PLATELETS STRUCTURE AND FUNCTIONS
COAGULATION MECHANISMS

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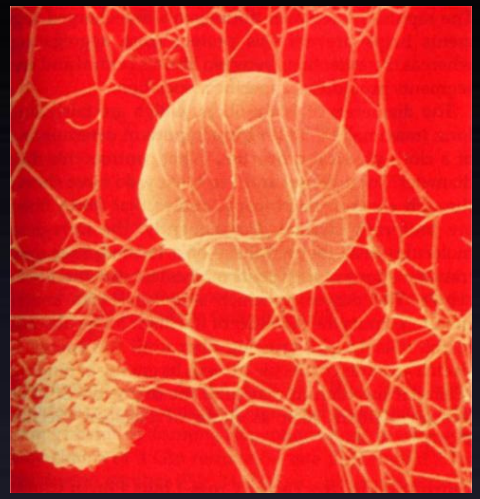


Vessel injury

Antithrombogenic
(Favors fluid blood)

Thrombogenic
(Favors clotting)

HANDOUTS…10/19/2016

OBJECTIVES

- **At the end of the lecture you should be able to describe…..**

1. Describe formation and development of platelets
2. Recognoize different stages of haemostasis
3. Explain the role of platelets in haemostasis.
4. Recognize different clotting factors & cascade of clotting.
5. Describe the intrinsic, extrinsic and common pathway.
7. Recognize the role of thrombin in coagulation
8. Explain process of fibrinolysis and function of plasmin

HEMOSTASIS

The spontaneous arrest of bleeding from ruptured blood vessels

STEPS OF HEMOSTASIS

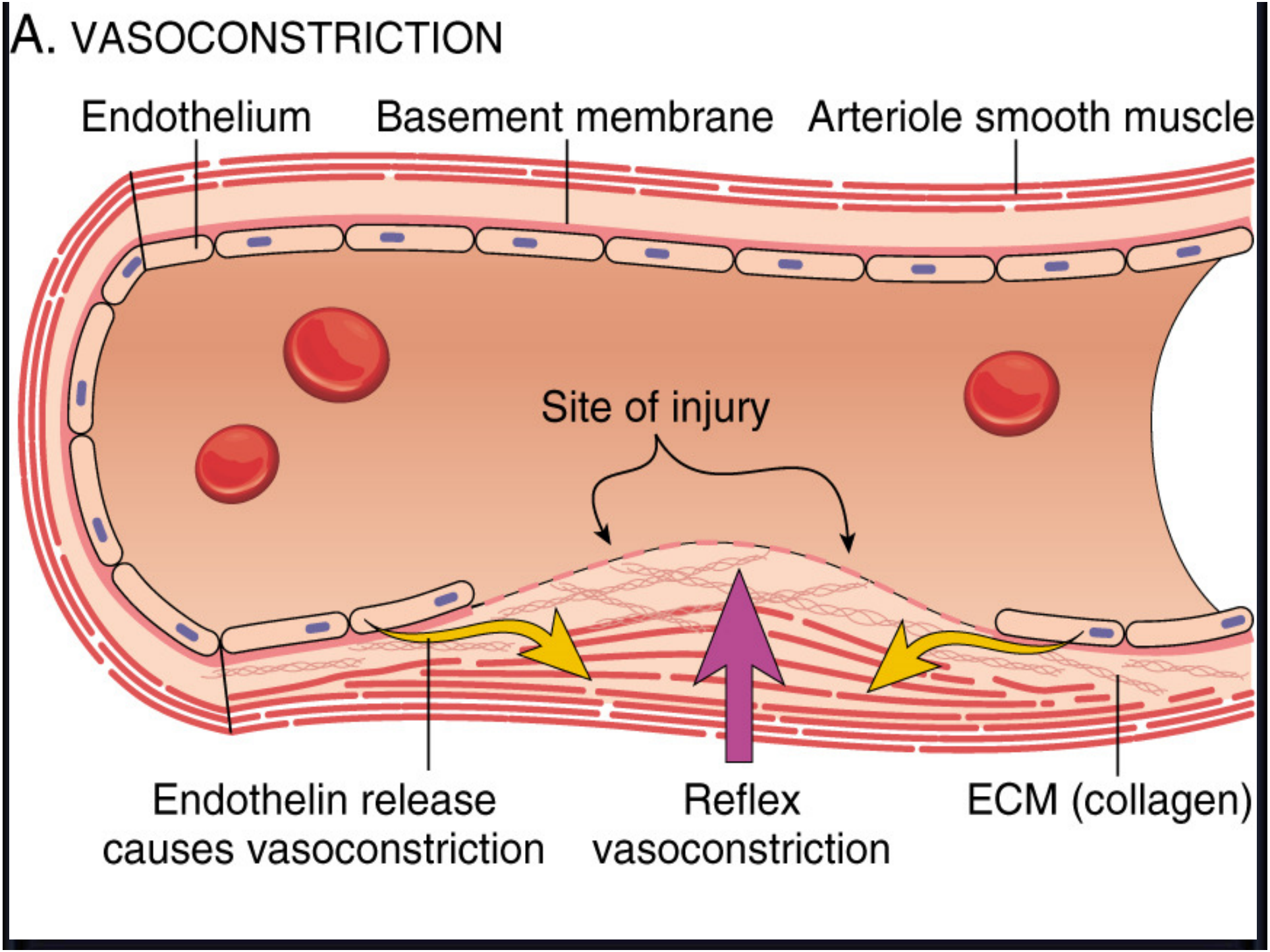
1. Vascular Spasm
2. Formation of platelet plug
3. Blood Coagulation & Clot Retraction
4. Fibrinolysis

1-VASCULAR SPASM (Vascular Constriction)

Immediately After injury there is localized Vasoconstriction.

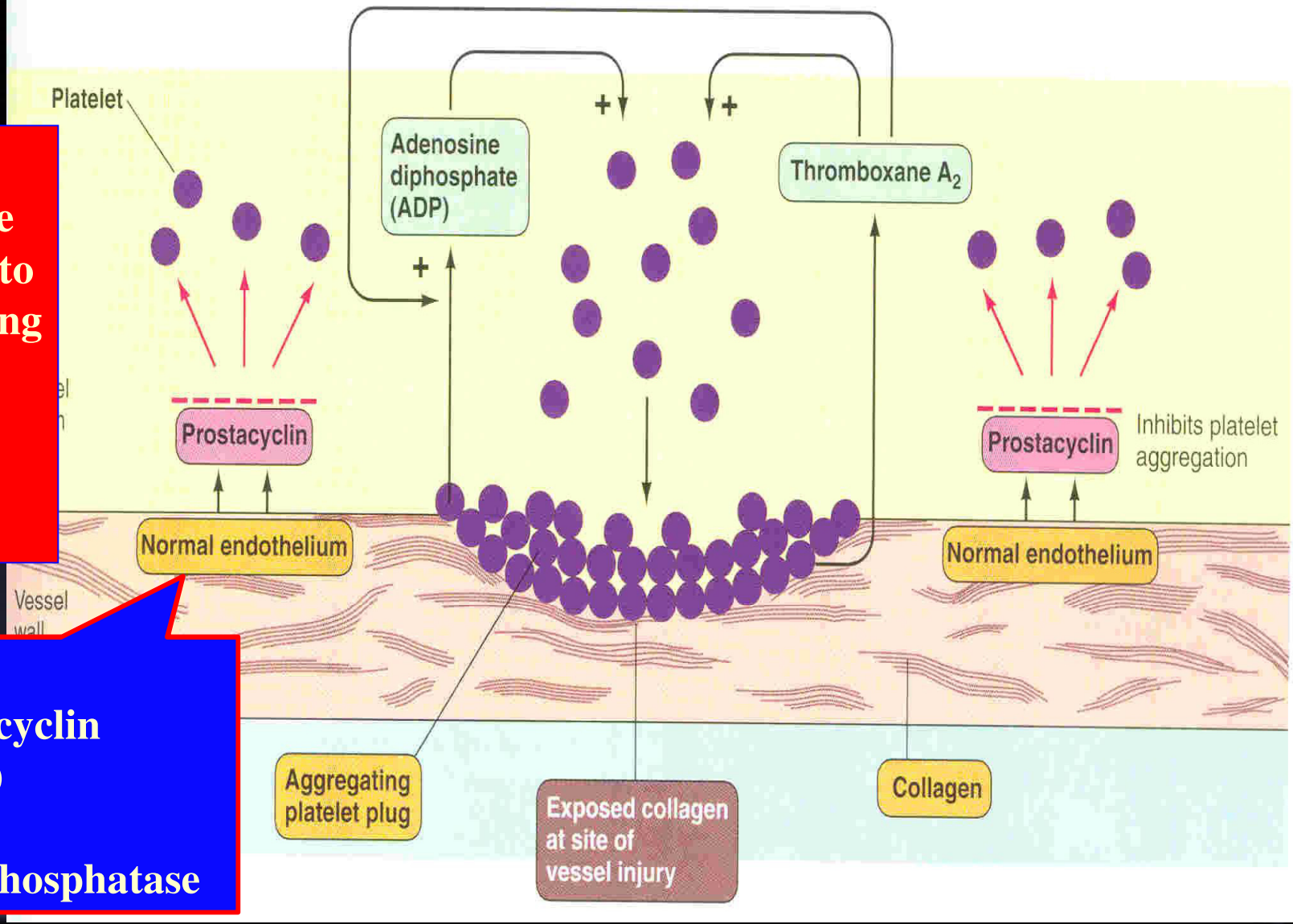
- **Causative Factors are three (3)**
  1. Nervous reflexes
  2. Local myogenic spasm
  3. Local humoral factors….Platelets → Thromboxane A_2 [TXA2] (Vasoconstrictor)
- **Importance**
  - Crushing injuries → Intense spasm → No lethal loss of blood

TXA2 is inhibited by aspirin…How?


A. VASOCONSTRICTION
Endothelium
Basement membrane
Arteriole smooth muscle
Site of injury
Endothelin release causes vasoconstriction
Reflex vasoconstriction
ECM (collagen)

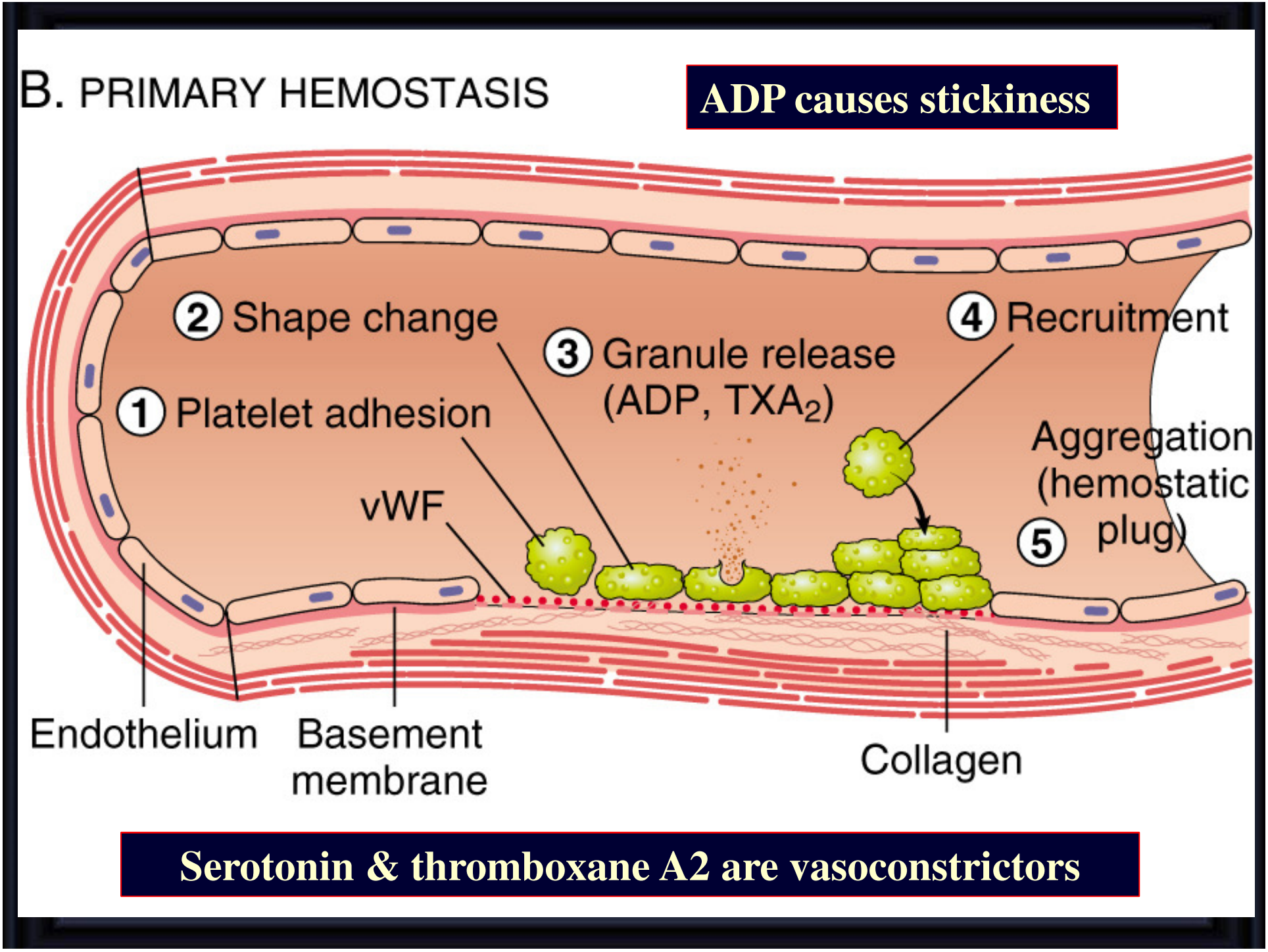
2-FORMATION OF PLATELET PLUG [PRIMARY HEMOSTASIS]

Importance → enough to stop bleeding from small vascular damage



Secrete

- **prostacyclin (PGI2)**
- **NO**
- **ADP phosphatase**

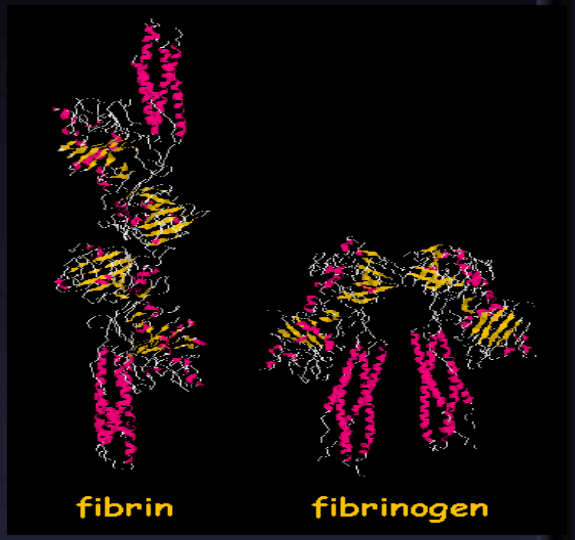

B. PRIMARY HEMOSTASIS
ADP causes stickiness
2 Shape change
3 Granule release (ADP, TXA2)
4 Recruitment
1 Platelet adhesion
vWF
Aggregation (hemostatic plug)
5
Endothelium
Basement membrane
Collagen
Serotonin & thromboxane A2 are vasoconstrictors

3-BLOOD COAGULATION

Formation of Clot or Thrombus

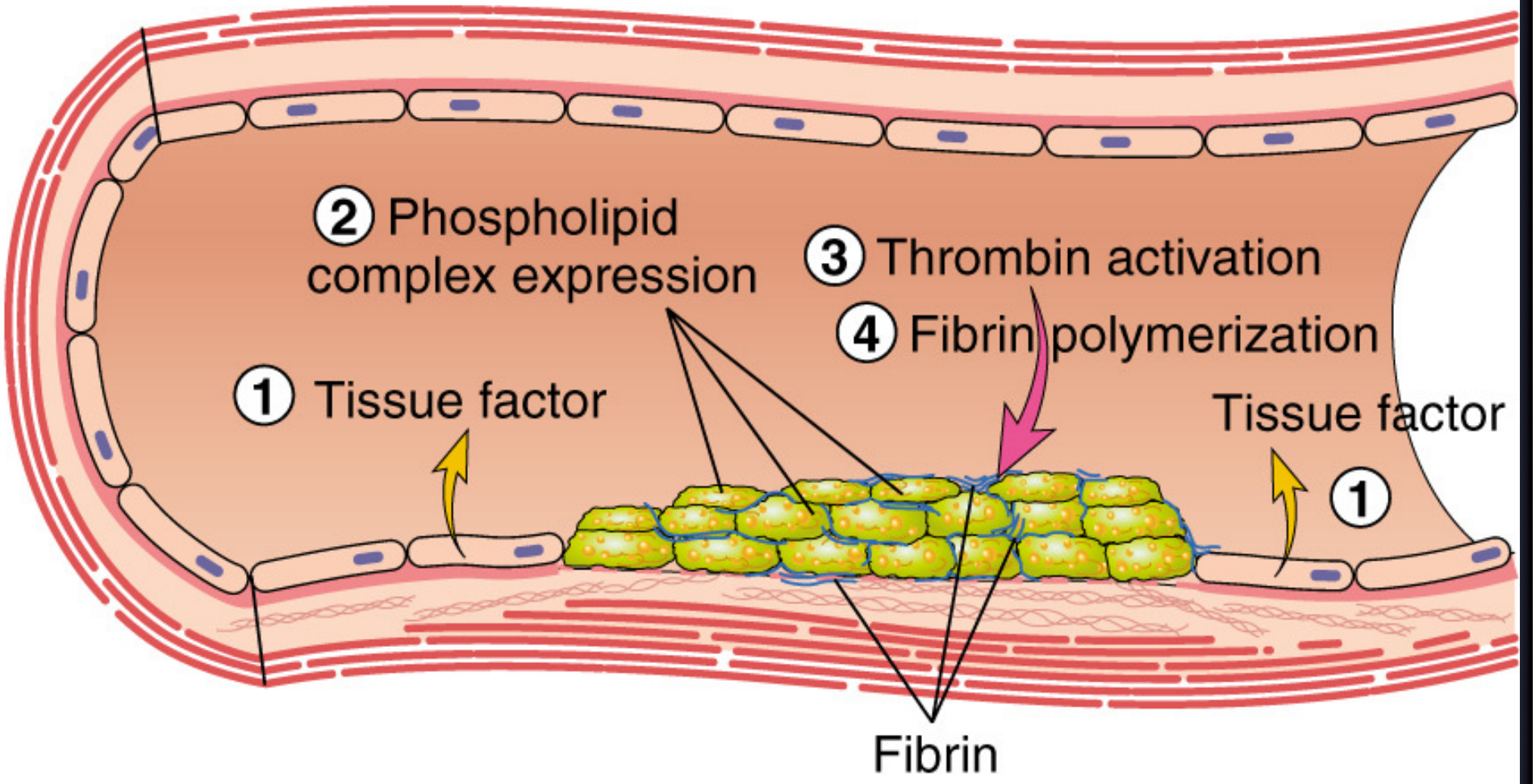
[SECONDARY HEMOSTASIS]

- **Blood clotting** is the transformation of blood (soluble fibrinogen) from a liquid into a solid gel form (insoluble fibrin strands)
- Pathways
  - Intrinsic
  - Extrinsic
- Begins to develop in
  - 15-20 sec → Minor trauma
  - 1-2 min → Severe trauma

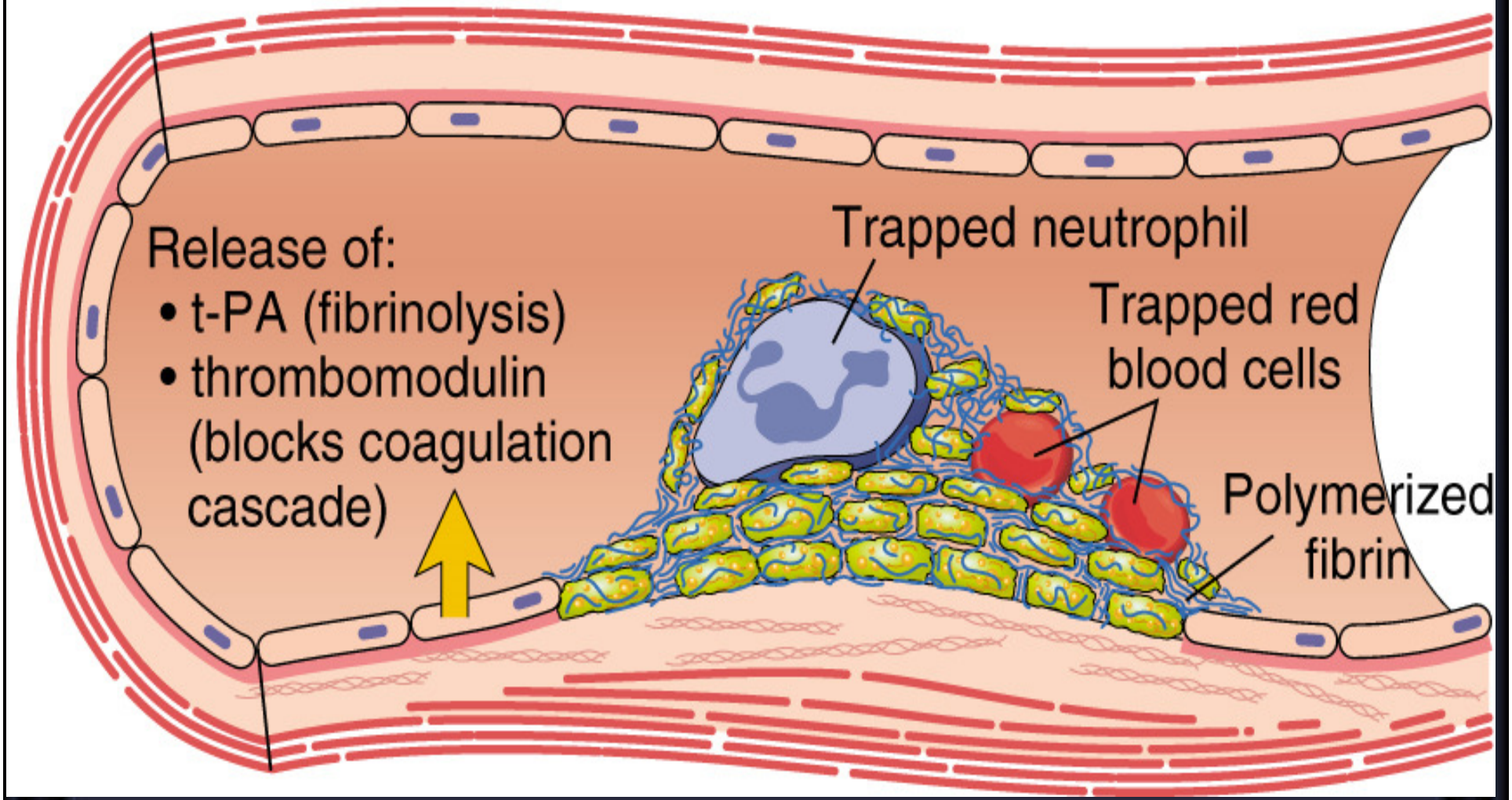


CLOT is a meshwork of fibrin fibres running in all directions entrapping blood cells, platelets and plasma.

C. SECONDARY HEMOSTASIS



D. THROMBUS AND ANTITHROMBOTIC EVENTS



MECHANISM OF CLOTTING - STEPS

1. Formation of Prothrombin activator complex (Xa+Ca+PF-3+V) by Extrinsic & Intrinsic Pathways leading to Common Pathway
2. Conversion of prothrombin into thrombin
3. Conversion of fibrinogen into fibrin
4. Fibrin converts to stable fibrin polymer

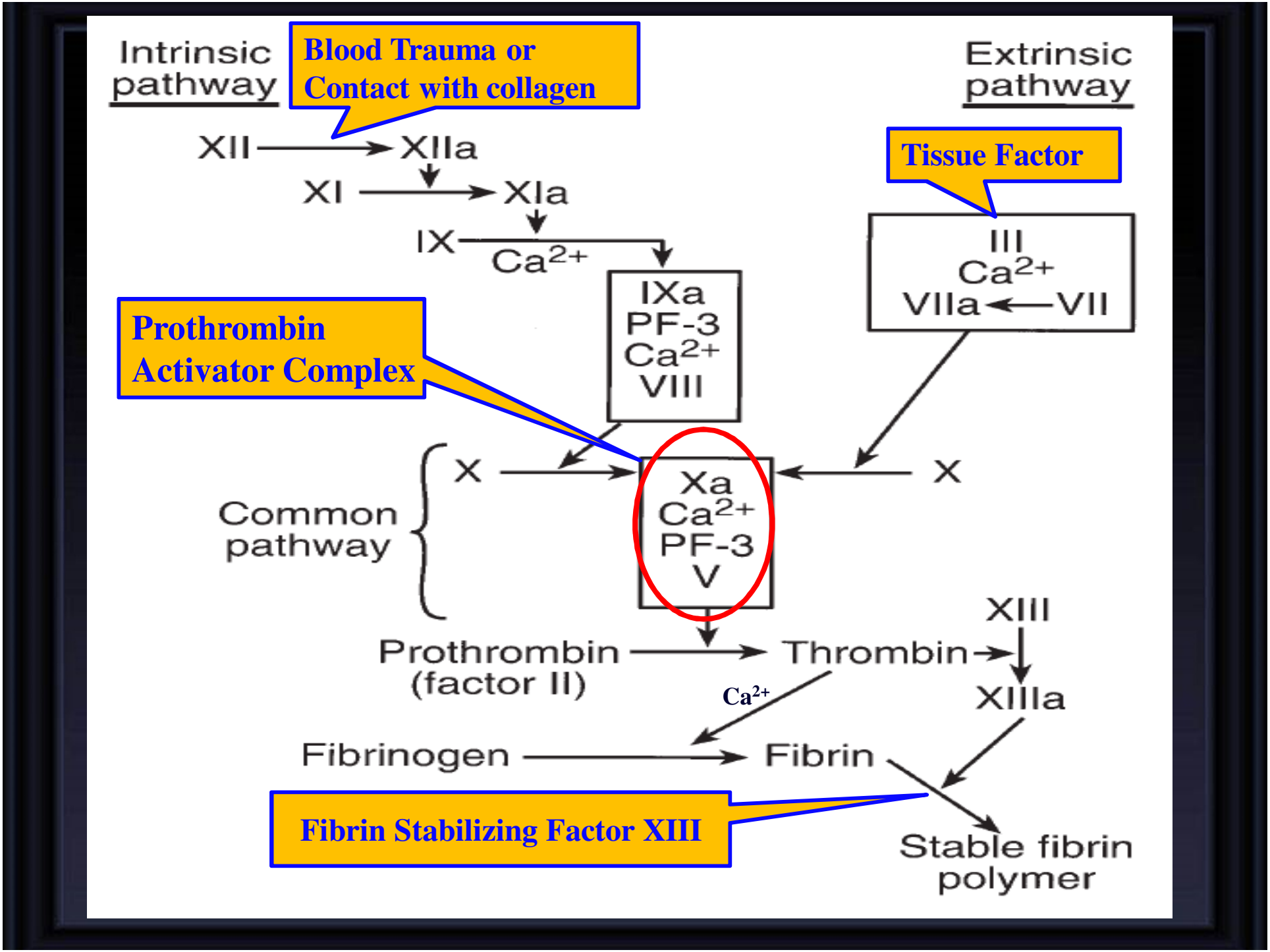
Clotting Factors

Ganong

TABLE 31–5 System for naming blood-clotting factors.

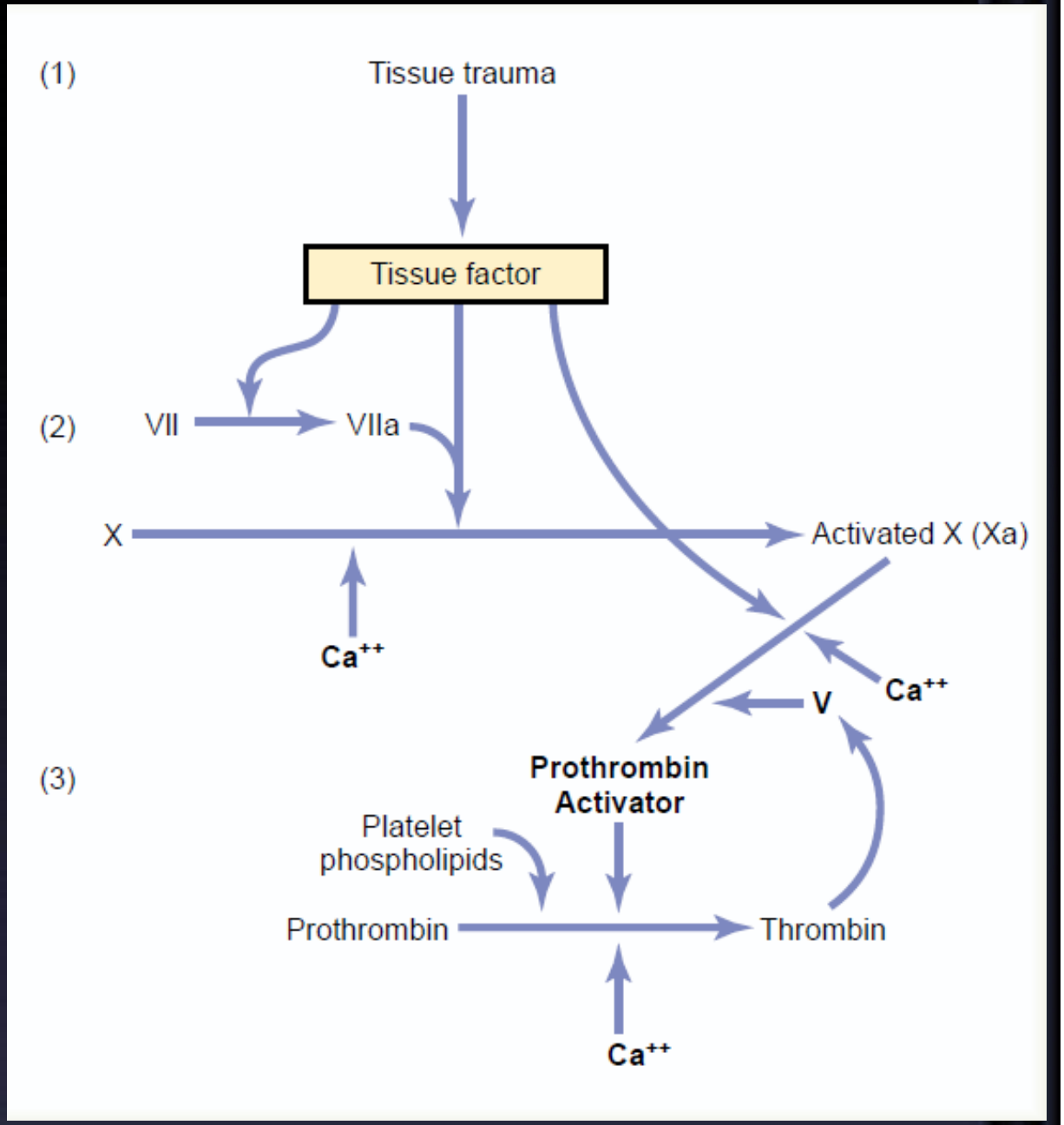
Factor[a]	Names
I	Fibrinogen
II	Prothrombin
III	Thromboplastin
IV	Calcium
V	Proaccelerin, labile factor, accelerator globulin
VII	Proconvertin, SPCA, stable factor
VIII	Antihemophilic factor (AHF), antihemophilic factor A, antihemophilic globulin (AHG)
IX	Plasma thromboplastic component (PTC), Christmas factor, antihemophilic factor B
X	Stuart–Prower factor
XI	Plasma thromboplastin antecedent (PTA), antihemophilic factor C
XII	Hageman factor, glass factor
XIII	Fibrin-stabilizing factor, Laki–Lorand factor
HMW-K	High-molecular-weight kininogen, Fitzgerald factor
Pre-Ka	Prekallikrein, Fletcher factor
Ka	Kallikrein
PL	Platelet phospholipid

[a]Factor VI is not a separate entity and has been dropped.


Intrinsic pathway
Blood Trauma or Contact with collagen
Extrinsic pathway
XII → XIIa
XI → XIa
IX
Ca2+
IXa PF-3 Ca2+ VIII
Tissue Factor
III Ca2+ VIIa ← VII
Prothrombin Activator Complex
X
Xa Ca2+ PF-3 V
X
Common pathway
Prothrombin (factor II)
Thrombin
XIII
XIIIa
Ca2+
Fibrinogen
Fibrin
Fibrin Stabilizing Factor XIII
Stable fibrin polymer

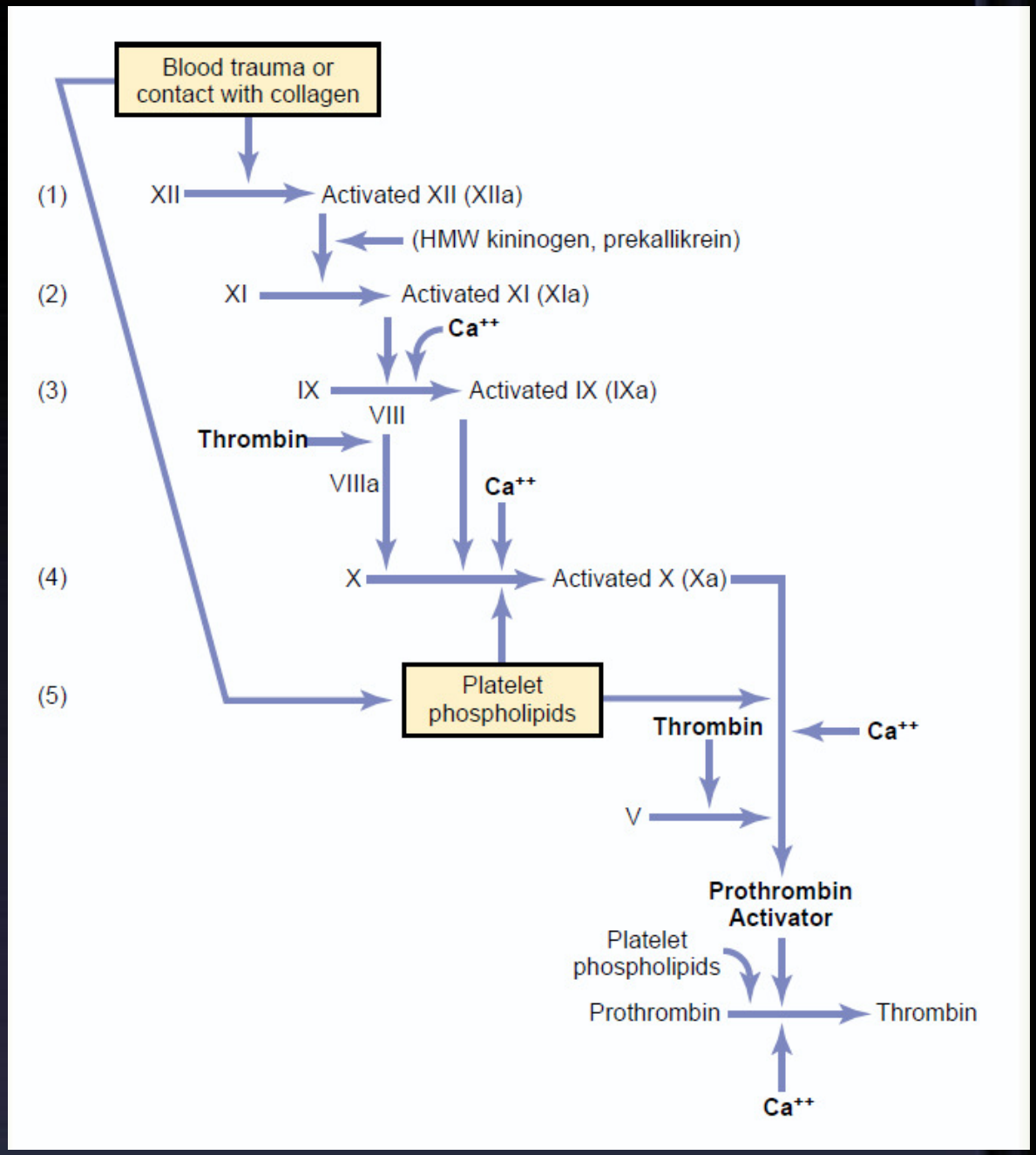
EXTRINSIC MECHNANISM FOR INITIATING CLOTTING

TF or tissue thromboplastin; includes phospholipids from the membranes of the tissue plus a lipoprotein complex that functions mainly as a proteolytic enzyme.

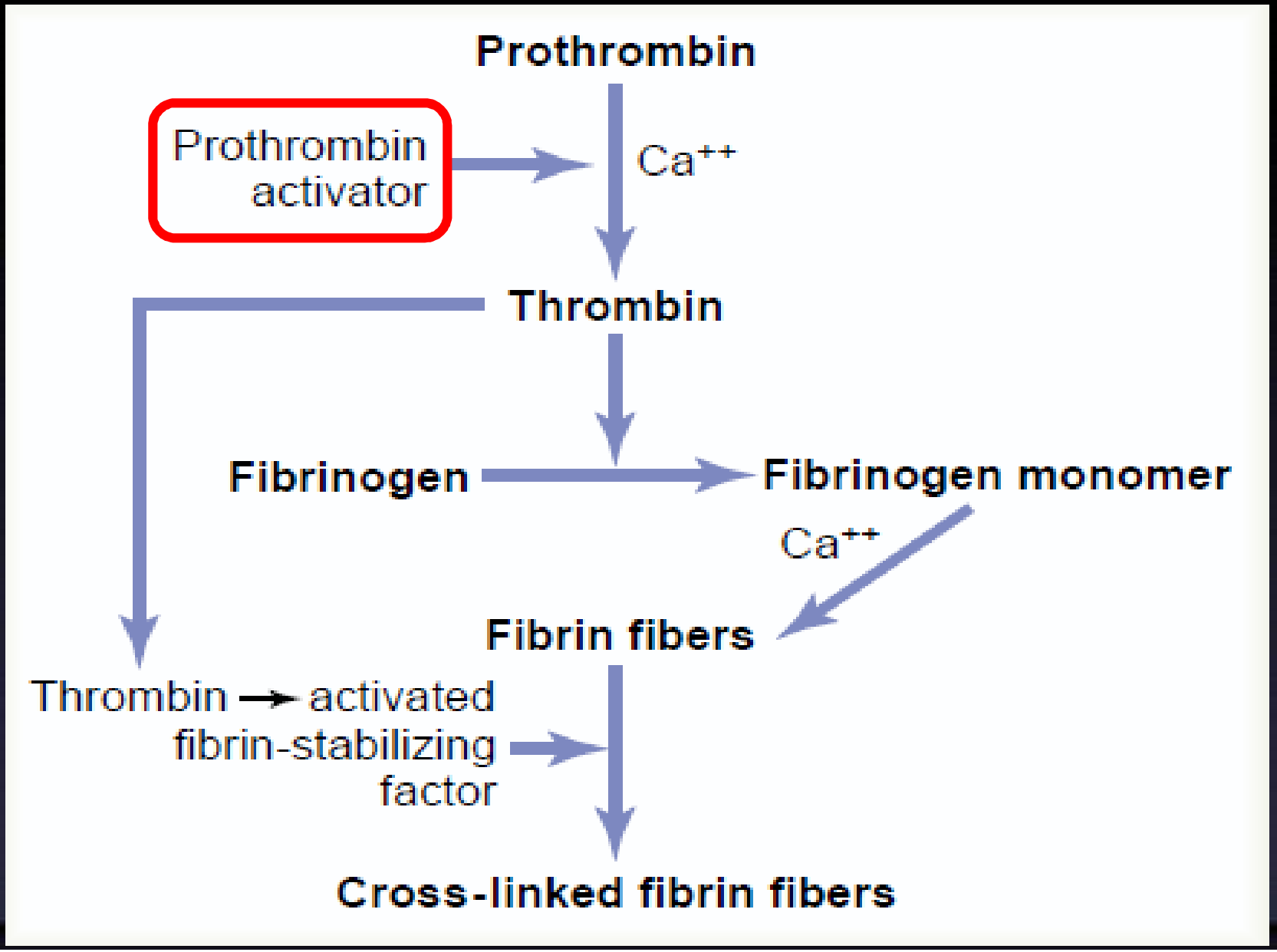


INTRINSIC MECHNANISM FOR INITIATING CLOTTING

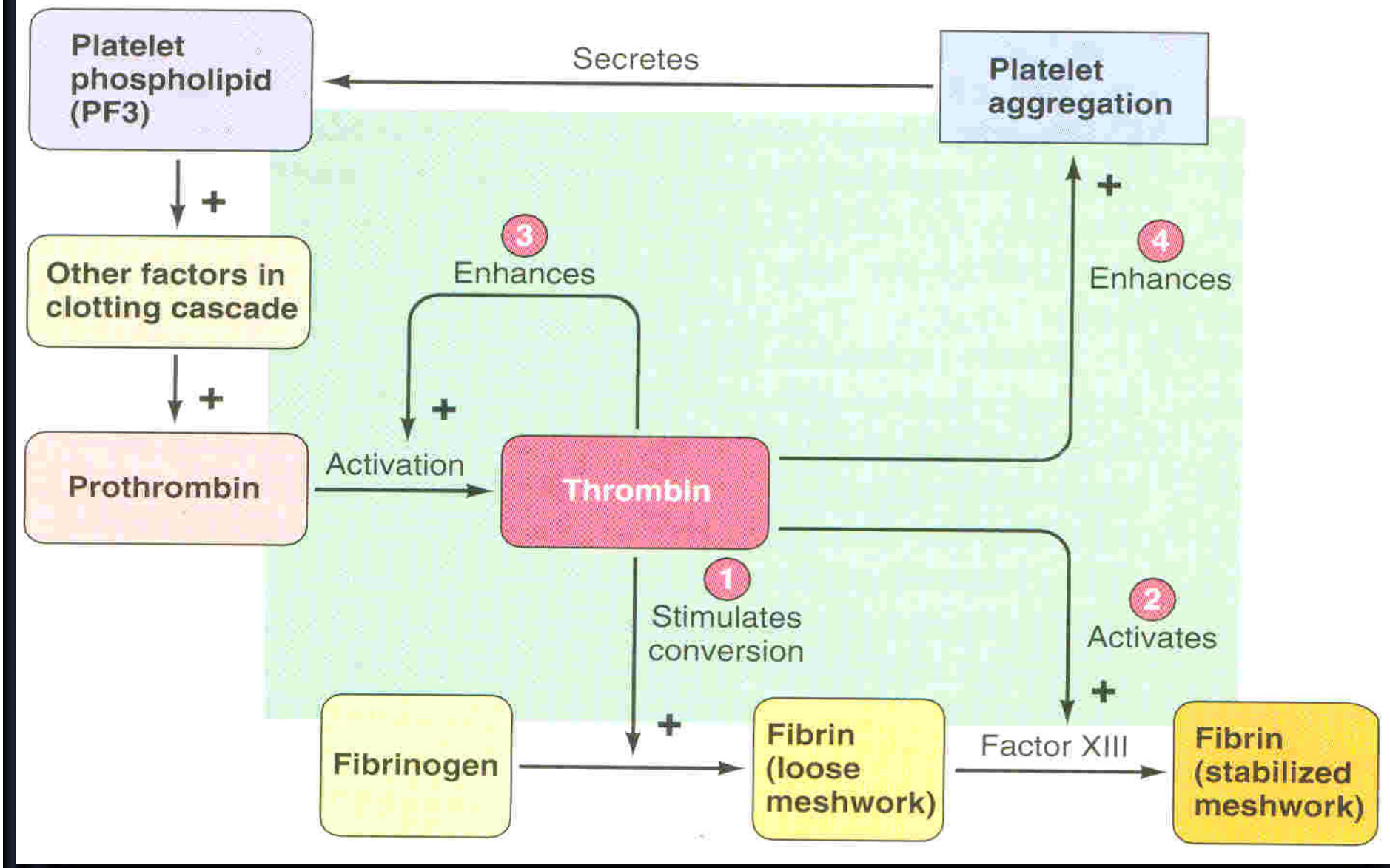
Trauma to the blood itself or exposure of the blood to collagen (from a traumatized blood vessel wall), foreign surface/glass



ACTION OF THROMBIN ON FIBRONOGEN TO FORM FIBRIN



ROLES OF THROMBIN IN HEMOSTASIS



CLOT RETRACTION

- When clot retracts (contracts), it expresses most of the fluid from the clot within 20-60 min called → Serum
- Serum cannot clot
- Role of platelets in clot formation & retraction……they are contractile.

ROLE OF CALCIUM IONS IN CLOTTING

No Ca^{++} → No Clotting (Needed in many steps)

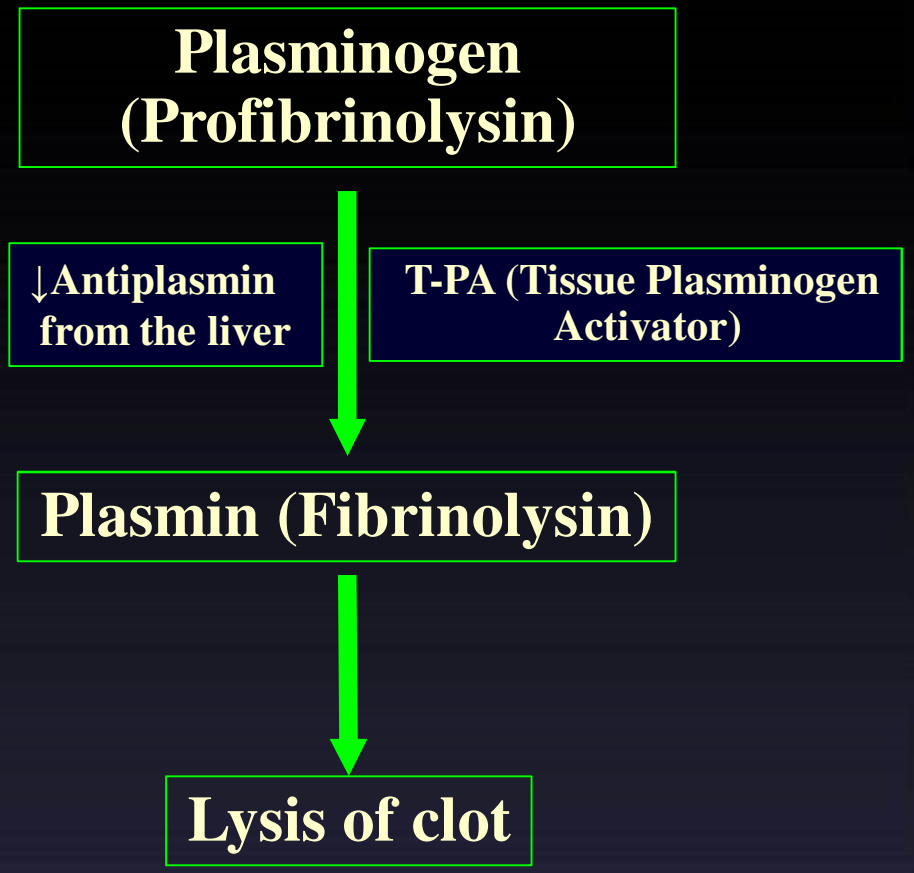
Blood samples are prevented from clotting by:

- **Citrate ions** → Deionization of Ca^{++}
- **Oxalate ions** → Precipitate the Ca^{++}
- **Heparin** → combines with antithrombin effectiveness increases by 100-1000 fold, Also remove Factors XII, XI, X, and IX
- **Warfarin:** ↓ production of Factors VII, IX and X by liver.
- **EDTA** → chelates (binds) calcium ions

LYSIS OF BLOOD CLOTS BY PLASMIN

Formed blood clot can either become fibrous or dissolve.

- **Fibrinolysis (dissolving) = Break down of fibrin by naturally occurring enzyme plasmin therefore prevent intravascular blocking.**



Tissue Plasminogen Activator (TPA) used to activate plasminogen to dissolve coronary and cerebral clots.

NATURAL INTRAVASCULAR ANTICOAGULANTS

1. **Endothelial Surface Factors**
   - Smoothness of Endothelium
   - Glycocalyx Layers
   - Thrombomodulin Protein binds to thrombin→Activates Protein C (with ProtS)→ inactivates factors V & VIII and inactivates an inhibitor of tPA → increasing the formation of plasmin.
2. **Antithrombin action of Fibrin and Antithrombin III**
   - 85-90 % Thrombin binds with Fibrin
   - 10-15 % Thrombin binds with Antithrombin III

Antithrombin III is a circulating protease blocking clot factors

NATURAL INTRAVASCULAR ANTICOAGULANTS

3. **Heparin**
   - - vely charged conjugated polysaccharide
     - Increase the effectiveness of Antithrombin III
     - Produced by
       - Mast cells
       - Basophil cells
   - Most widely used anticoagulant clinically e.g. in stroke
4. **$Alpha_2$ – Macrogobulin**
   - Acts as a binding agent for several coagulation factors

THROMBOCYTOPENIA

- Platelet count upto 50,000 ul
- Less than 10,000 ------ Fatal
- ETIOLOGY

Decreased production

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

Increased destruction

- ITP
- Drugs
- Infections

Clinical Features

- Easy brusability
- Epistaxis
- Gum bleeding
- Hemorrhage after minor trauma
- Petechiae/Ecchumosis

HEMOPHILIA

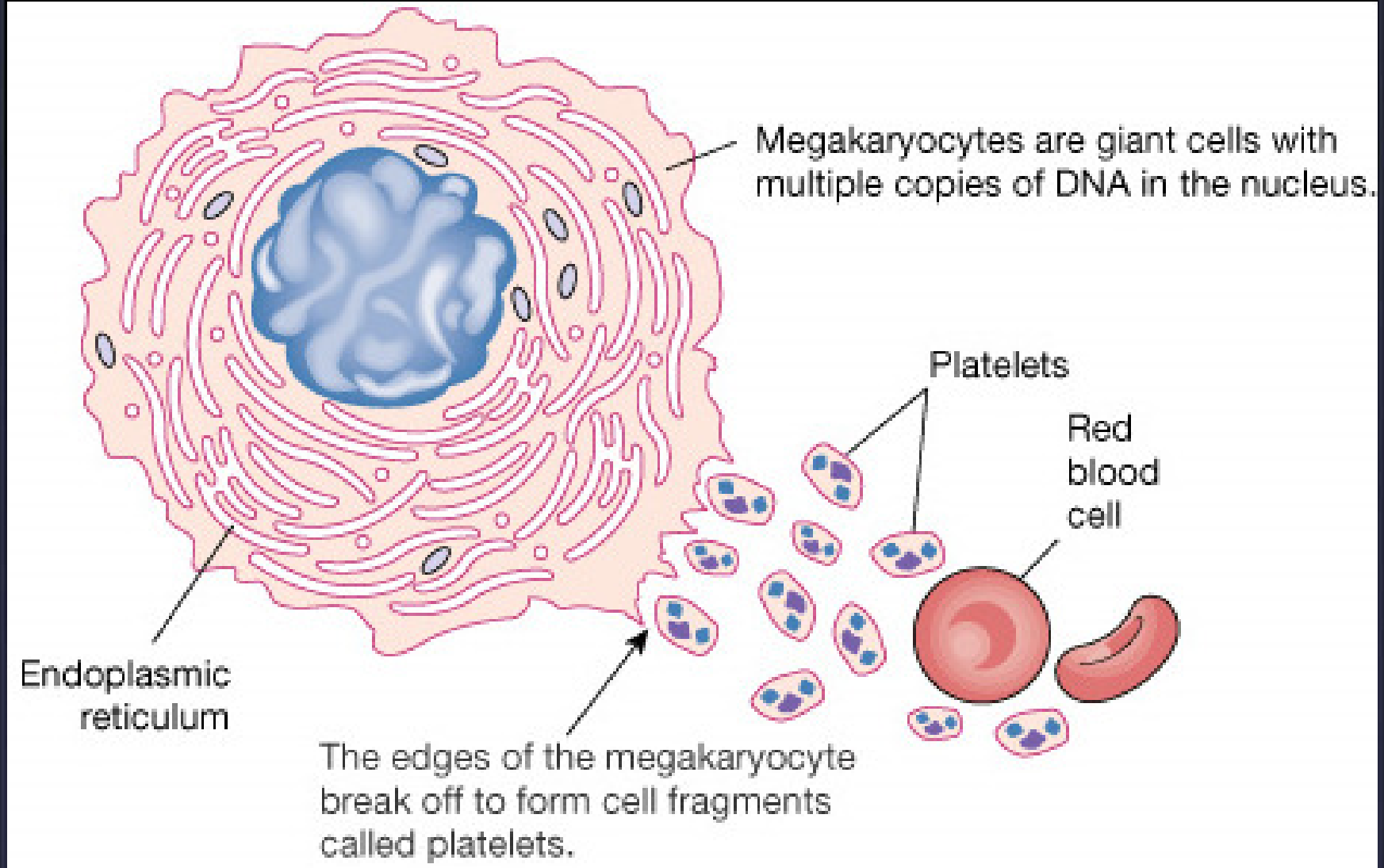
- Genetic disorders
- Transmitted by female chromosome as recessive trait
- Transmitted by female chromosome as recessive trait. Occurs exclusively in male Females are carriers

- **HEMOPHILIA A**
  - Classic Hemophilia
  - 85 % cases
  - Def. Of factor VIII
- **HEMOPHILIA B**
  - 15 % cases
  - Def. Of factor IX

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

PLATELETS

Formed by fragmentation from megakaryoctyes

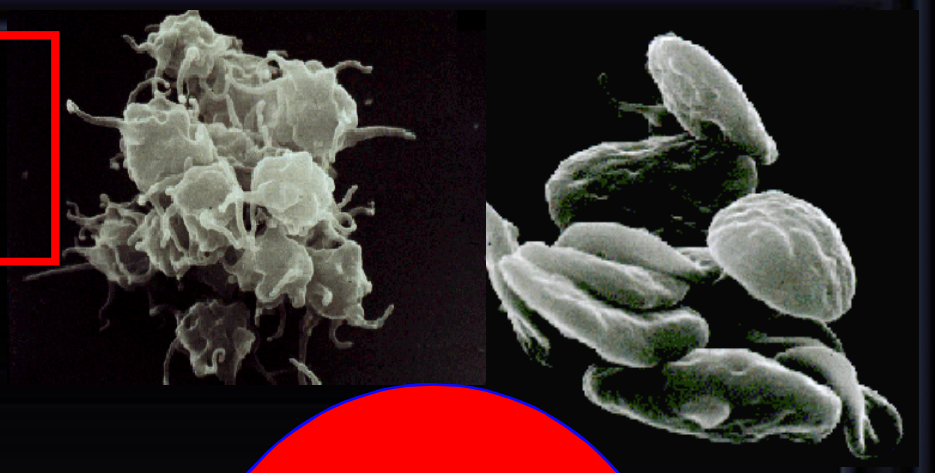


PLATELETS (Characteristics)

SHAPE: MINUTE ROUND OR OVAL DISCS
SIZE: 1-4 um IN DIAMETER
HALF LIFE: 8-12 DAYS
COUNT: 150,000 – 300,000/ microlitrer
LOCATION: 80% in blood & 20% in spleen

- **Contractile, adhesive, cell fragments.**
- **Store coagulation factors & enzymes**
- **Surface Binding sites Glycoproteins (surface Antigens) for like ….. GP 1b for vW Factor**

FUNCTIONAL CHARACTERISTICS

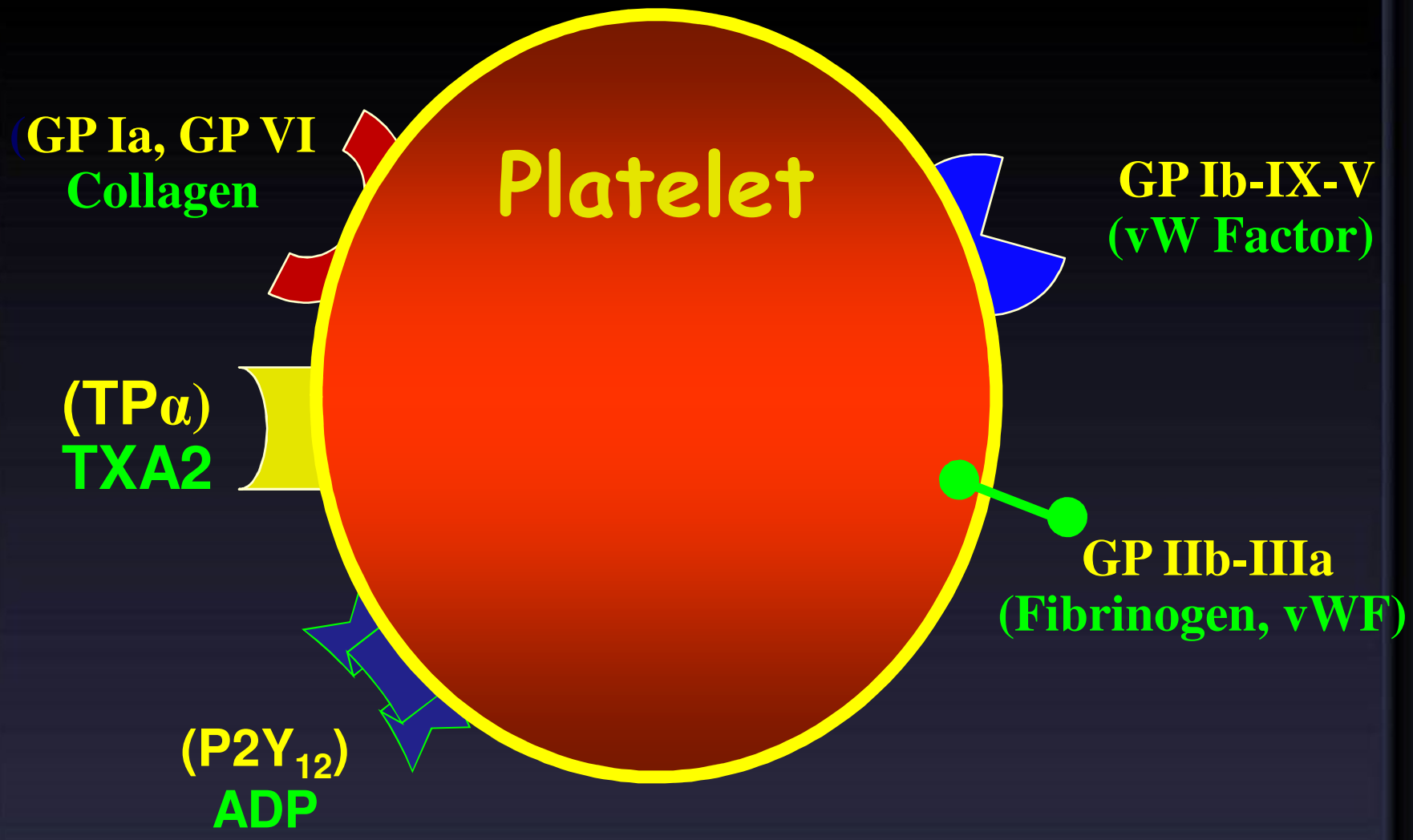


- **Motile:** Actin And Myosin Molecules
- **Active:** Endoplasmic Reticulum, Golgi Apparatus & Mitochondria
- **Enzymes** Systems For Synthesis Of Prostaglandins
- **Garnules**

Dense or δ granules
- Serotonin
- ADP
- Ca^{++}

α granules
- Coag Factors
- PDGF

Platelet Receptors



Summary of reactions involved in hemostasis.