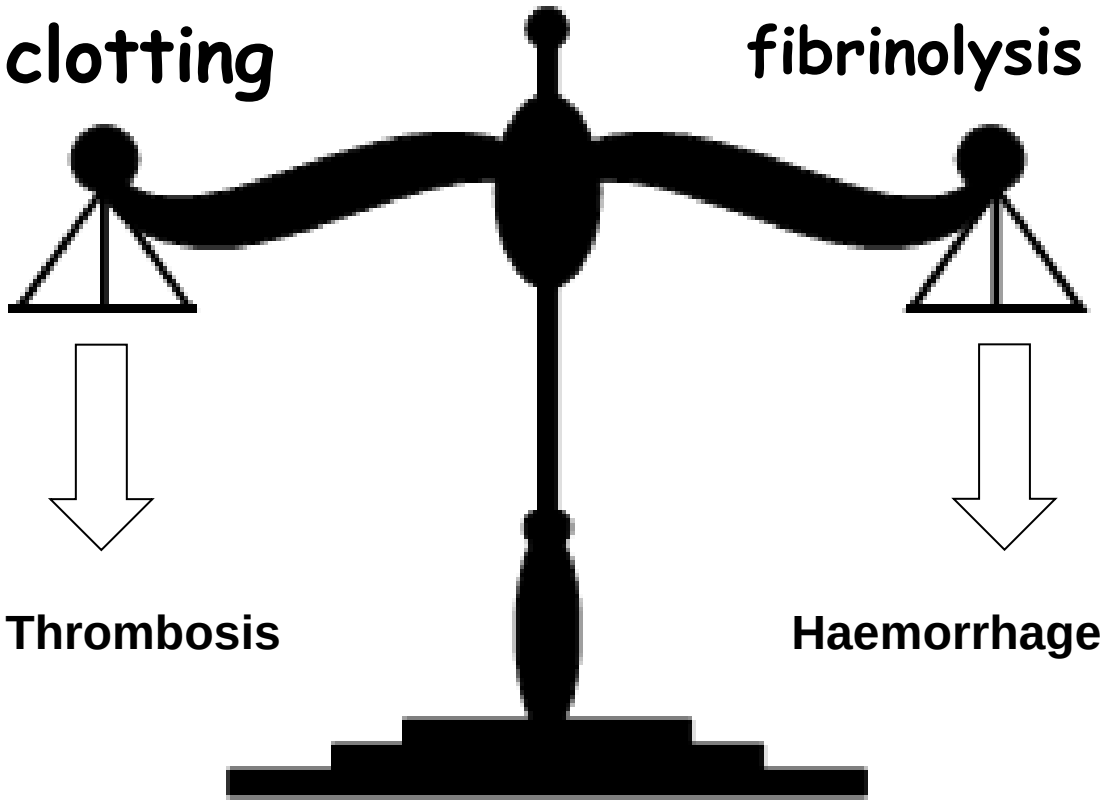
the spontaneous arrest of bleeding from ruptured blood vessels

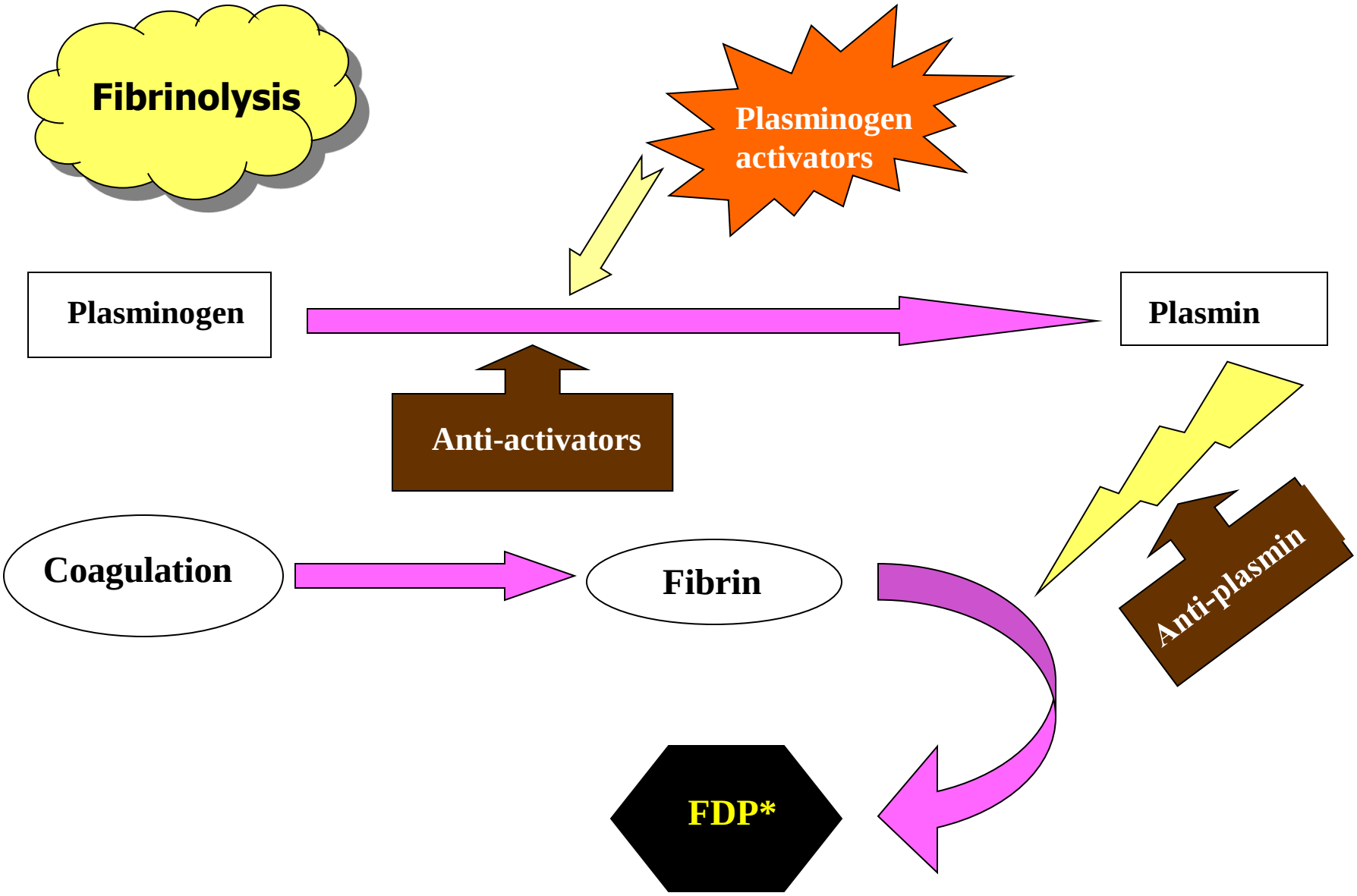
Mechanisms:

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

Fibrinolysis

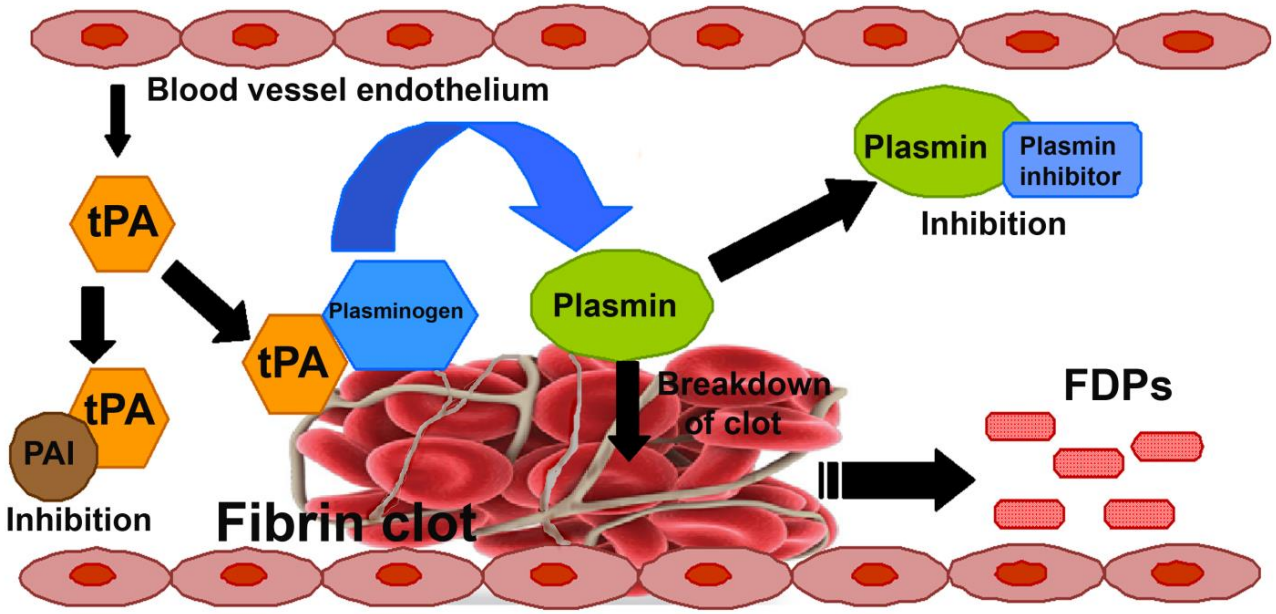
- Formed blood clot can either become fibrous or dissolve
- Fibrinolysis (dissolving) = Break down of fibrin by naturally occurring enzyme plasmin therefore prevent intravascular blocking
- There is balance between clotting and fibrinolysis
  - Excess clotting → blocking of Blood Vessels
  - Excess fibrinolysis → tendency for bleeding


clotting
fibrinolysis
Thrombosis
Haemorrhage

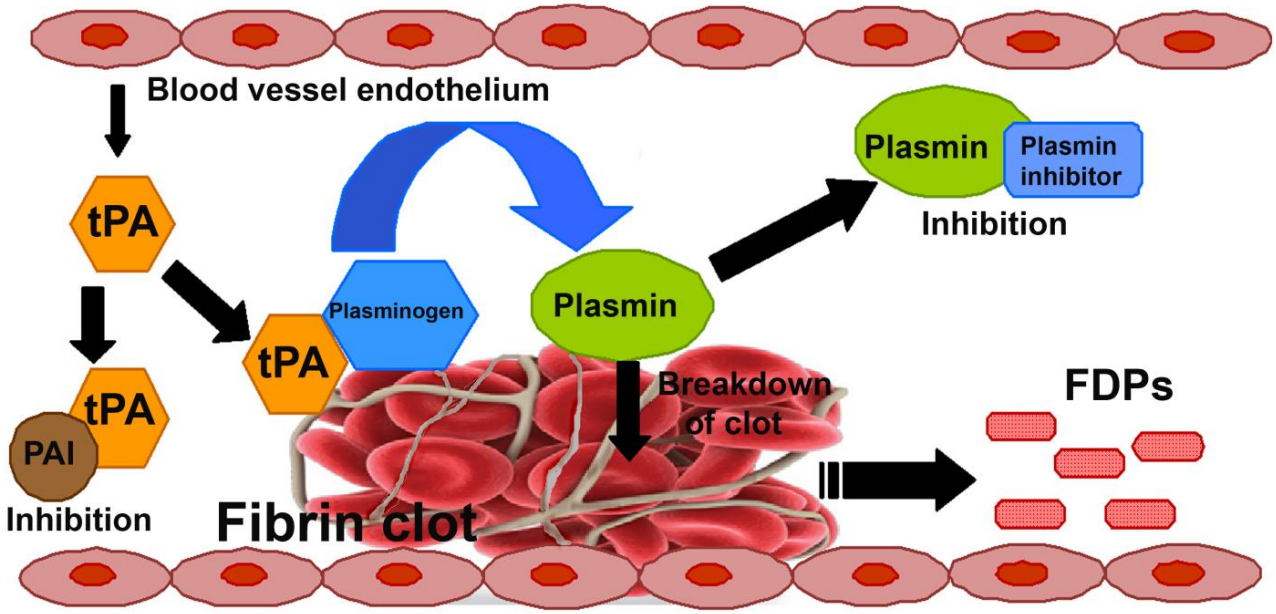


The fibrinolytic System

FDP*: Fibrin Degradation Products



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



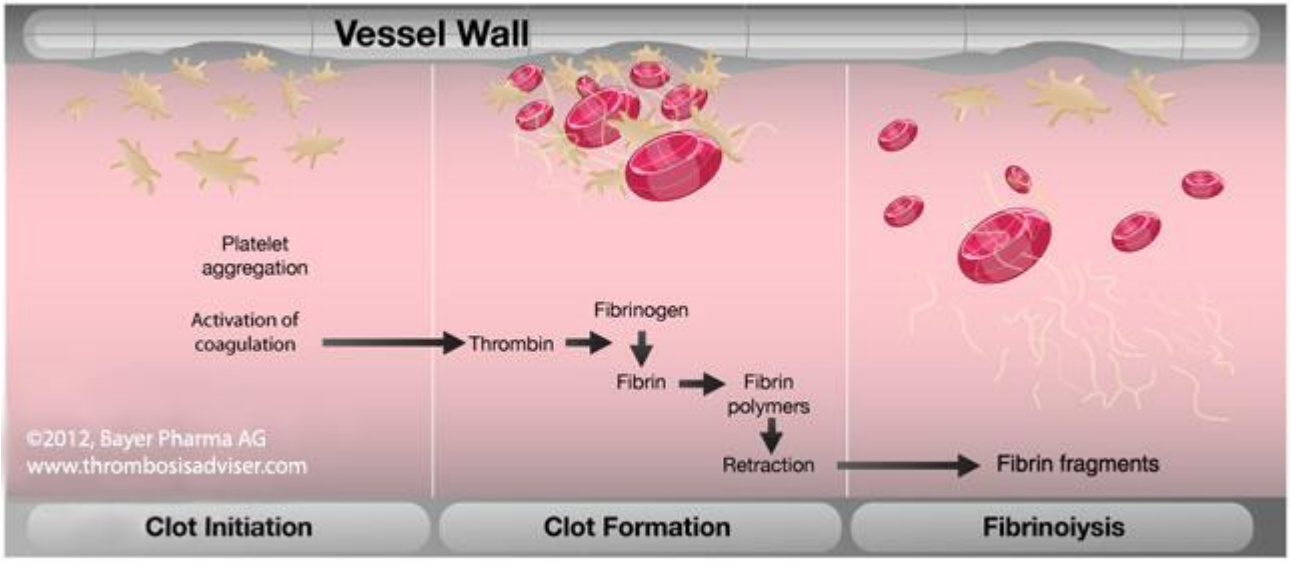
- Plasmin is controlled by:
  - Plasminogen Activator Inhibitor (PAI)
  - Antiplasmin from the liver
- Uses:
  - Tissue Plasminogen Activator (t-PA) used to activate plasminogen to dissolve coronary clots

Plasmin

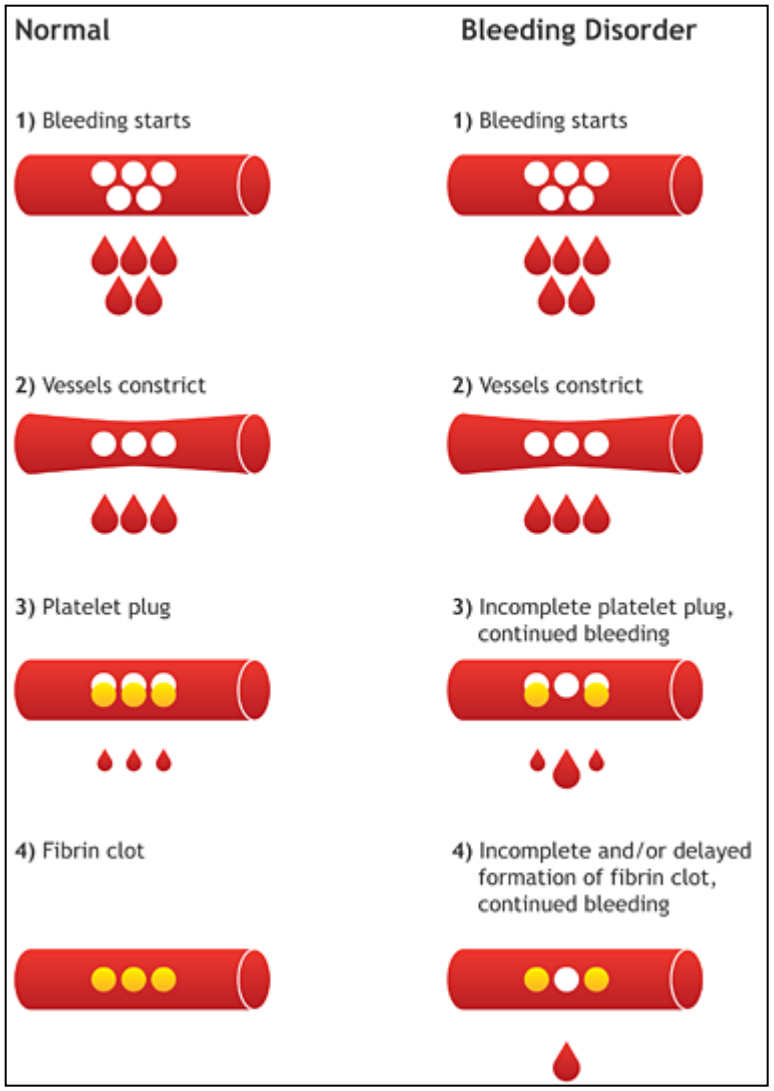
Fibrin

Fibrin degradation product

Haemostatic Mechanisms



Bleeding disorders



- Excessive 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.

Cont. 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.


Goseau Village, Austria
THANK YOU