Thrombosis

Thrombosis

- It is a process of thrombus formation
- A thrombus is an **adherent intravascular coagulation** (blood clot or solid mass of blood constituents) which develops **in intact circulatory system** (artery/ vein or heart chambers).
- Often causes significant interruption to blood flow.
- It is composed of varying proportions of coagulation factors, RBCs and platelets.

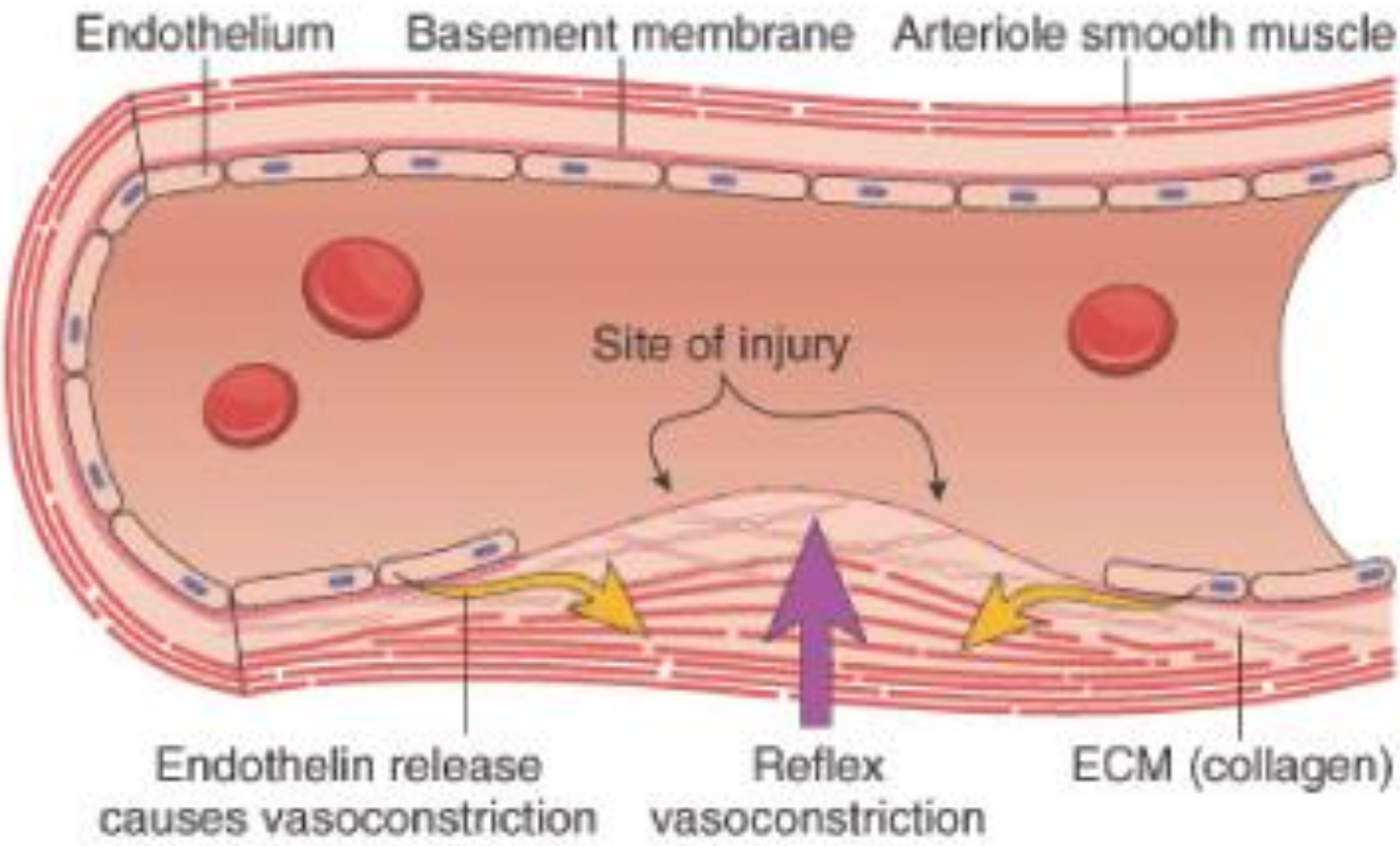
Normal hemostasis

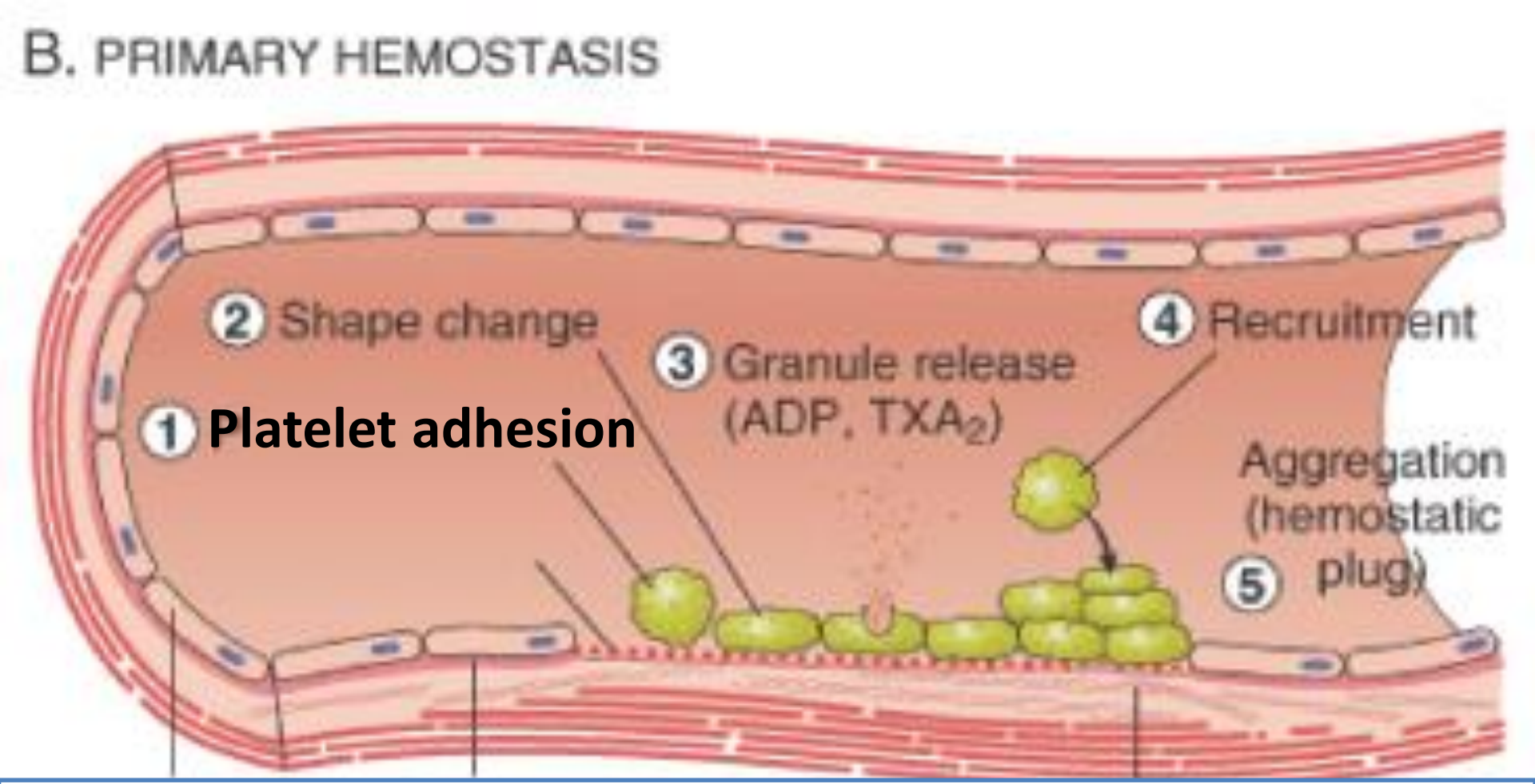
- Maintain blood in a fluid state in normal vessels
- Localized hemostatic plug (blood clot) formation at the site of vascular injury

3 components involved:

- Vascular wall (endothelium)
- Platelets
- Coagulation cascade

A. VASOCONSTRICTION



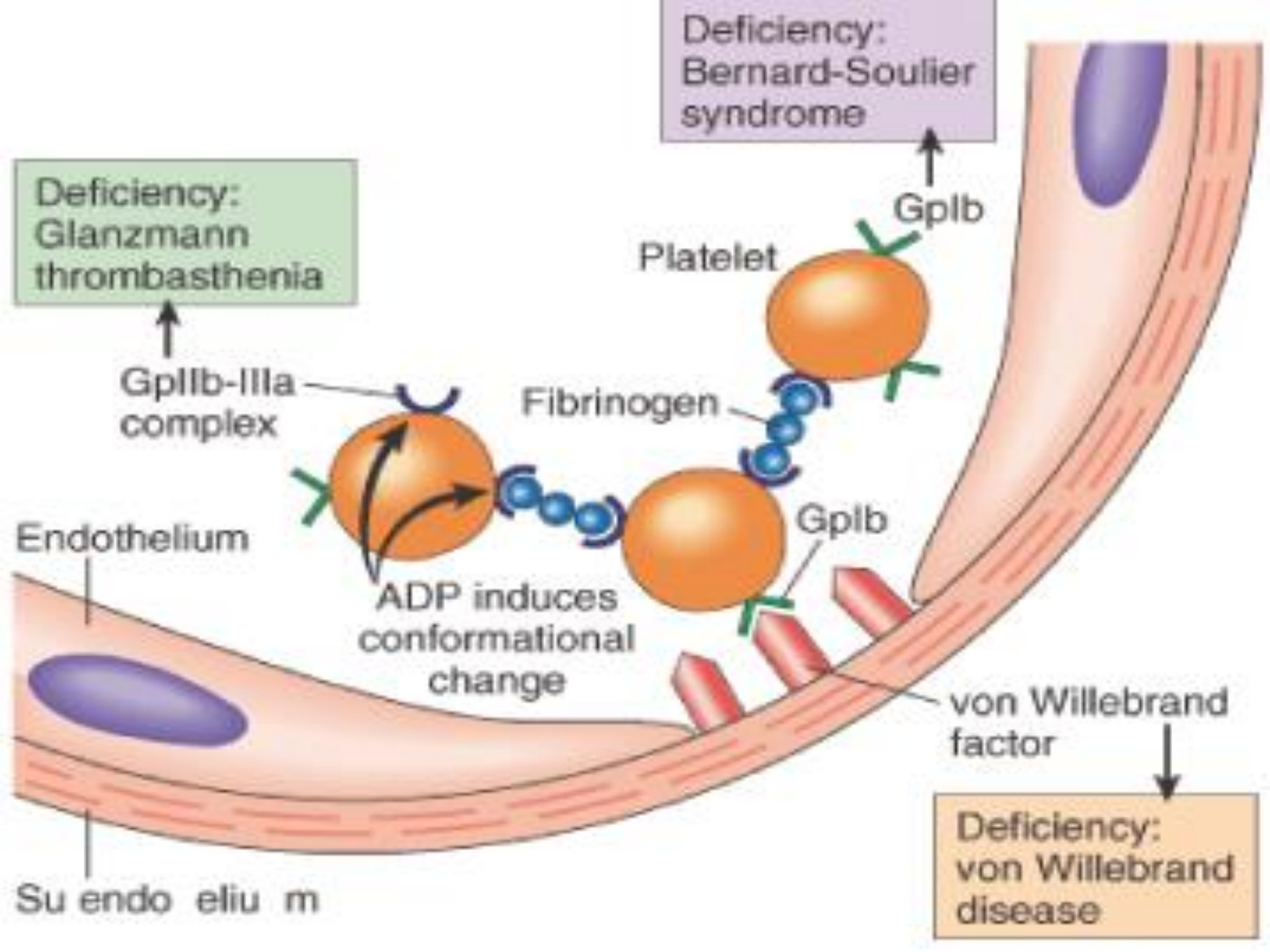


Platelets :

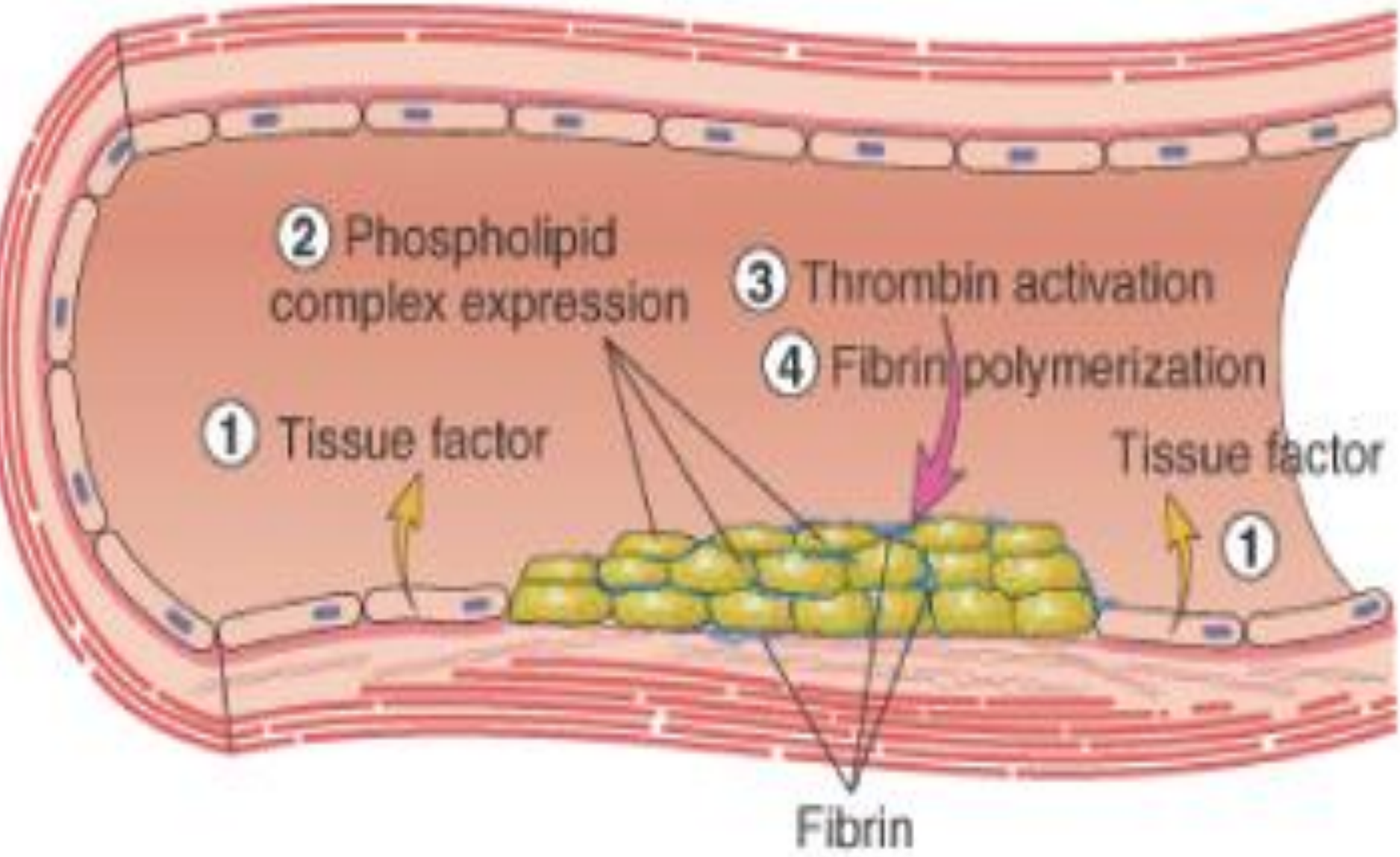
a. **A**dhesion

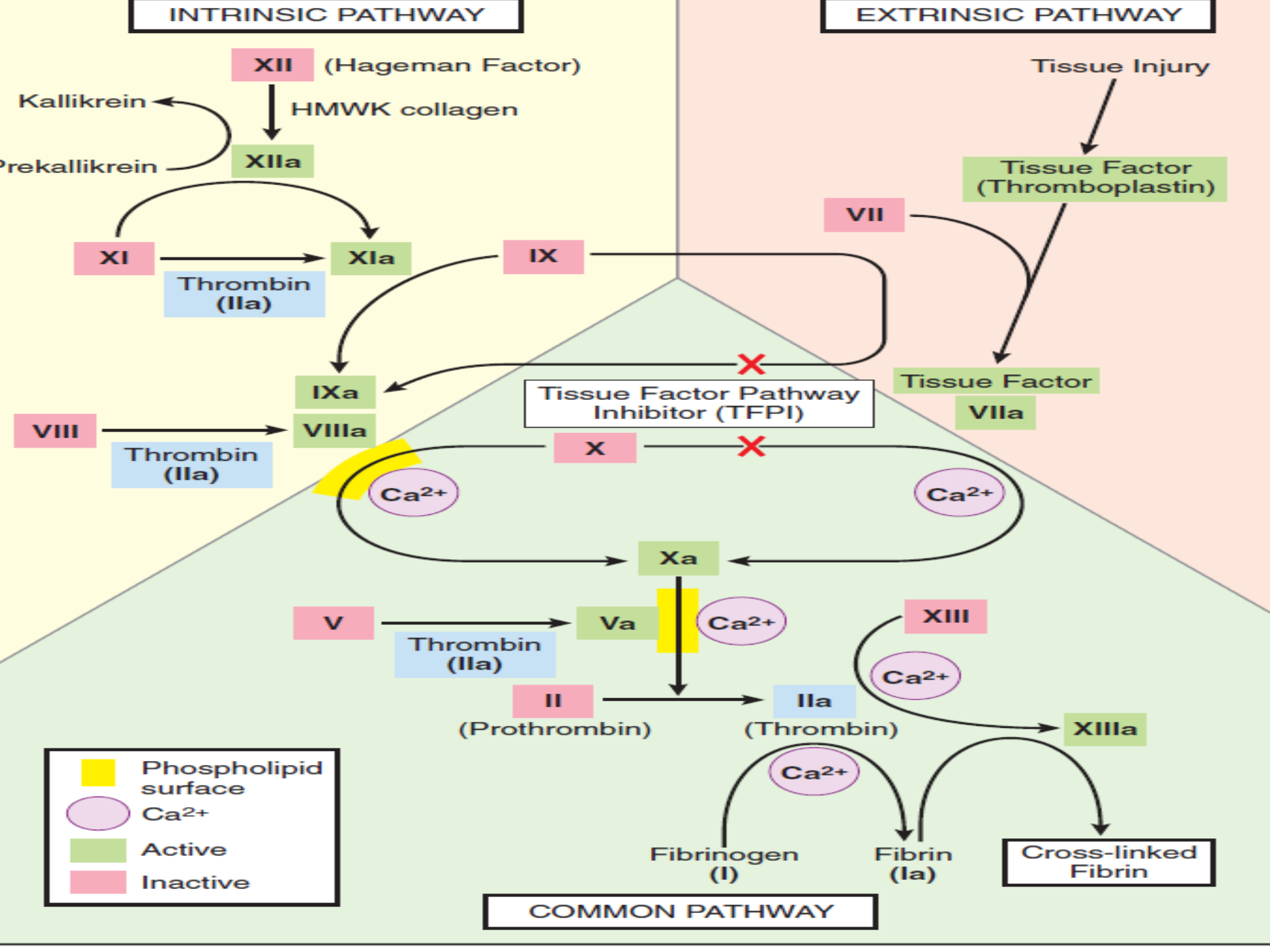
b. **A**ctivation- shape change and granule release

c. **A**ggregation

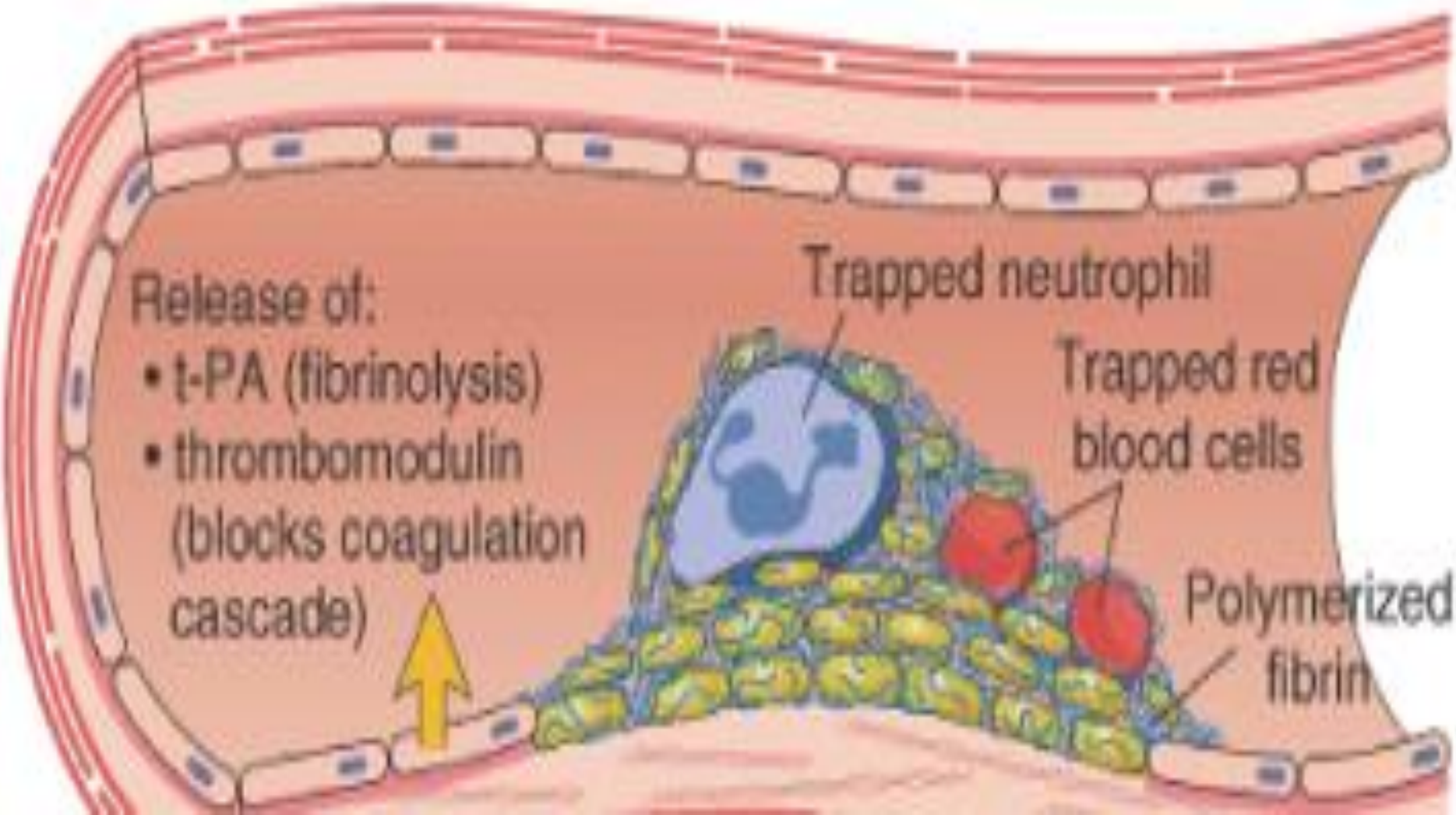

Deficiency:
Bernard-Soulier
syndrome
Deficiency:
Glanzmann
thrombasthenia
GpIb
Platelet
GpIIb-IIIa
complex
Fibrinogen
GpIb
Endothelium
ADP induces
conformational
change
von Willebrand
factor
Su endo eliu m
Deficiency:
von Willebrand
disease

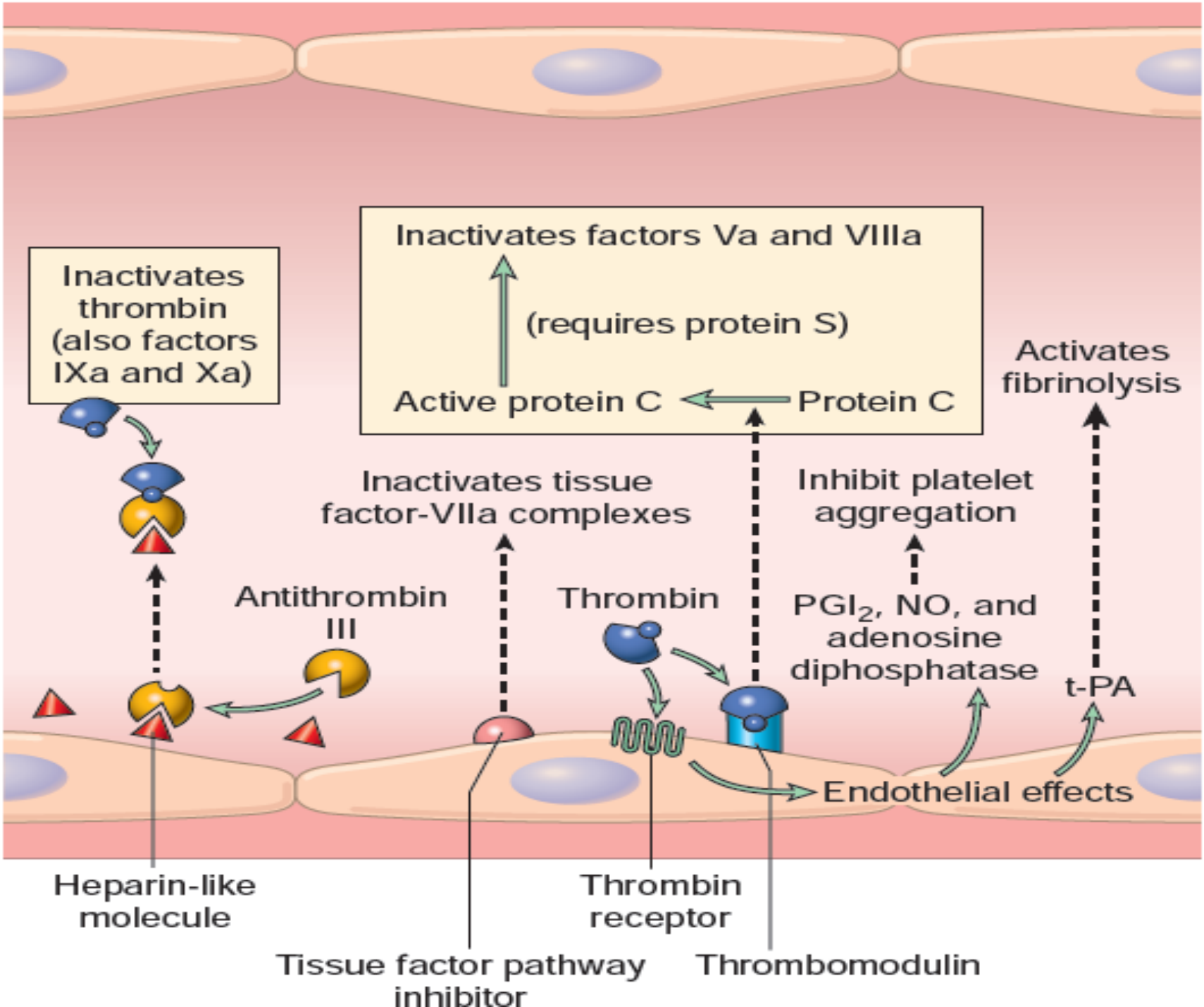
C. SECONDARY HEMOSTASIS

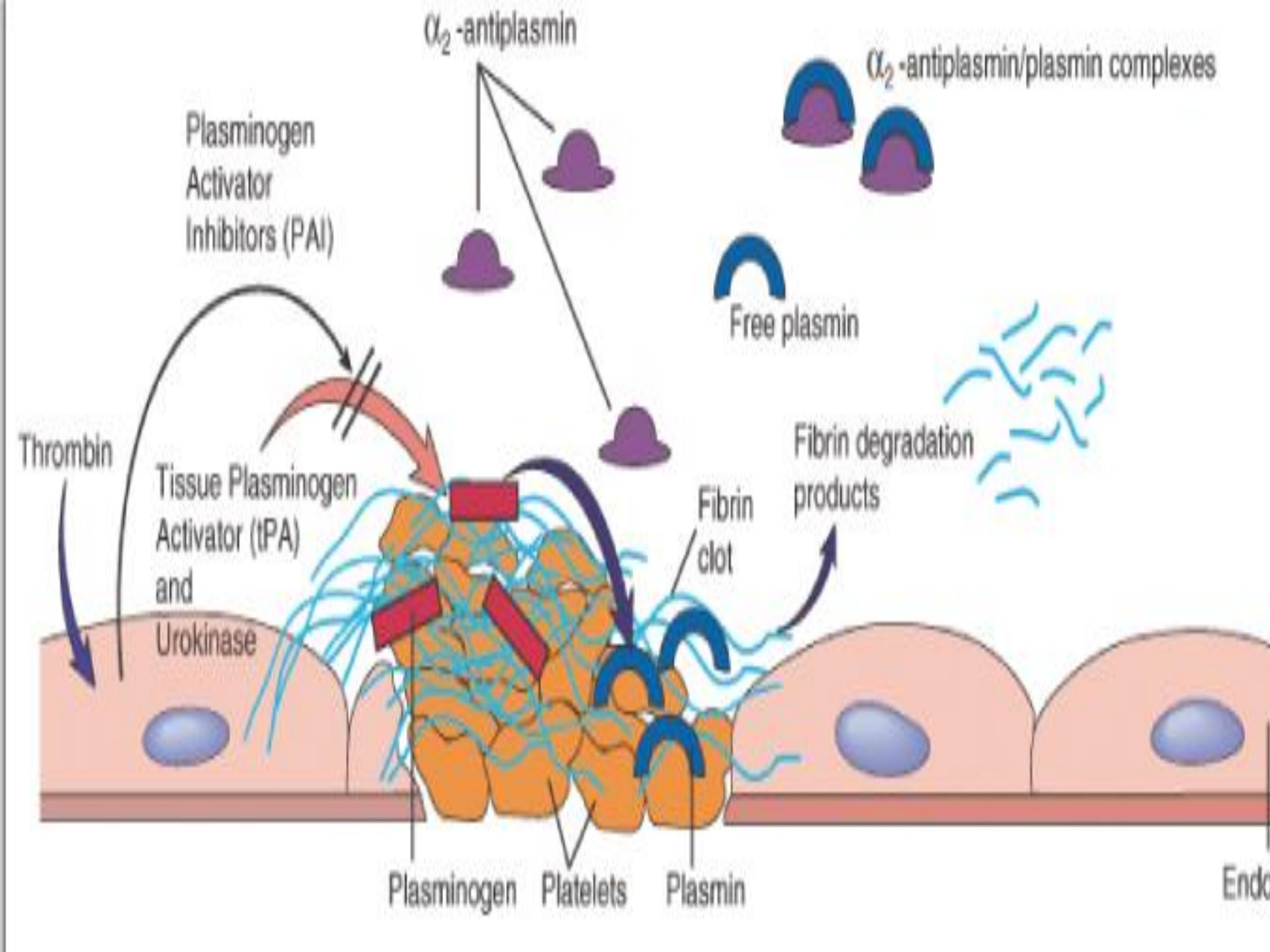



INTRINSIC PATHWAY
EXTRINSIC PATHWAY
XII
(Hageman Factor)
Kallikrein
HMWK collagen
Prekallikrein
XIIa
Tissue Injury
Tissue Factor
(Thromboplastin)
VII
XI
XIa
Thrombin
(IIa)
IX
IXa
Tissue Factor Pathway
Inhibitor (TFPI)
Tissue Factor
VIIa
VIII
VIIIa
Thrombin
(IIa)
X
Ca2+
Ca2+
Xa
V
Va
Ca2+
Thrombin
(IIa)
XIII
Ca2+
II
(Prothrombin)
IIa
(Thrombin)
XIIIa
Ca2+
Fibrinogen
(I)
Fibrin
(Ia)
Cross-linked
Fibrin
COMMON PATHWAY
Phospholipid
surface
Ca2+
Active
Inactive

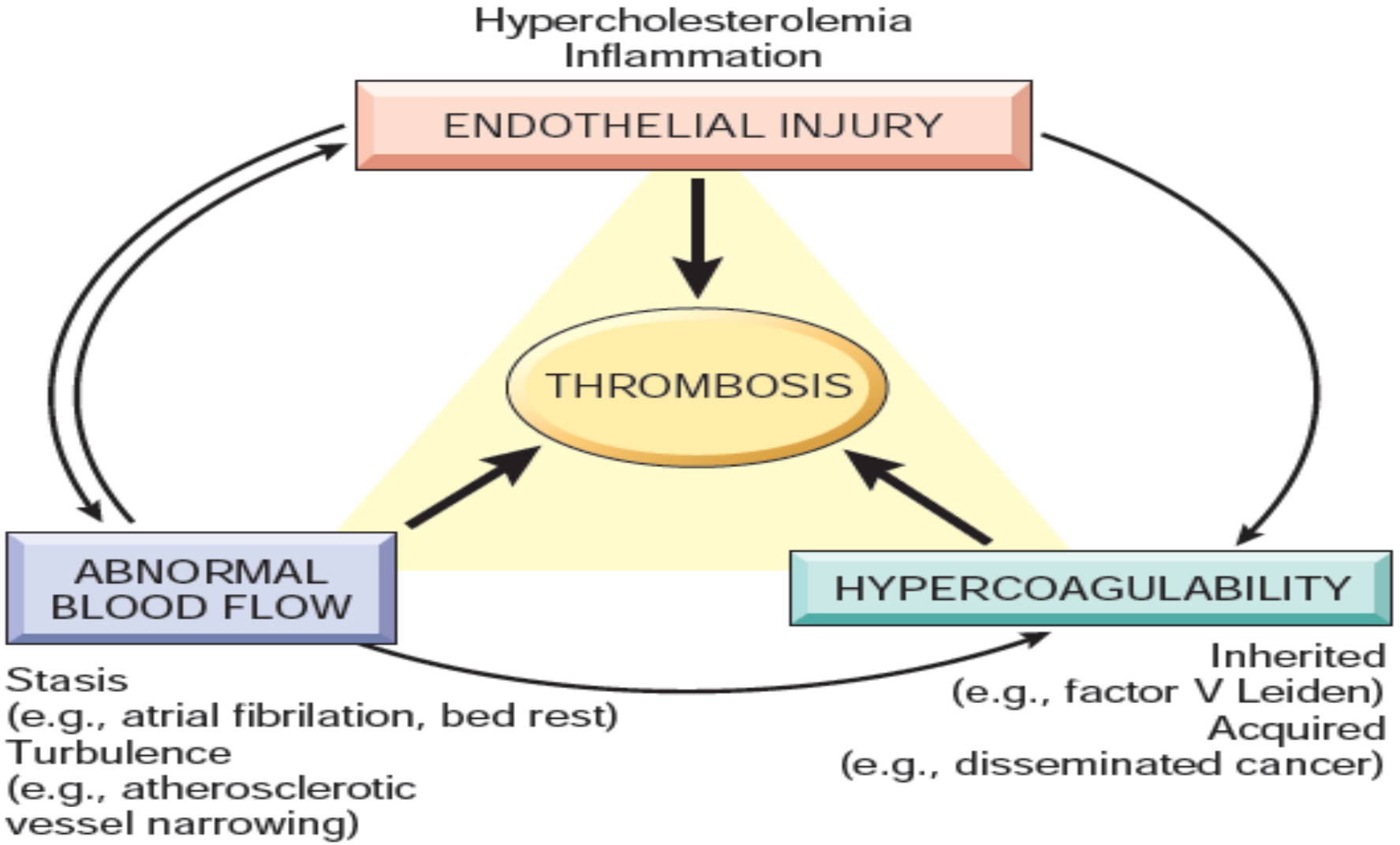
D. THROMBUS AND ANTITHROMBOTIC EVENTS




Inactivates factors Va and VIIIa
(requires protein S)
Active protein C
Protein C
Inactivates thrombin (also factors IXa and Xa)
Activates fibrinolysis
Inactivates tissue factor-VIIa complexes
Inhibit platelet aggregation
Antithrombin III
Thrombin
PGI2, NO, and adenosine diphosphatase
t-PA
Endothelial effects
Heparin-like molecule
Thrombin receptor
Tissue factor pathway inhibitor
Thrombomodulin


α_2-antiplasmin
α_2-antiplasmin/plasmin complexes
Plasminogen Activator Inhibitors (PAI)
Free plasmin
Thrombin
Tissue Plasminogen Activator (tPA) and Urokinase
Fibrin clot
Fibrin degradation products
Plasminogen
Platelets
Plasmin
Endo

Pathogenesis: Virchow's triad in thrombosis



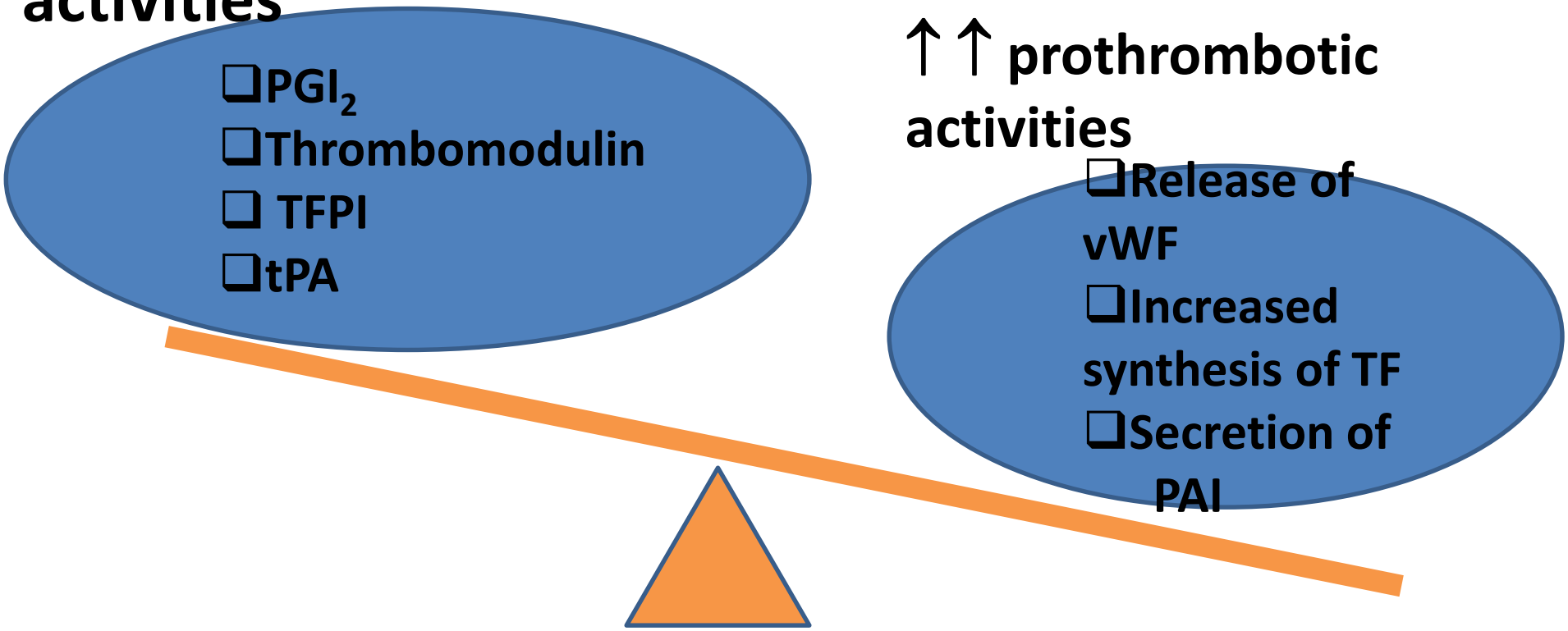
Endothelial injury: endothelial dysfunction

↓↓ antithrombotic activities

- PGI_2
- Thrombomodulin
- TFPI
- tPA

↑↑ prothrombotic activities

- Release of vWF
- Increased synthesis of TF
- Secretion of PAI



Endothelial injury

- This is the dominant influence to thrombus formation.
- Endothelial injury is particularly important in thrombus formation in the heart (e.g. Myocardial infarction) and arterial circulation (vasculitis), atherosclerosis, hypertension.
- Overt loss of endothelium exposes sub-endothelial ECM.
- Endothelium dysfunction.
- More procoagulaot factors (e.g., platelet adhesion molecules, tissue factor, inhibitors of plasminogen actvator (PAIs) or less anticoagulants effectors (e.g. thrmbomodulin, PGI2, t-PA).

Endothelial injury

- Causes of endothelial dysfunction
  - Hemodynamic disturbances- HTN
  - Bacterial endotoxins
  - Tobacco smoke
  - Inflammation
  - hypercholesterolemia

Abnormal blood flow

- **Turbulence**
  - Arterial and cardiac thrombus formation

- **Stasis** -Sluggish blood flow development of venous thrombus formation

Abnormal blood flow

- Endothelial cell activation resulting in increased prothrombotic activity
- Normal laminar blood flow is disturbed which
  - allows platelets and other cells to flow in the central column
  - Peripheral slowly flowing plasma fluid layers separate platelets from endothelial contact
- Stasis prevents washout of activated clotting factors and inflow of clotting factor inhibitors

Turbulence and stasis

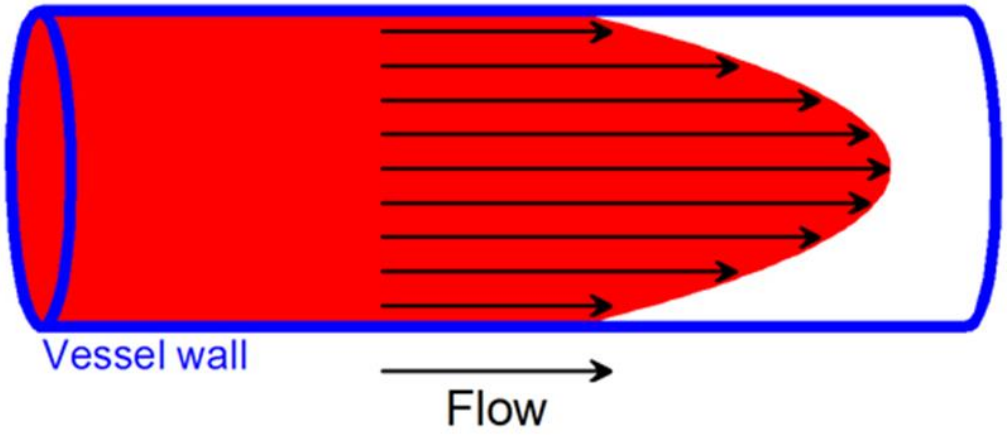
Causes of turbulence

- HTN
- Ulcerated atherosclerotic plaque in the vessel wall

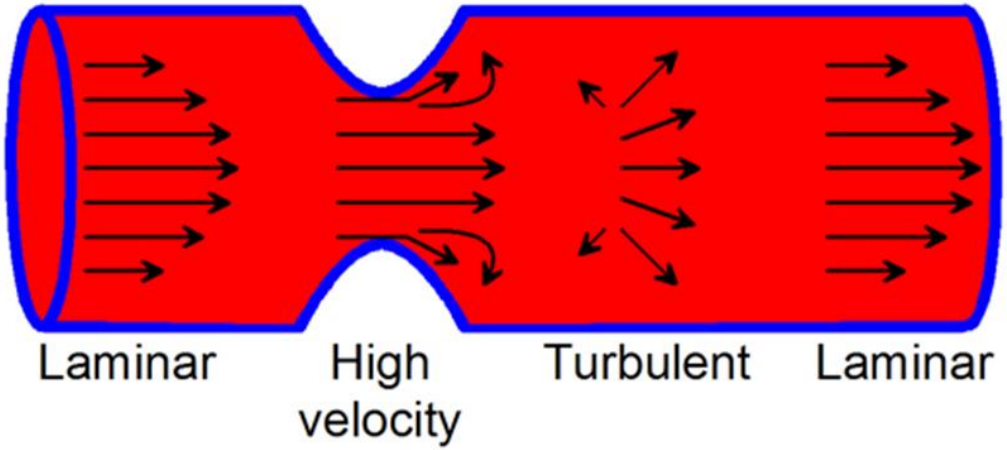
Causes of stasis

- Myocardial infarction- areas of noncontractile myocardium
- Aortic or arterial aneurysm

Laminar blood flow



Turbulent blood flow



Hypercoagulability

- **Any alteration of the coagulation pathways that predisposes to thrombosis**

Hypercoagulable states

- **Primary (genetic)**
- **Secondary (acquired)**

Hypercoagulable states: Primary causes

Common

- Factor V mutation (factor V Leiden)
- Prothrombin mutation
- Increased levels of factors VIII, IX, XI, or fibrinogen

Rare

- Antithrombin III deficiency
- Protein C deficiency
- Protein S deficiency

Hypercoagulable states: Secondary (acquired)

- Prolonged bed rest or immobilization
- Myocardial infarction
- Atrial fibrillation
- Tissue injury (surgery, fracture, burn)
- Cancer
- **Heparin-induced thrombocytopenia**
- **Antiphospholipid antibody syndrome**
- Hyperestrogenic states (pregnancy and postpartum)

Morphology : gross

- Size and shape depends upon the site of origin
- **Firmly adherent** focally to the underlying vascular surface
- Cut section:- **Lines of zahn-** laminated dark and pale zones
- These **represent pale** platelet and fibrin **layers** alternating with **darker red cell–rich layers.**
- Lines of Zahn are only found in thrombi that form in flowing blood. (Helps to differentiate antemortem thrombus from postmortem thrombus)

Morphology : microscopic features

- Thrombus
  - **platelet + fibrin+ RBCs+ WBCs**
- Firmly adherent to the vessel wall
- Lines of zahn
  - Paler zone= platelet + fibrin
  - Darker zone= RBCs

Types of thrombi

According to the site of origin:

- Cardiac thrombi
- Arterial thrombi
- Venous thrombi (red or stasis thrombi)
- Cardiac valves thrombi (vegetations)
  - Infective
  - sterile
- Capillaries thrombi

Cardiac thrombi

- **Mural thrombi**
- turbulence or endothelial injury
- Propagate in the retrograde direction
- Predisposing clinical conditions: **Myocardial infarction, atrial fibrillation, cardiac aneurysm, myocarditis**

Arterial thrombi

- **Mural thrombi**
- Endothelial injury/ turbulence
- Grow in the retrograde direction
- Usually occlusive
- Common sites: **coronary, cerebral, and femoral arteries**
- Predisposing conditions: **Ulcerated atherosclerotic plaque in the arterial wall, Aortic or arterial aneurysm**

Venous thrombi

- Stasis
- **red or stasis thrombi**
- Occlusive
- Propagate in the anterograde direction (direction of the blood flow toward the heart)
- Propagating tail fragmentation and embolization
- Common site: **deep veins of the lower extremities**

Cardiac valves thrombi

- **Vegetations**

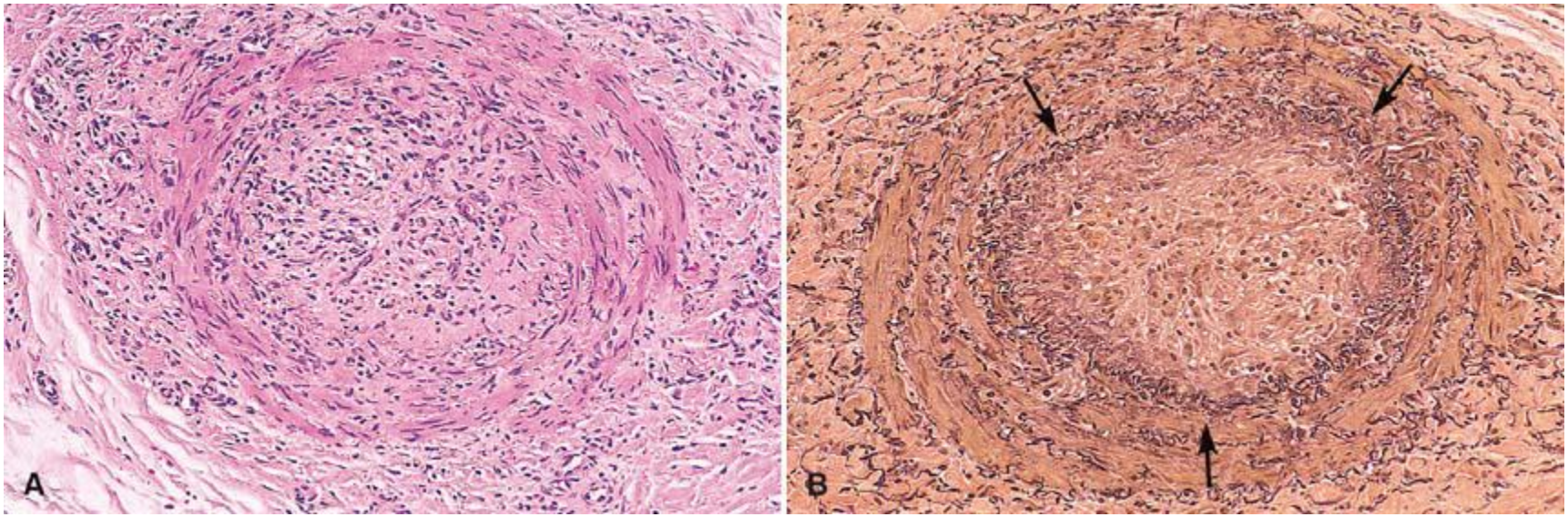
1. Infected

   e.g. infective endocarditis

2. Sterile

   - Non bacterial thrombotic endocarditis
   - Hypercoagulable states

Thrombosed vessel

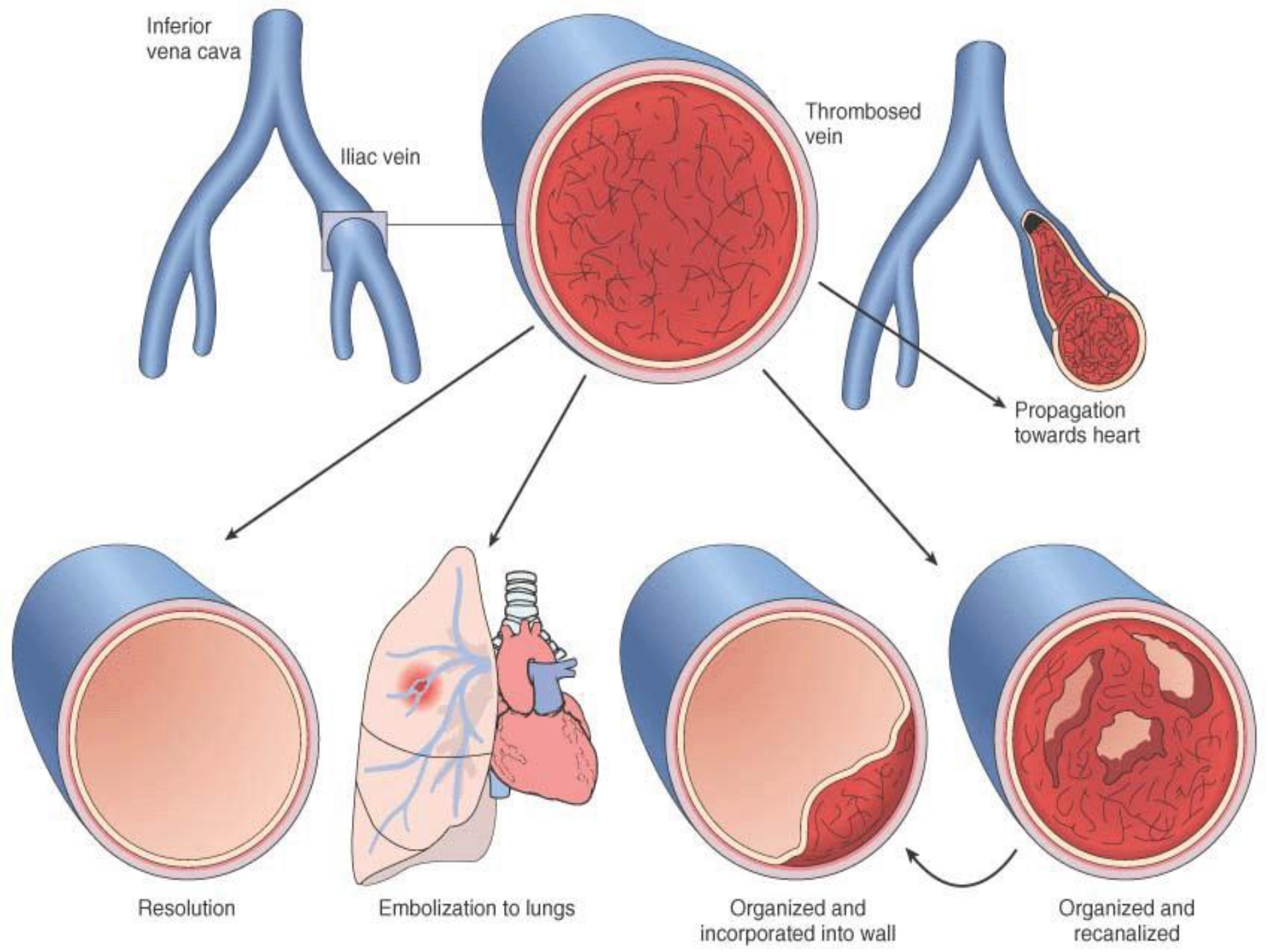


Fate of the thrombus (@PEDOR)

- **Propagation**
- **Embolization**
- **Dissolution**
  - **Recent** thrombi
- **Organization**
  - **Older** thrombi
- **Recanalization**

Fate of Thrombus (@PEDOR)

- **Propagation :** The thrombus enlarges.
- **Embolization:** Part or all of the thrombus is dislodged and transported elsewhere in the vasculature.
- **Dissolution**: If a thrombus is newly formed, activation of fibrinolytic factors may lead to its rapid shrinkage and complete dissolution.
- **Organization and Recanalization:** In growth of endothelial cells, smooth muscle cells, and fibroblasts into the fibrin rich thrombus. Capillary channels are formed.


Inferior vena cava
Iliac vein
Thrombosed vein
Propagation towards heart
Resolution
Embolization to lungs
Organized and incorporated into wall
Organized and recanalized

Differences between venous thrombi and postmortem clot

Antemortem venous thrombi	Postmortem clot
• Firm • Attached to the vessel wall • Gross and microscopy: – Lines of zahn	• Gelatinous • not attached to the underlying vessel wall • absence of lines of zahn • dark red dependent portion where red cells have settled by gravity • Upper portion--yellow “chicken fat”