PLATELETS STRUCTURE AND FUNCTIONS
COAGULATION MECHANISMS

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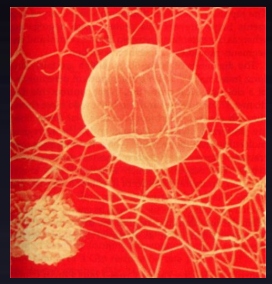


Vessel injury

Antithrombogenic

(Favors fluid blood)

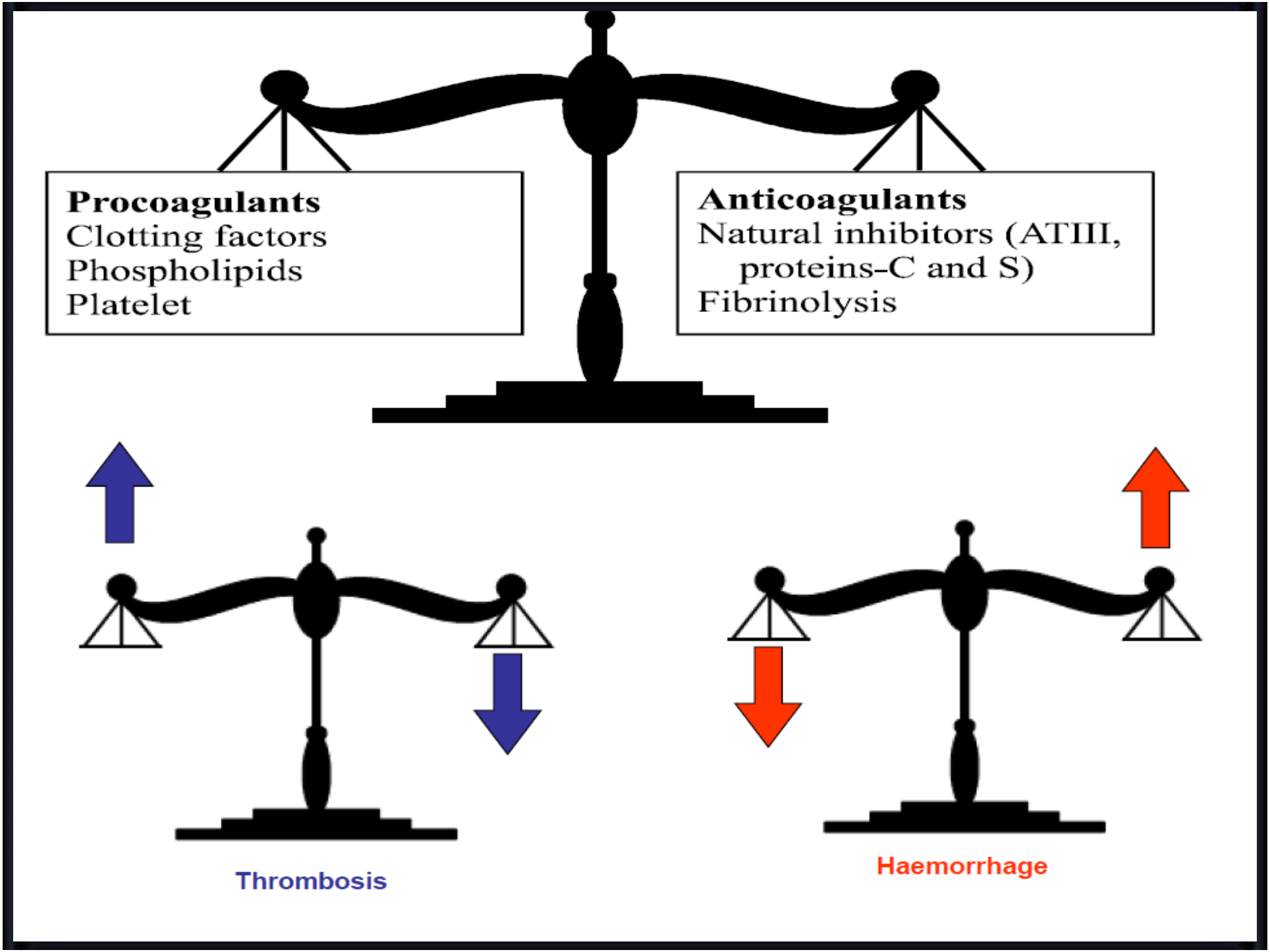
Thrombogenic

(Favors clotting)

OBJECTIVES

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

1. Describe formation and development of platelet
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

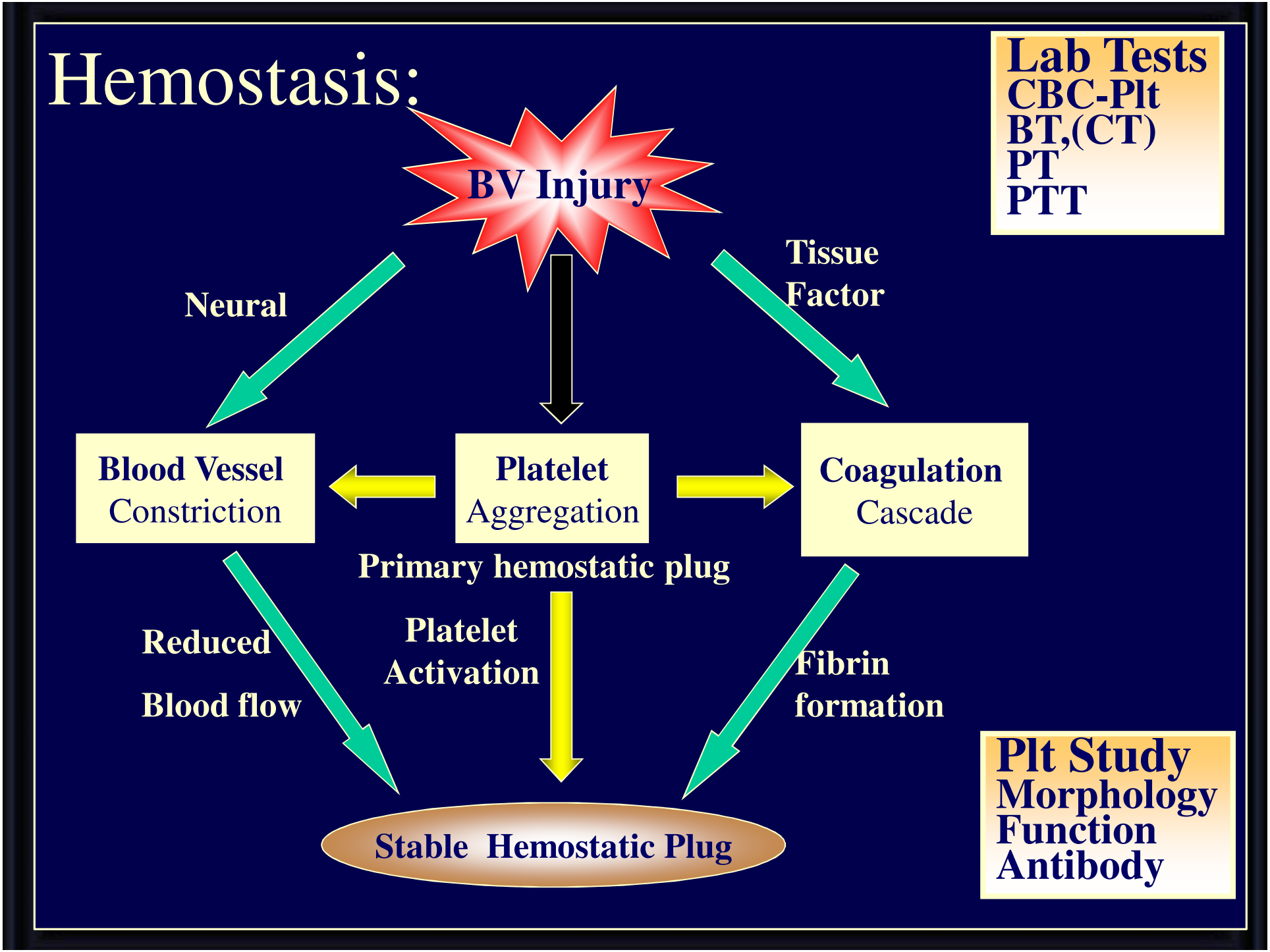

Procoagulants
Clotting factors
Phospholipids
Platelet
Anticoagulants
Natural inhibitors (ATIII, proteins-C and S)
Fibrinolysis
Thrombosis
Haemorrhage

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**

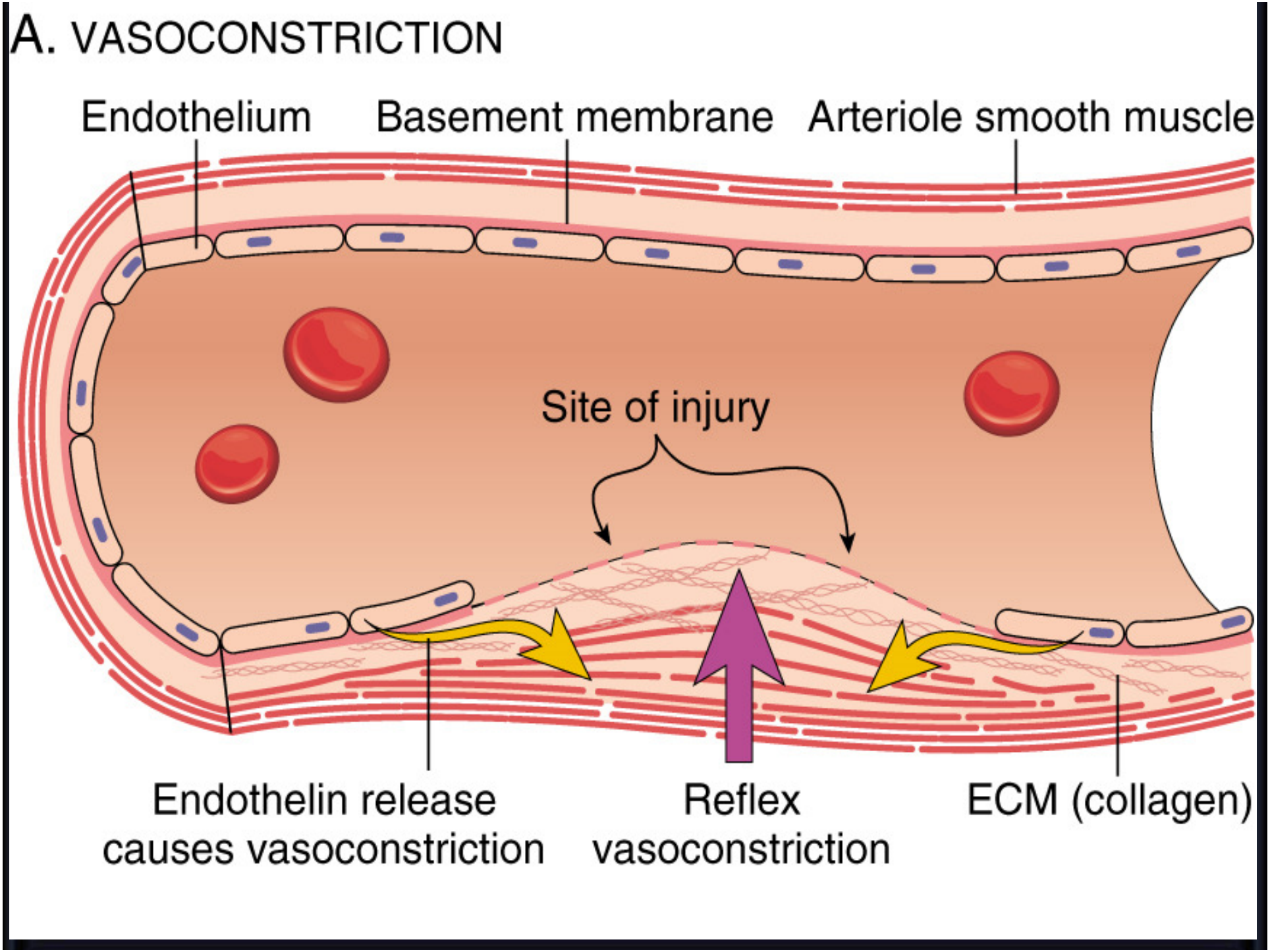

Hemostasis:
BV Injury
Neural
Tissue Factor
Blood Vessel Constriction
Platelet Aggregation
Coagulation Cascade
Primary hemostatic plug
Reduced Blood flow
Platelet Activation
Fibrin formation
Stable Hemostatic Plug
Lab Tests
CBC-Plt
BT,(CT)
PT
PTT
Plt Study
Morphology
Function
Antibody

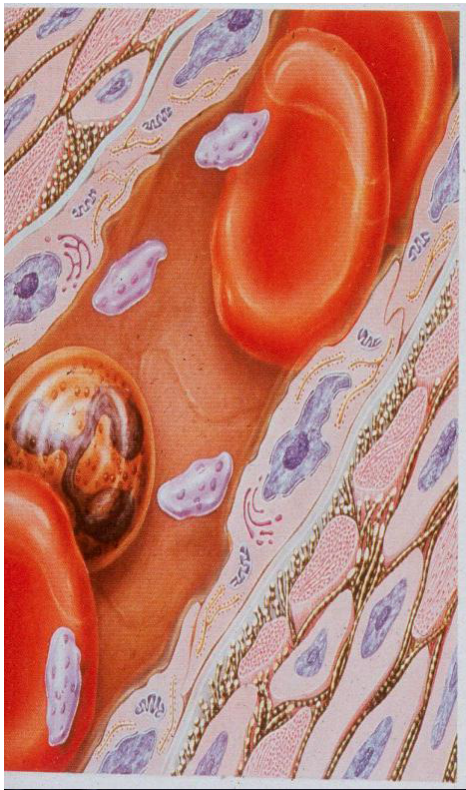
1-VASCULAR SPASM (Vascular Constriction)

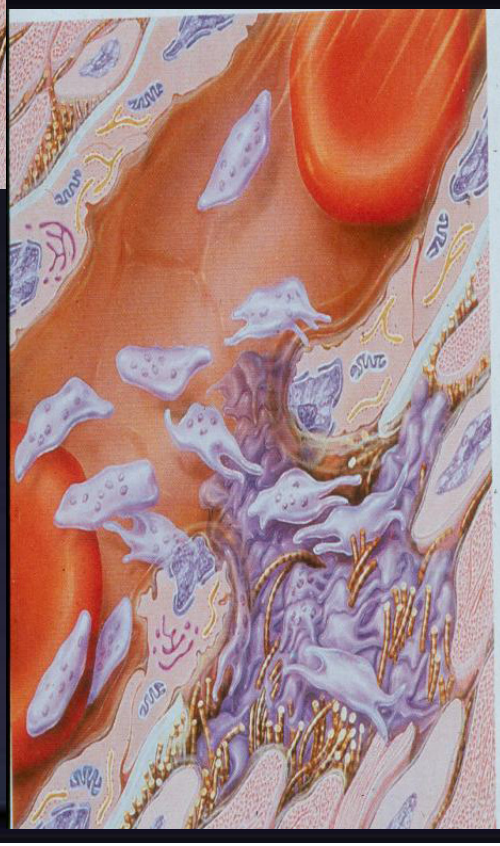
Immediately After injury there is localized Vasoconstriction.

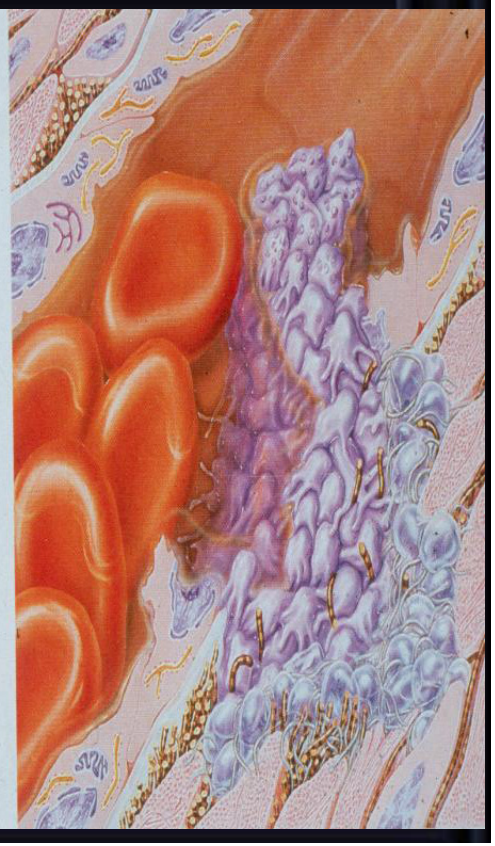
- **Causative Factors are three (3)**
  1. **Nervous reflexes**
  2. **Local myogenic spasm**
  3. **Local humoral factors**
- **For smaller vessels**
  - **Platelets → Thromboxane A_2 (Vasoconstrictor)**
- **Importance**
  - **Crushing injuries → Intense spasm → No lethal loss of blood**

TXA2 is inhibited by aspirin


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

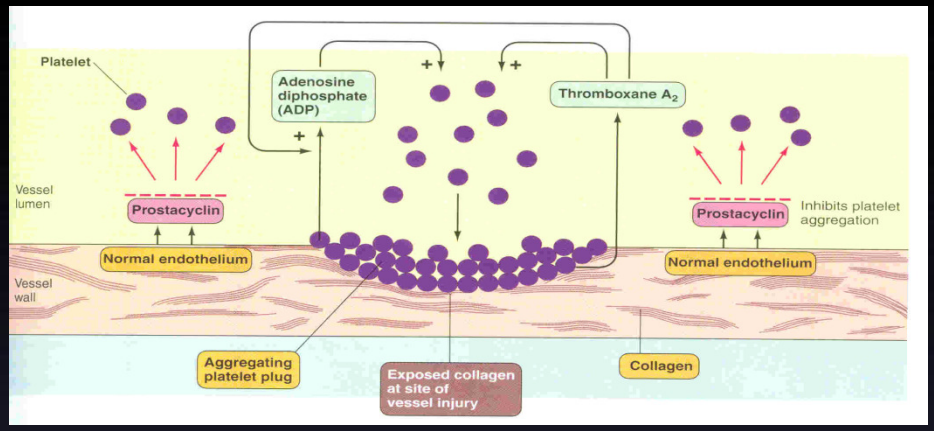




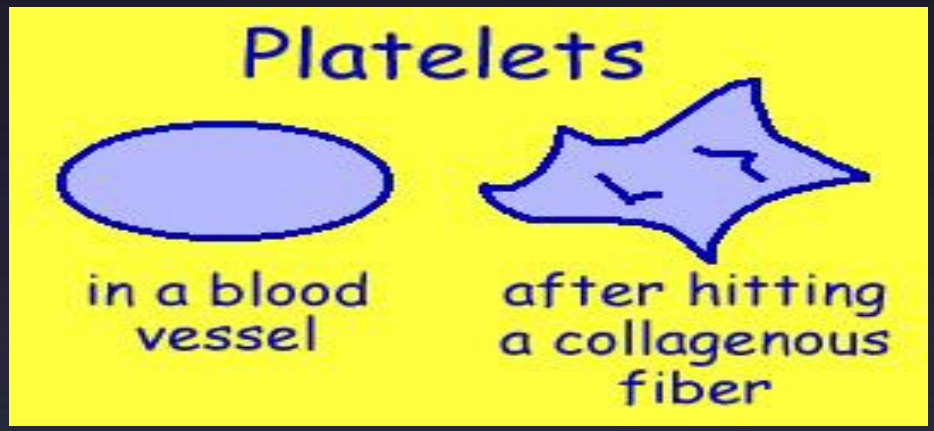


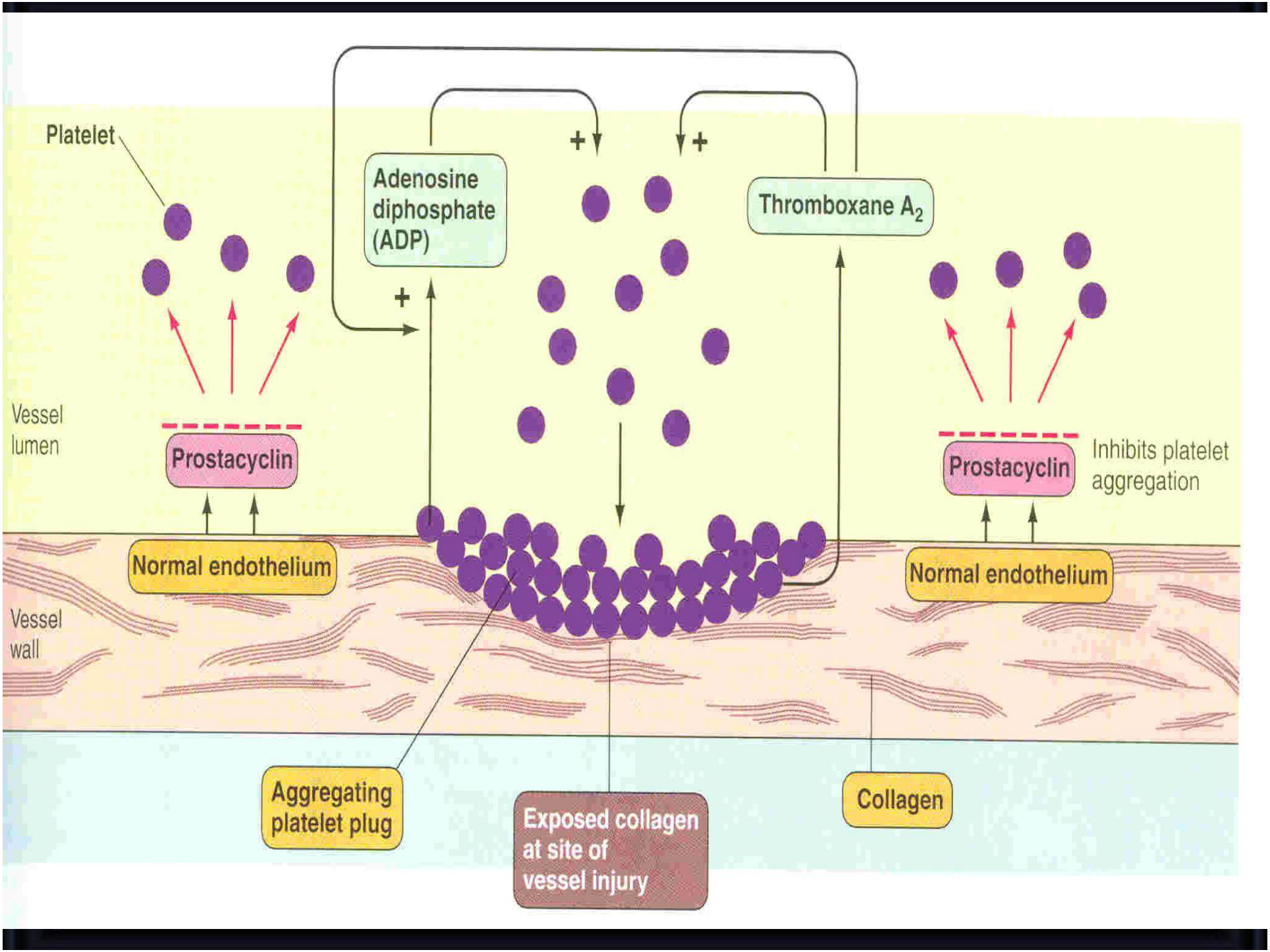
2-FORMATION OF PLATELET PLUG

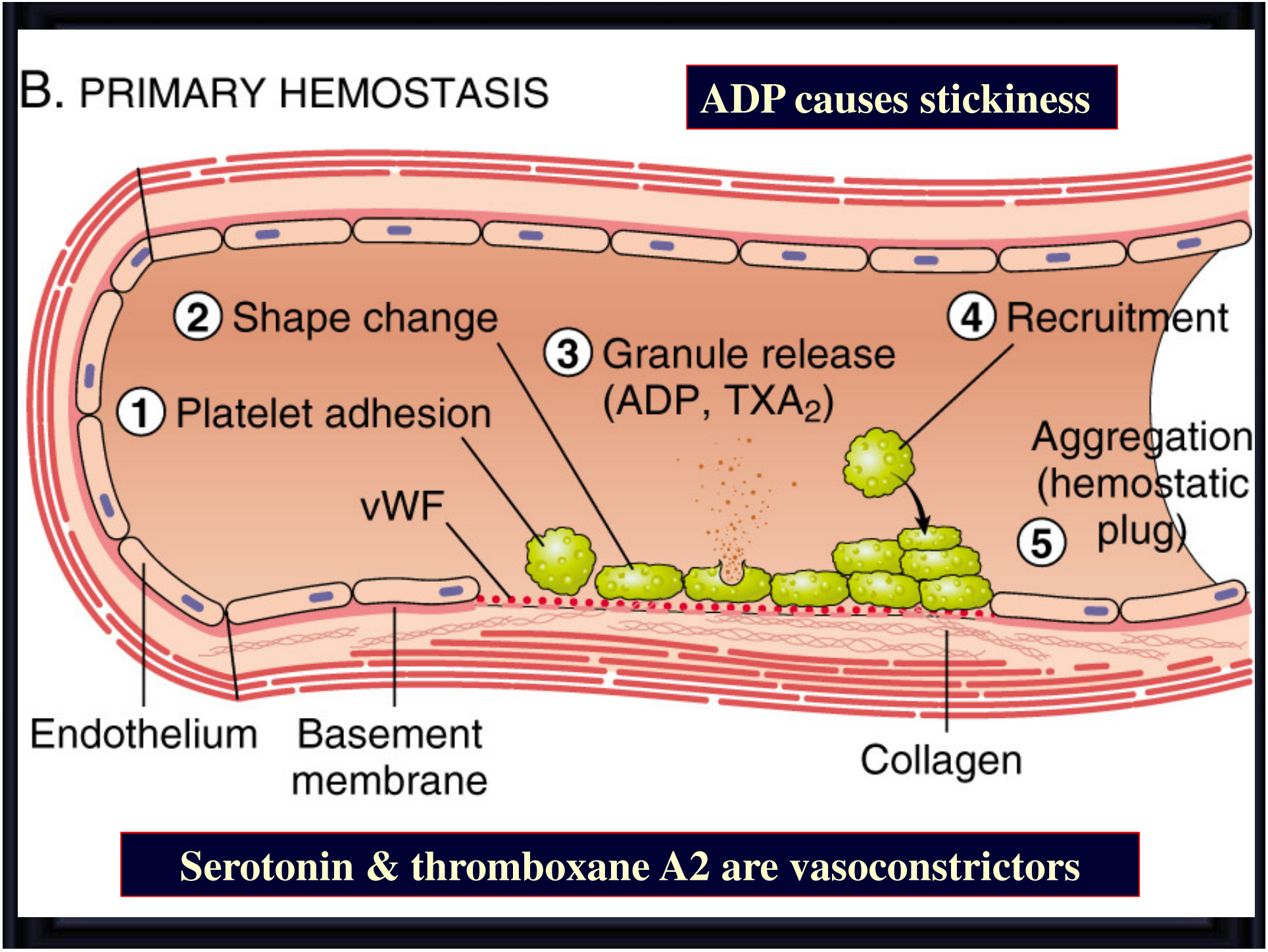
- **Importance of platelet plug → small vascular damage**



Intact endothelium secrete prostacyclin



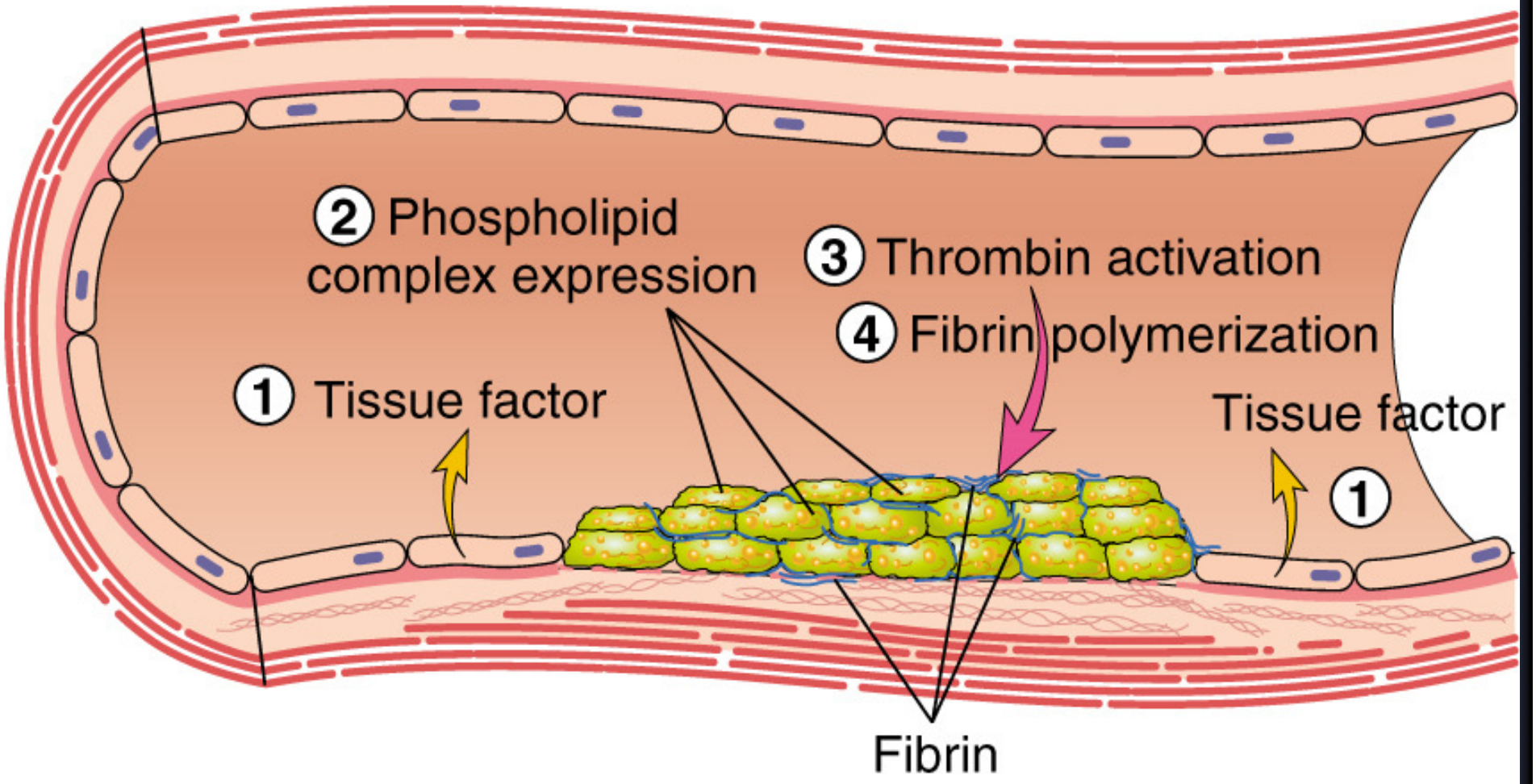

Platelet
Adenosine diphosphate (ADP)
Thromboxane A_2
+
+
+
Vessel lumen
Prostacyclin
Prostacyclin
Inhibits platelet aggregation
Normal endothelium
Normal endothelium
Vessel wall
Aggregating platelet plug
Exposed collagen at site of vessel injury
Collagen


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

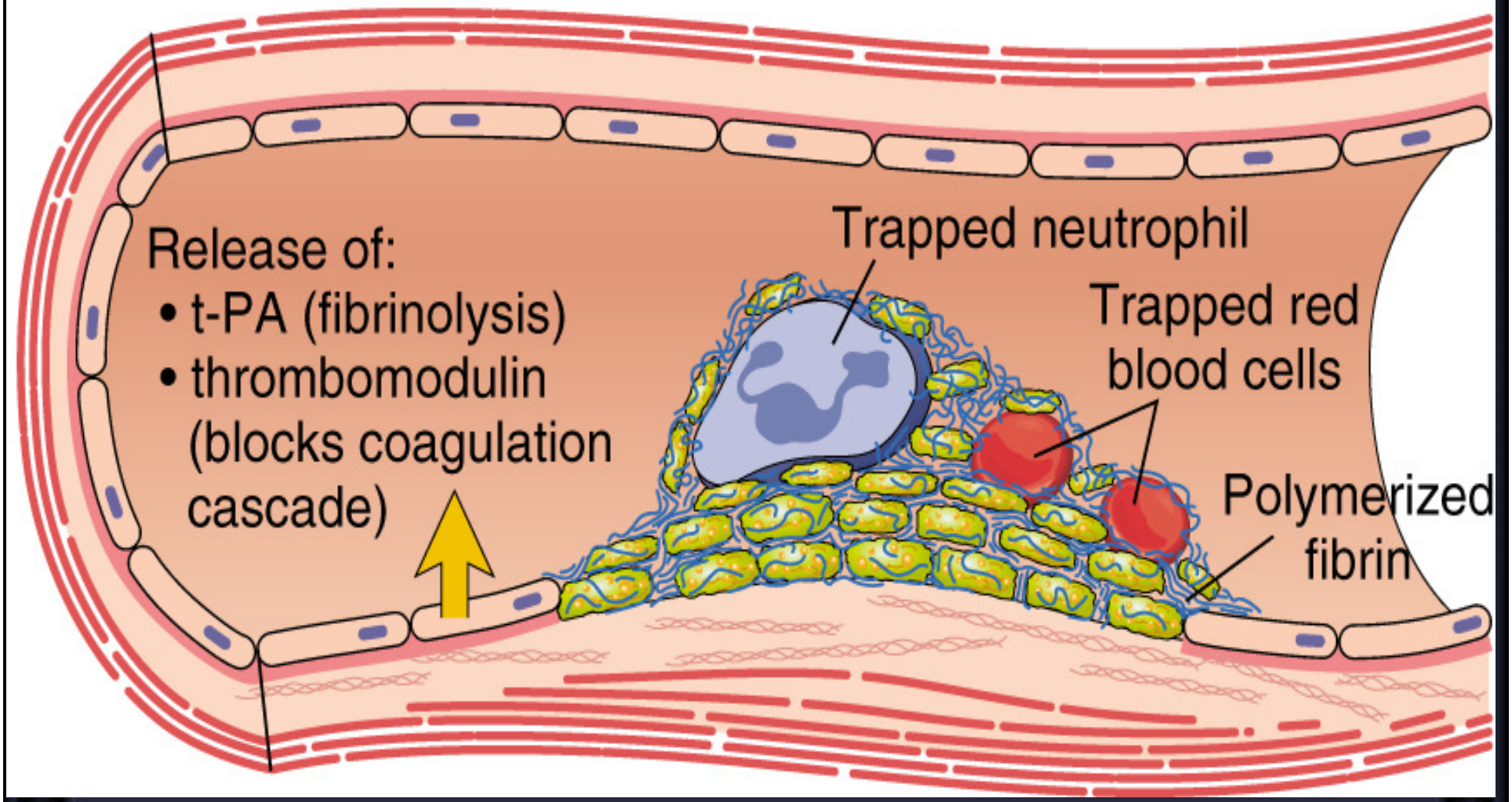
3-BLOOD COAGULATION
Formation of Clot

- **Blood clotting is the transformation of blood from a liquid into a solid gel form**
- **Pathways**
  - **Intrinsic**
  - **Extrinsic**
- **Initiated by: Activator substances from traumatized vascular wall, platelets & blood proteins**
- **Begins to develop in**
  - **15-20 sec → Minor trauma**
  - **1-2 min. → Severe trauma**

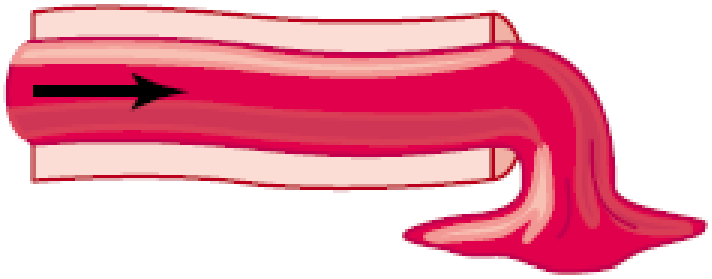
C. SECONDARY HEMOSTASIS



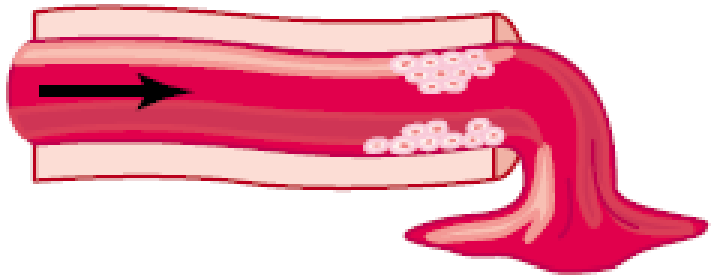
D. THROMBUS AND ANTITHROMBOTIC EVENTS



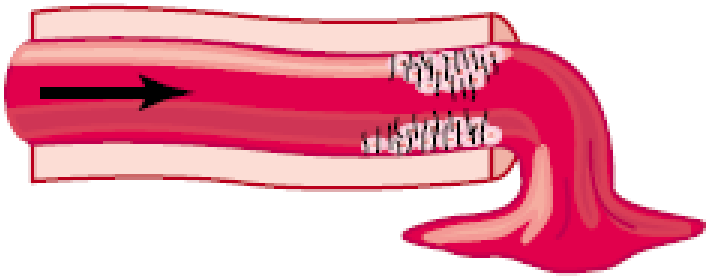
Physical Events Of Clotting Process



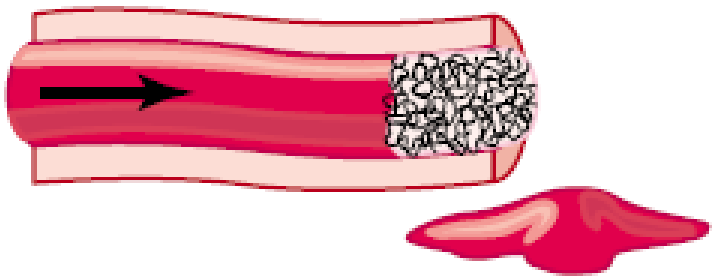
1. Severed vessel



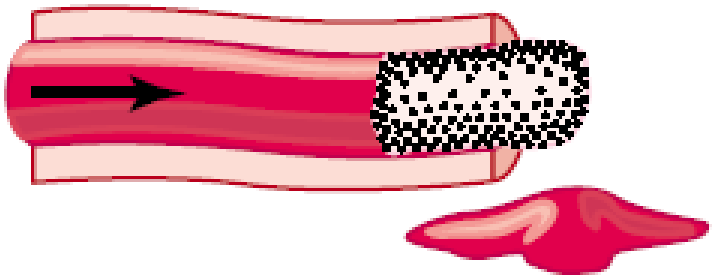
2. Platelets agglutinate



3. Fibrin appears



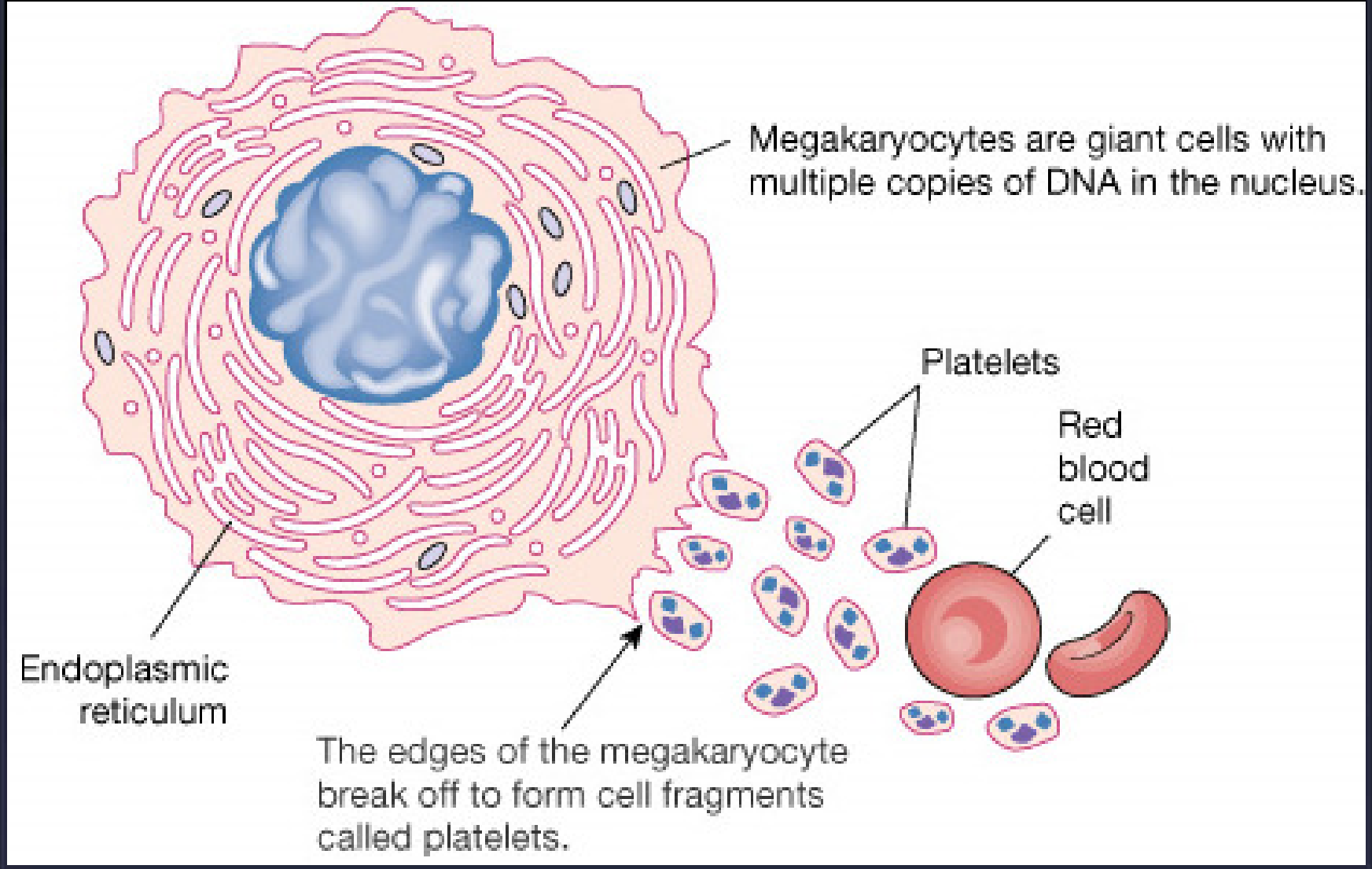
4. Fibrin clot forms



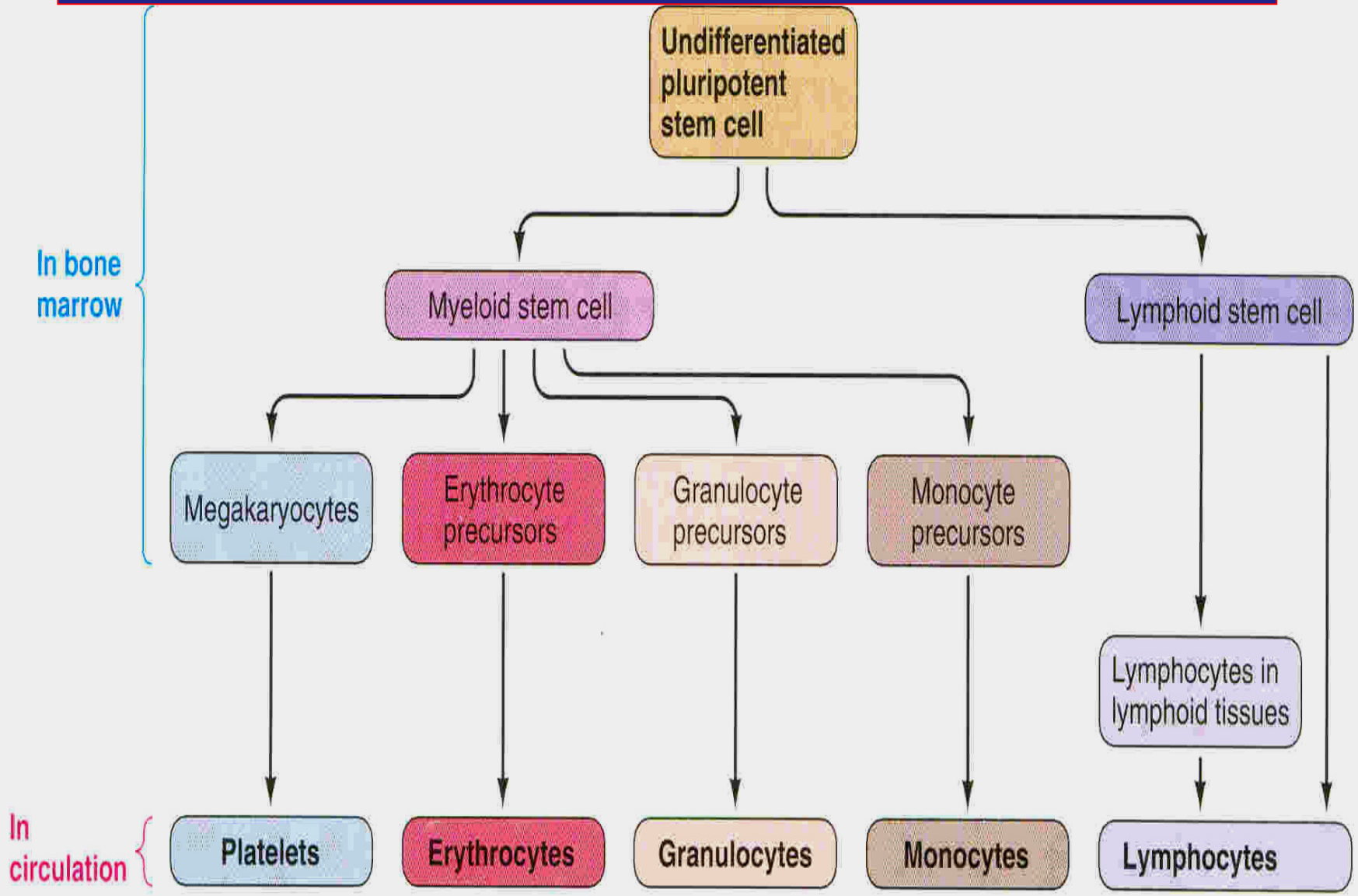
5. Clot retraction occurs

PLATELETS

Formed by fragmentation from megakaryoctyes



SITE OF FORMATION
Bone-marrow



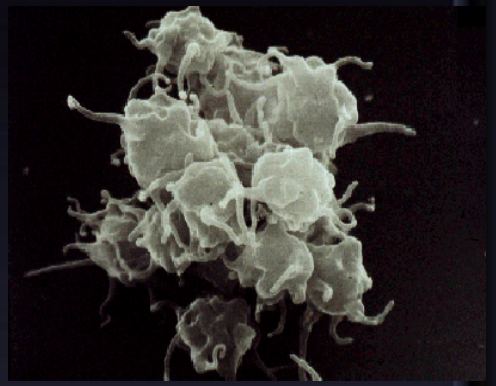
PLATELETS (Characteristics)

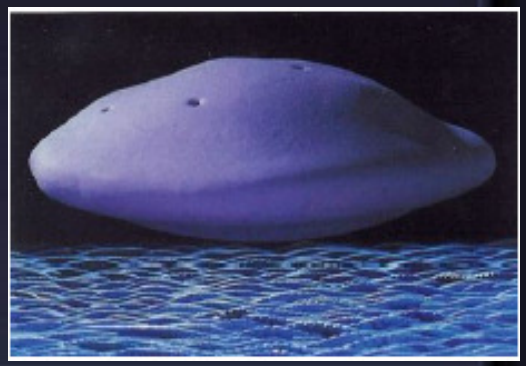
SHAPE: MINUTE ROUND OR OVAL DISCS
SIZE: 1-4 um IN DIAMETER
HALF LIFE: 8-12 DAYS
COUNT: 150,000 – 300,000/ microlitrer
LOCATION: 80% in blood & 20% in spleen

- **Contractile, adhesive, cell fragments.**
- **Store coagulation factors & enzymes**
- **Surface Binding sites for fibrinogen**
- **Surface Glycoprotein Antigens-HPA1.**

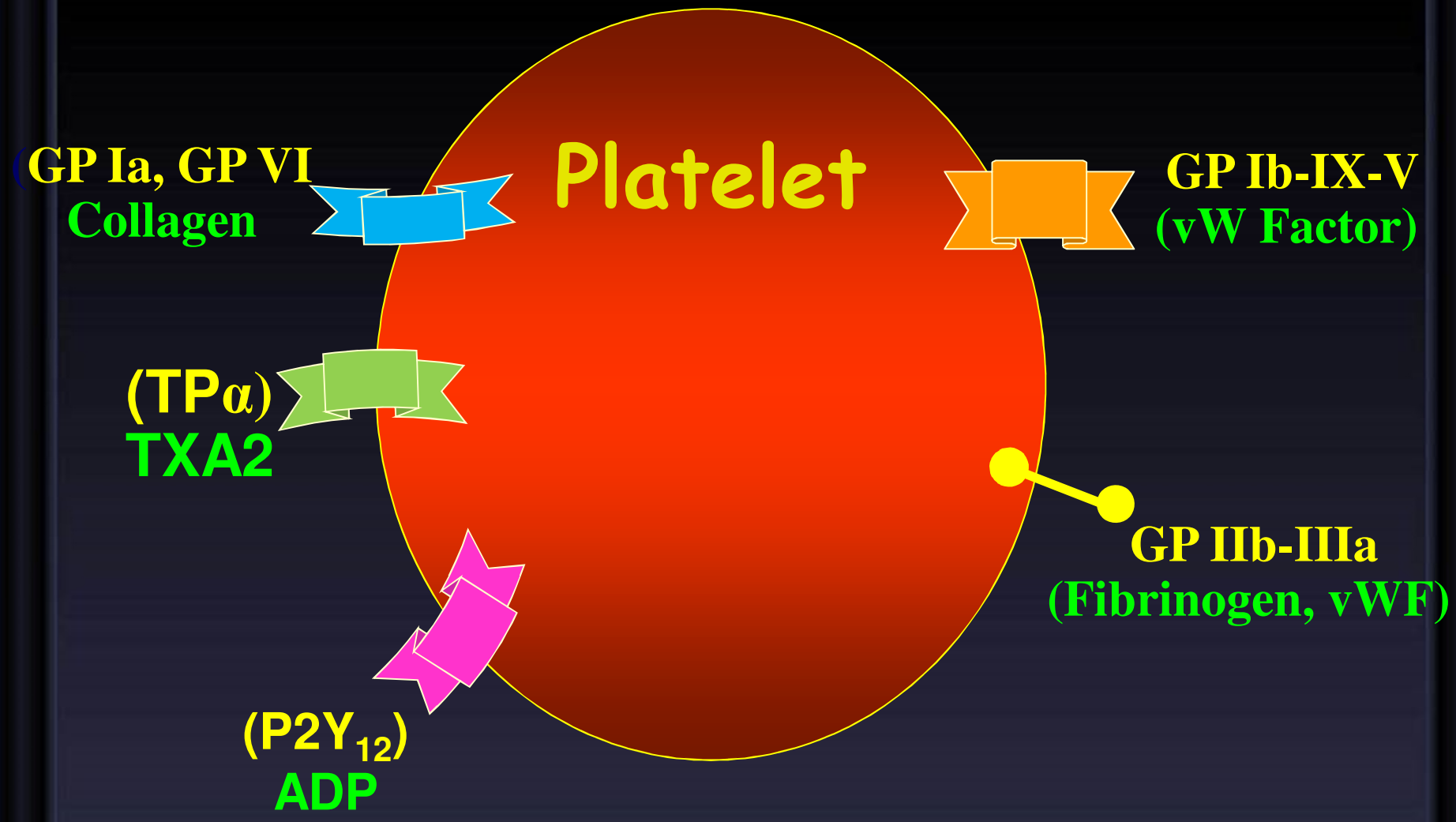
FUNCTIONAL CHARACTERISTICS

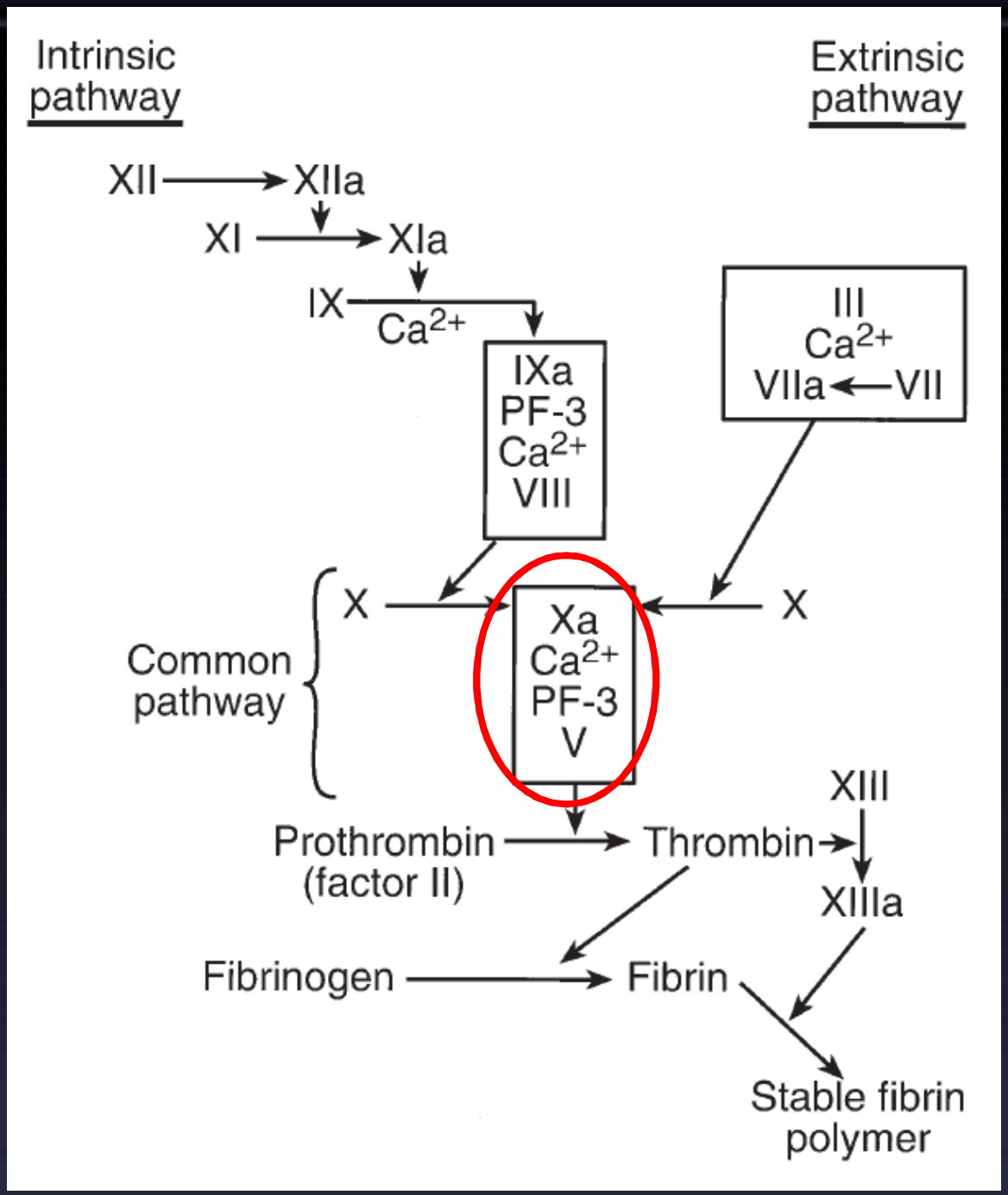
- Actin And Myosin Molecules
- Thrombesthenin
- Endoplasmic Reticulum And Golgi Apparatus
- Mitochondria
- Enzyme Systems For Synthesis Of Prostaglandins
- Fibrin Stabilizing Factor
- Growth Factor





Platelet Receptors




Intrinsic pathway
Extrinsic pathway
XII
XIIa
XI
XIa
IX
Ca2+
IXa
PF-3
Ca2+
VIII
III
Ca2+
VIIa
VII
X
X
Xa
Ca2+
PF-3
V
Common pathway
Prothrombin (factor II)
Thrombin
XIII
XIIIa
Fibrinogen
Fibrin
Stable fibrin polymer

MECHANISM OF CLOTTING

1. **Formation of Prothrombin activator complex**
2. **Conversion of prothrombin into thrombin**
3. **Conversion of fibrinogen into fibrin**

COAGULATION CASCADE

1-*Formation Of Prothrombin Activator Complex is by:*

- **2 Ways**
  - **By Extrinsic pathway → trauma to vascular wall and surrounding tissues**
  - **By Intrinsic pathway → trauma to the blood → Is the rate - limiting factor**

2-CONVERISON OF PRTHROMBIN TO THROMBIN

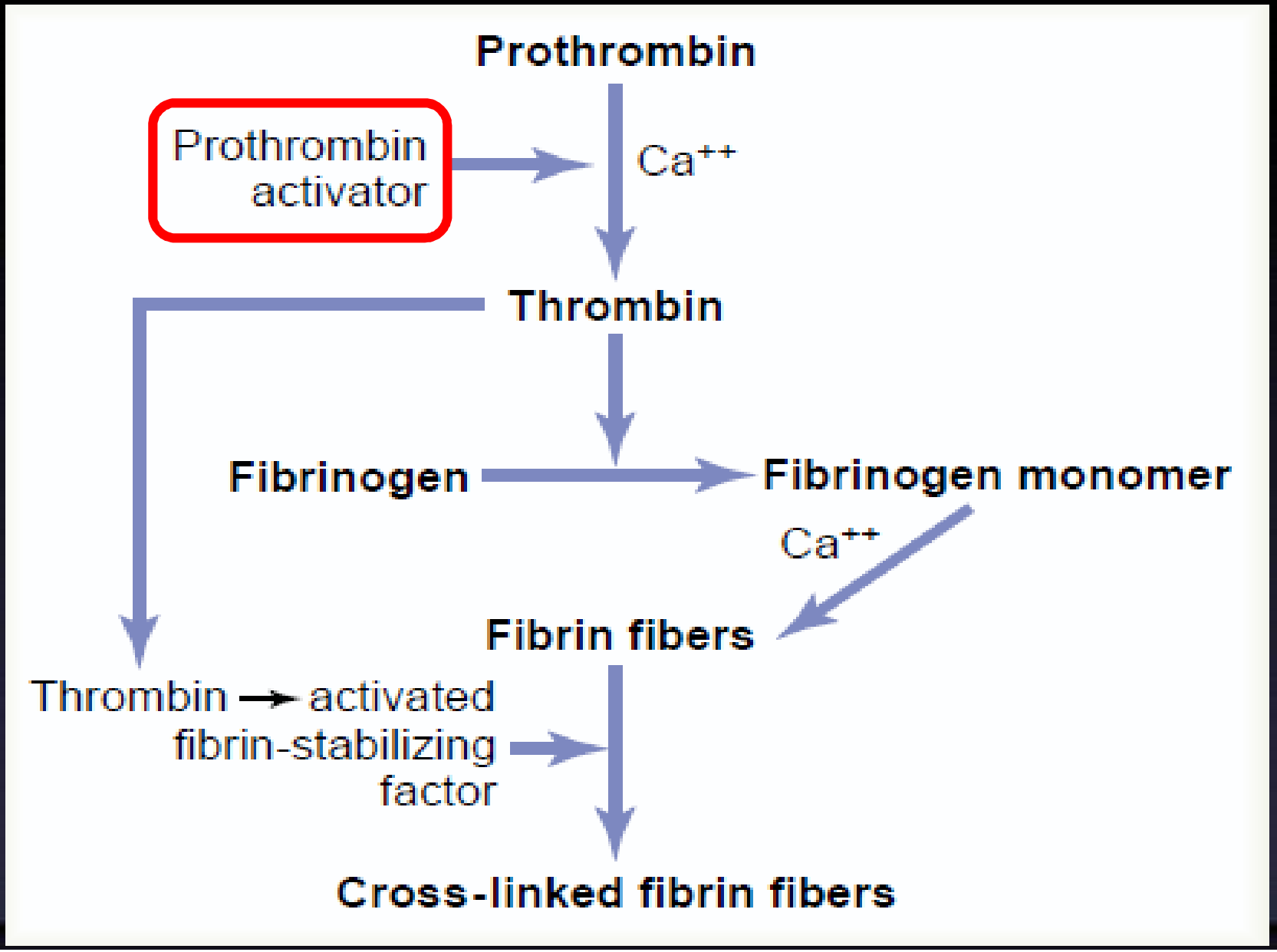
By Prothrombin Activator Complex

- **Prothrombin**
  - Plasma protein (Alpha$_2$ globulin)
  - Mol. Wt. - 68,700
  - Plasma conc. - 15 mg/dl
  - Unstable protein
  - Synthesized by liver
  - Vitamin-K is required for synthesis

3-CONVERSION OF FIBRINOGEN TO FIBRIN
Formation Of Clot

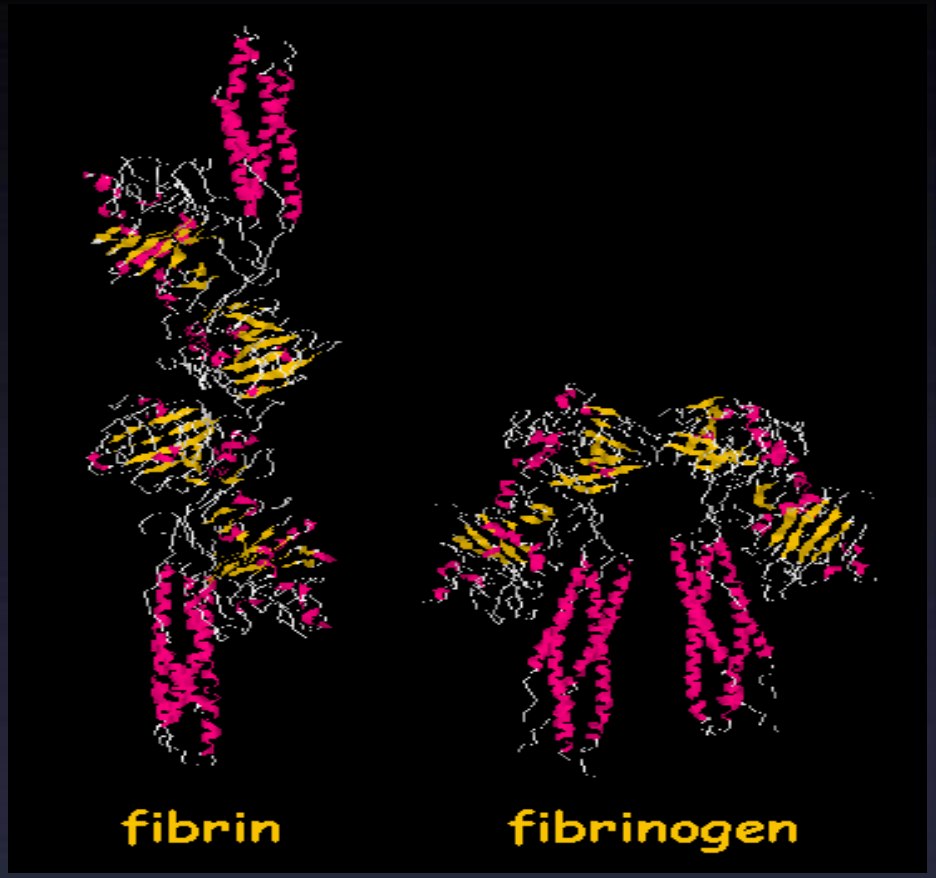
- **Fibrinogen**
  - **Mol. Wt. – 340,000**
  - **Plasma conc. – 100 – 700 mg/dl**
  - **Synthesized in liver**

ACTION OF THROMBIN ON FIBRONOGEN TO FORM FIBRIN



BLOOD CLOT

- A meshwork of fibrin fibres running in all directions entrapping blood cells, platelets and plasma



Clotting Factors Guyton

Table 36–1

Clotting Factors in Blood and Their Synonyms

Clotting Factor	Synonyms
Fibrinogen	Factor I
Prothrombin	Factor II
Tissue factor	Factor III; tissue thromboplastin
Calcium	Factor IV
Factor V	Proaccelerin; labile factor; Ac-globulin (Ac-G)
Factor VII	Serum prothrombin conversion accelerator (SPCA); proconvertin; stable factor
Factor VIII	Antihemophilic factor (AHF); antihemophilic globulin (AHG); antihemophilic factor A
Factor IX	Plasma thromboplastin component (PTC); Christmas factor; antihemophilic factor B
Factor X	Stuart factor; Stuart-Prower factor
Factor XI	Plasma thromboplastin antecedent (PTA); antihemophilic factor C
Factor XII	Hageman factor
Factor XIII	Fibrin-stabilizing factor
Prekallikrein	Fletcher factor
High-molecular-weight kininogen	Fitzgerald factor; HMWK (high-molecular-weight) kininogen
Platelets	

Clotting Factors Ganong

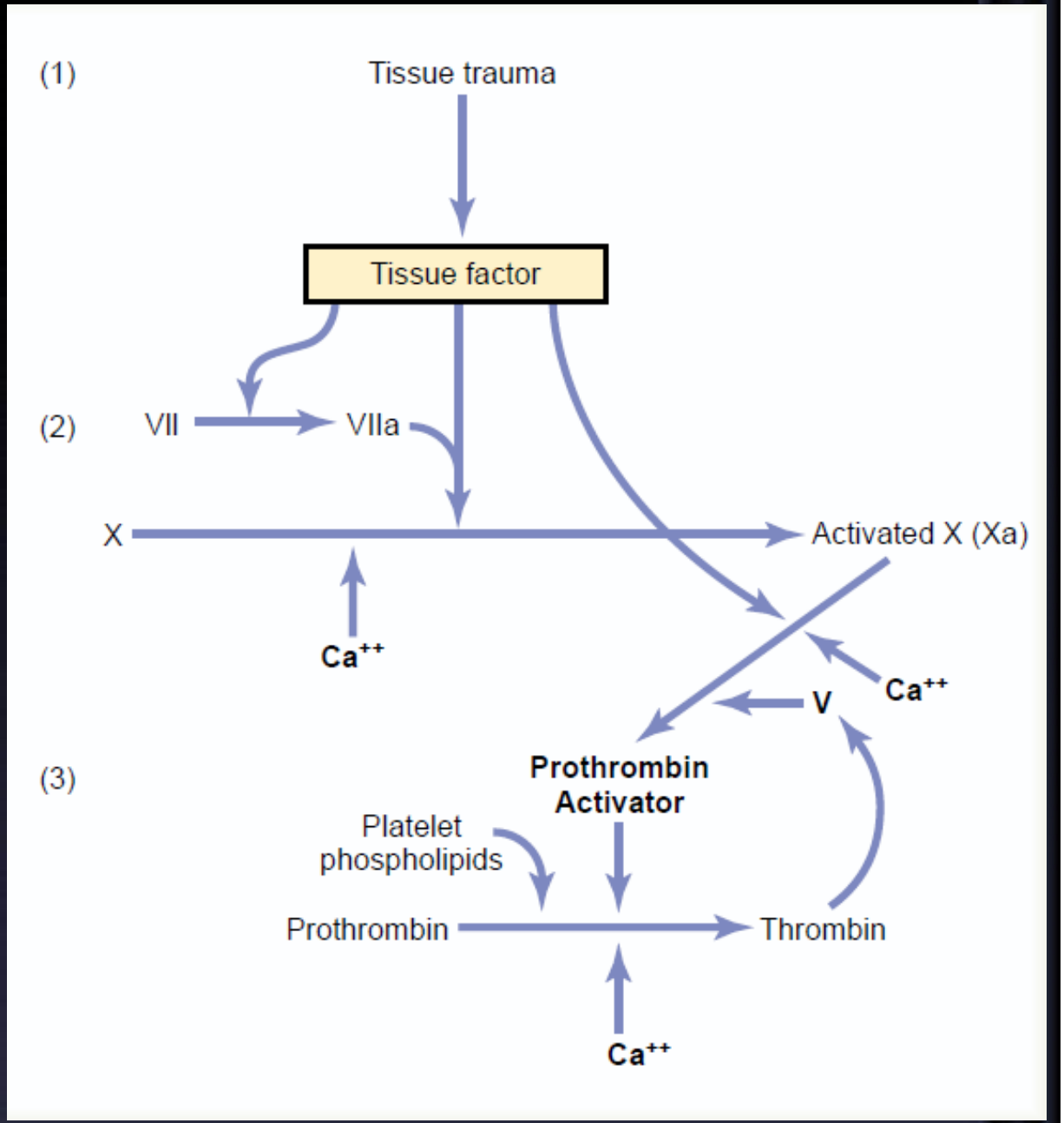
TABLE 31–5 System for naming blood-clotting factors.

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.

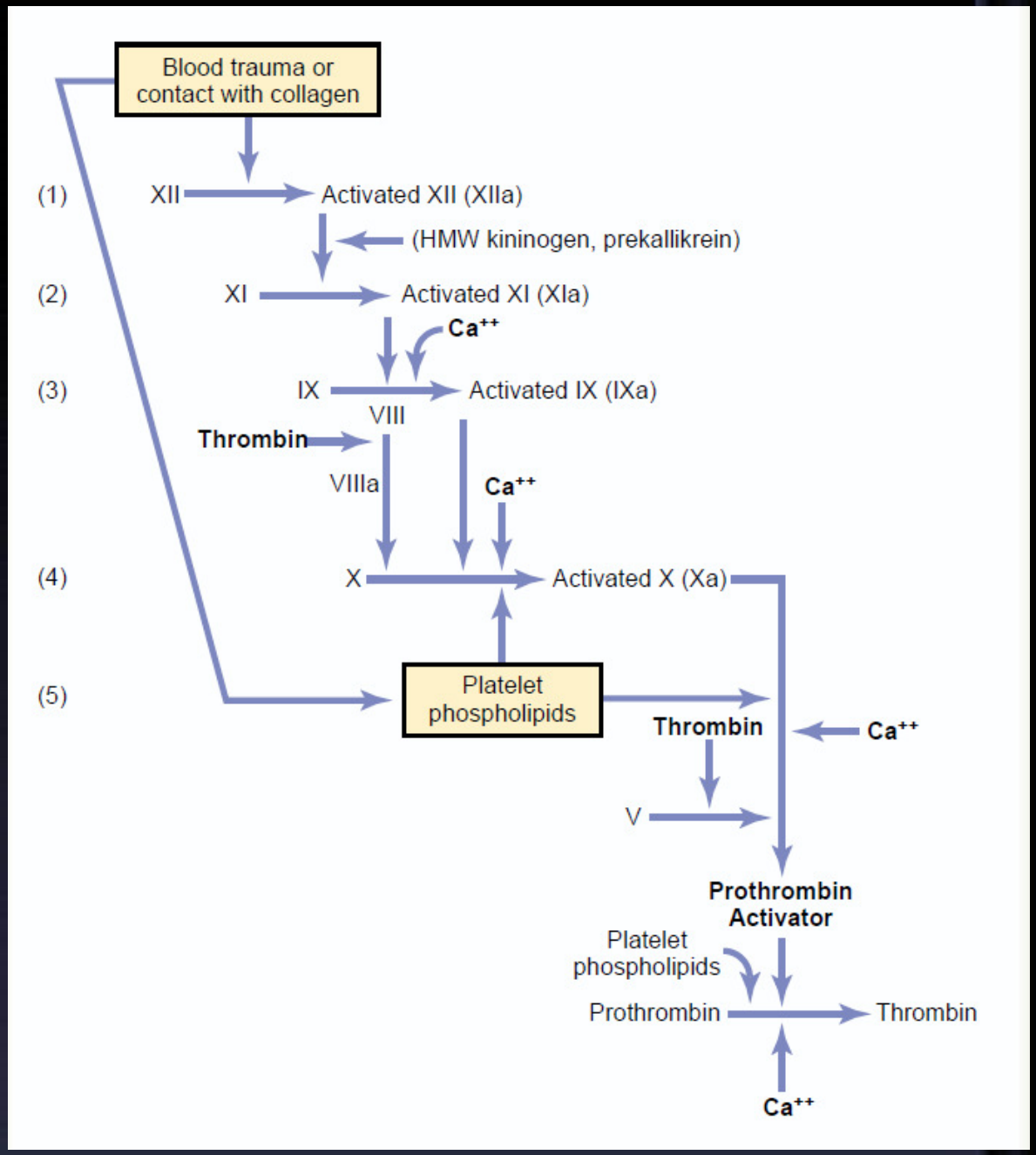
EXTRINSIC MECHNANISM FOR INITIATING CLOTTING

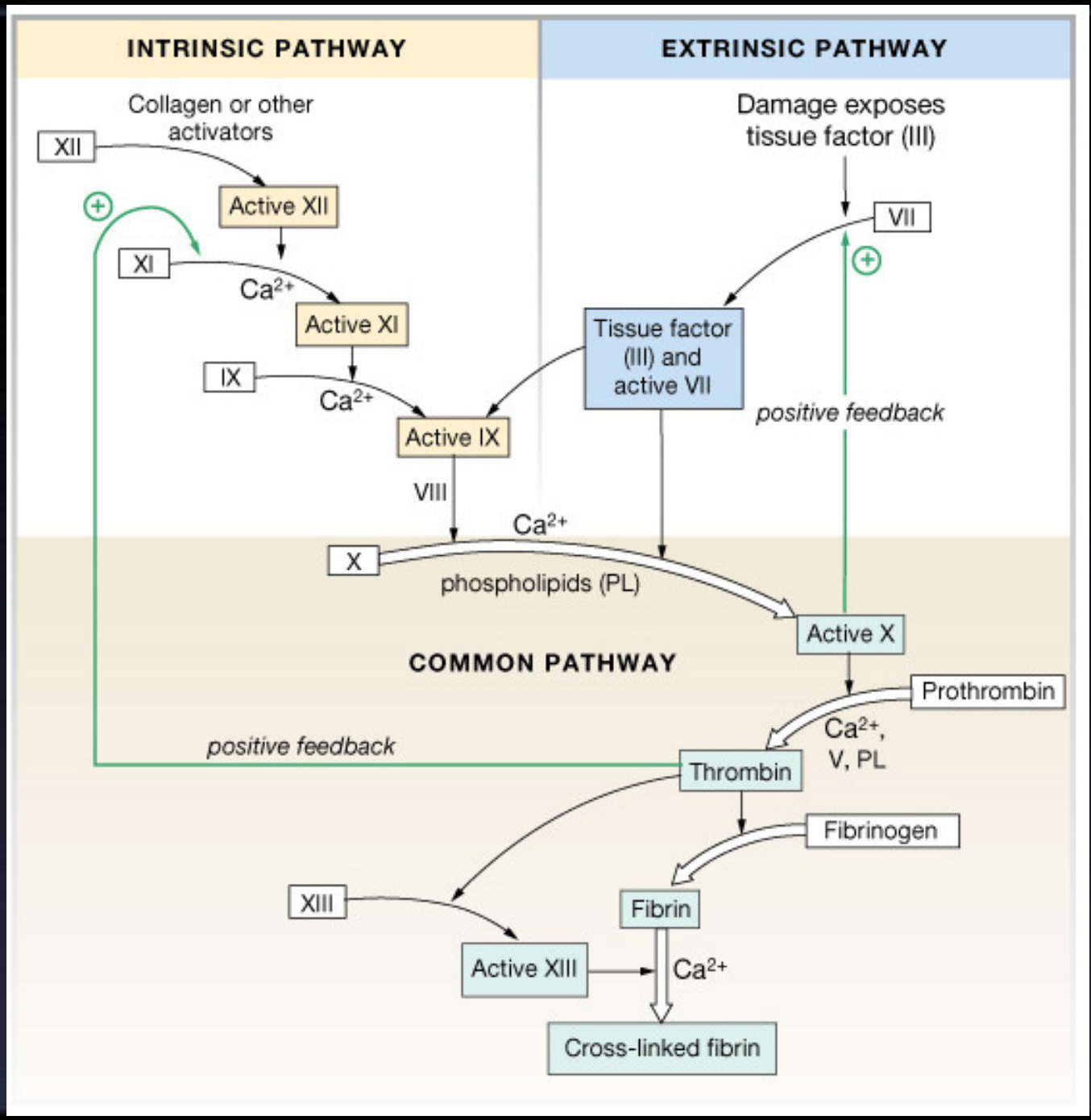
TF or tissue thromboplastin; includes phospholipids from the membranes of the tissue plus a lipoprotein complex that functions mainly as a proteolytic enzyme.



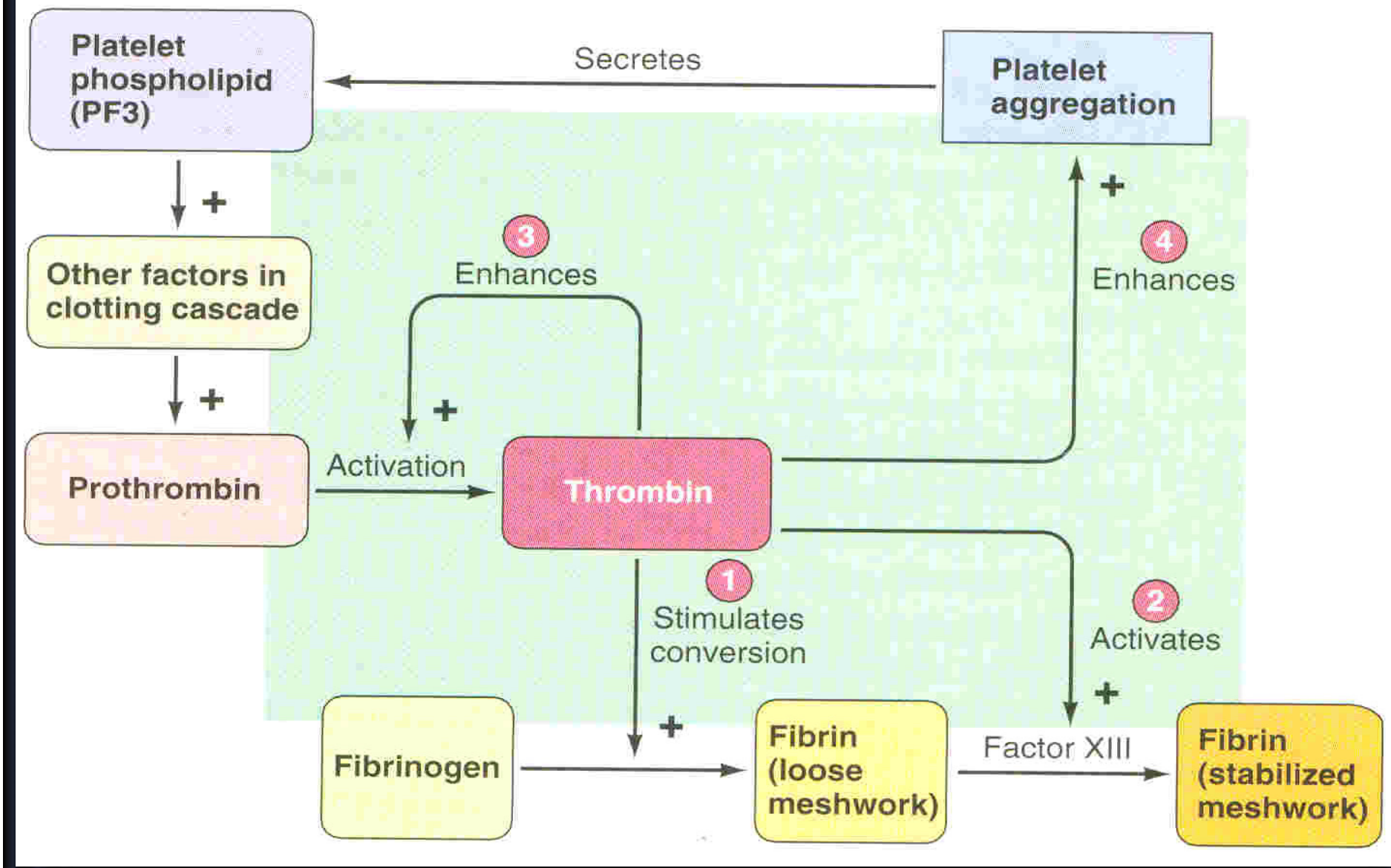
INTRINSIC MECHNANISM FOR INITIATING CLOTTING

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




INTRINSIC PATHWAY
EXTRINSIC PATHWAY
Collagen or other activators
XII
Active XII
XI
Ca2+
Active XI
IX
Ca2+
Active IX
VIII
Damage exposes tissue factor (III)
VII
Tissue factor (III) and active VII
positive feedback
Ca2+
X
phospholipids (PL)
Active X
COMMON PATHWAY
Prothrombin
Ca2+, V, PL
positive feedback
Thrombin
Fibrinogen
XIII
Fibrin
Active XIII
Ca2+
Cross-linked fibrin

ROLES OF THROMBIN IN HEMOSTASIS



CLOT RETRACTION

- When clot 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
- Vicious circle of clot formation

ROLE OF CALCIUM IONS IN CLOTTING

- **No Ca^{++} → No Clotting**

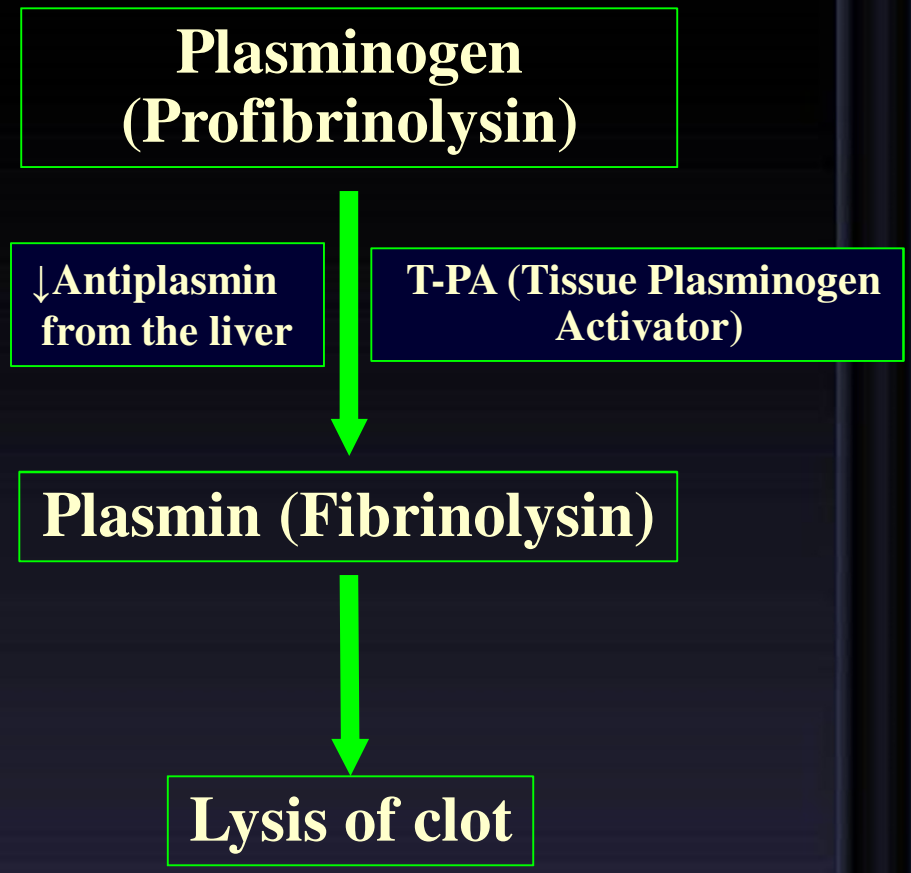
Blood samples are prevented from clotting by:

- **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** →

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

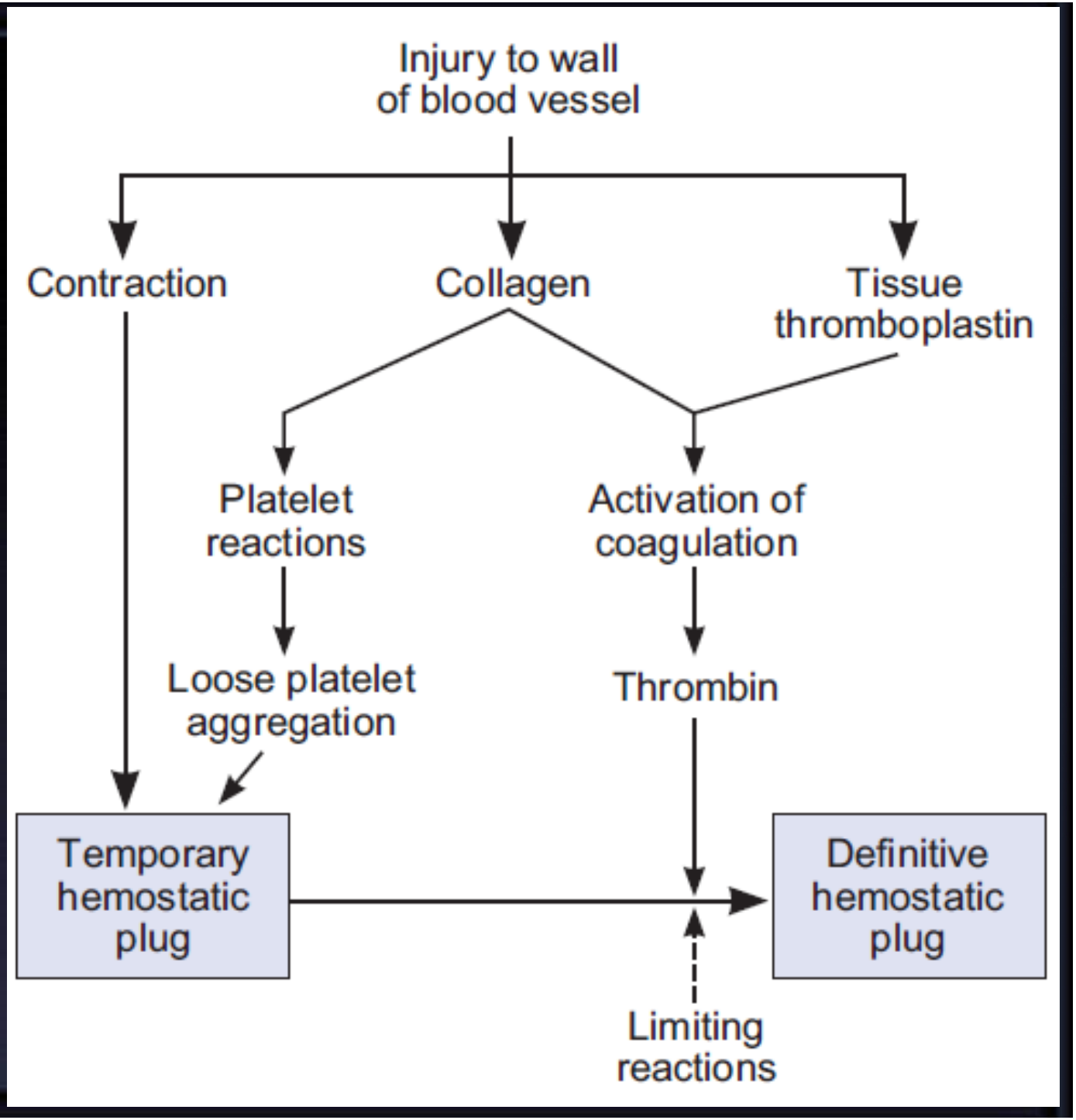
NATURAL INTRAVASCULAR ANTICOAGULANTS

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

BLEEDING & CLOTTING DISORDERS

A. Liver diseases & Vitamin-K deficiency
B. Hemophilia
C. Thrombocytopenia

Summary of reactions involved in hemostasis.



BLEEDING DISORDERS

A. **Liver diseases & Vitamin-K deficiency**

- **e.g. Hepatitis, Cirrhosis**
  - **Decreased formation of clotting factors**
  - **Icnreased clotting time**
- **Vitamin K dependent factors**
  - **Prothrombin, Factor VII, IX, X**

BLEEDING DISORDERS

A. **Vitamin-K**

- Fat soluble vitamin
- Required by liver for formation 4 clotting factors
- Sources
  - Diet
  - Sythesized in the intestinal tract by bacteria
- Deficiency
  - Malabsorption syndromes
  - Biliary obstruction
  - Broad spectrum antibiotics
  - Dietary def (in Neonates)
  - Rx.: Treat the underlying cause Vit K injections

THROMBOCYTOPENIA

- Platelet count upto 50,000 ul
- Less than 10,000 ------ Fatal
- ETIOLOGY
- Decreased production
  - Aplastic anemia
  - Leukemia
  - Drugs
  - Infections (HIV, Measles)

THROMBOCYTOPENIA (cont.)

- **Increased destruction**
  - **ITP**
  - **Drugs**
  - **Infections**
- **Clinical Features**
  - **Easy brusability**
  - **Epistaxis**
  - **Gum bleeding**
  - **Hemorrhage after minor trauma**
  - **Petechiae/Ecchumosis**

THROMBOCYTOPENIA (cont.)

- Diagnosis
  - PLT decreased
  - B.T increased
- Rx
  - Rx of the underlying cause
  - PLT concentrates
  - Fresh whole blood transfusion
  - Splenectomy

HEMOPHILIA

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

HEMOPHILIA

- Genetic disorders
- Transmitted by female chromosome as recessive trait
- Occurs exclusively in male Females are carriers
- Types
  - Hemophilia A
  - Hemophilia B

HEMOPHILIA

- **Clinical Features**
  - **Easy bruising, massive bleeding after trauma or operation, hemorrhages in joints**
  - **Factor VIII**
    - **Small Comp. → Hemophilia A**
    - **Large Comp. → Von-Willebrand's disease**
  - **Rx**
    - **Injection of factor VIII (Hemophilia A)**
    - **Injection of factor IX (Hemophilia B)**

FACTORS AFFECTING BLOOD PLATELET COUNT

- AGE : ↓ in newborn
- Menstrual cycle:
  - ↓ prior to menstruation
  - ↑ After menstruation
- Pregnancy: ↓
- Injury: ↑
- Adrenaline: ↑
- Hypoxia: ↑
- Smoking: ↓
- Nutritional deficiencies: ↓ eg; vitamin b12, folic acid and iron