# Hemodynamic Disorders II

## Hemostasis

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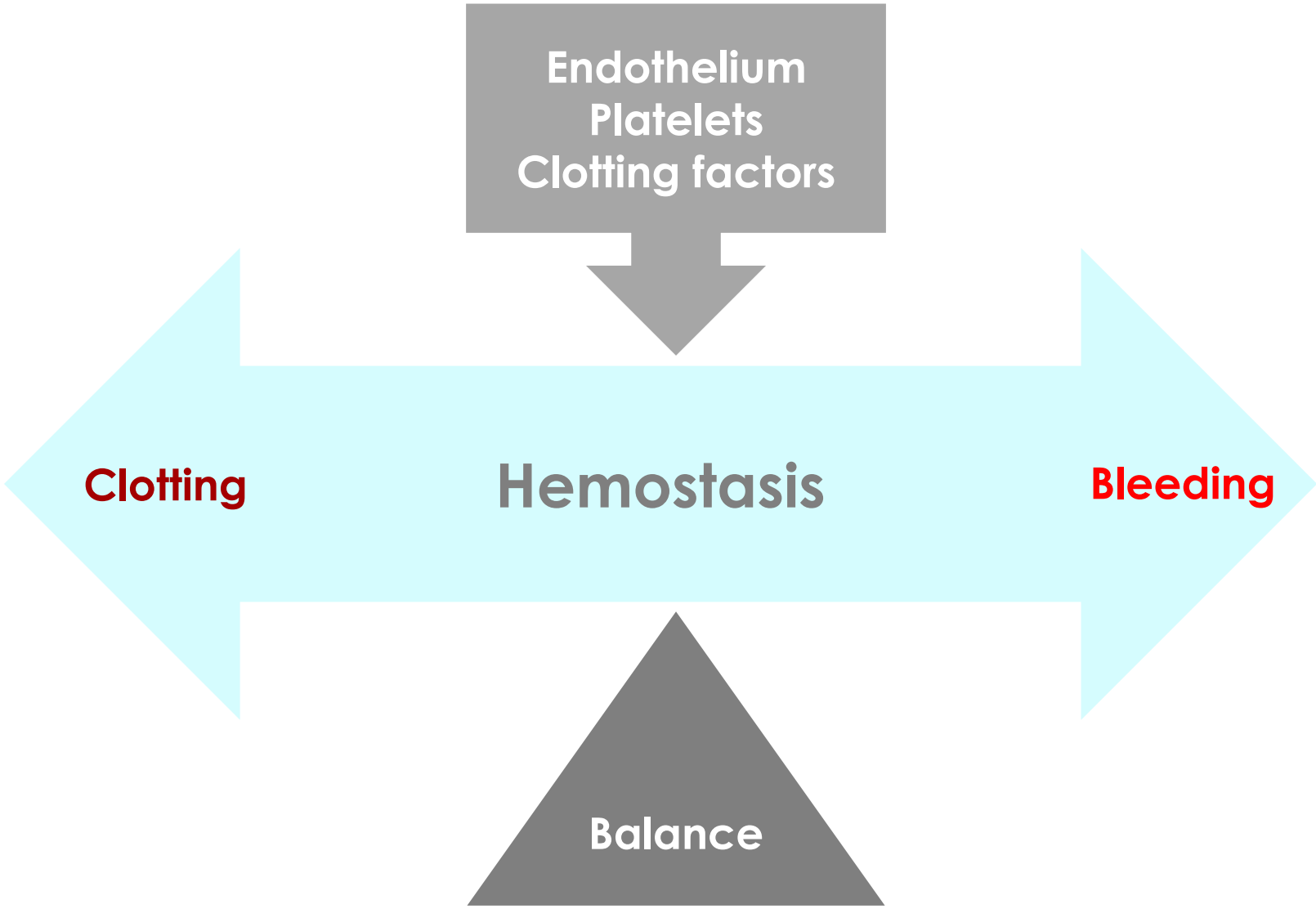
# Hemostasis

- **Hemostasis is a precisely orchestrated process occurs at the site of vascular injury & culminates in the formation of a blood clot, to prevent or limit the extent of bleeding.**
- **Involves platelets, clotting factors, & endothelium.**
- **The arrest of bleeding – Hemo = Blood , Stasis = stop, slow**
- **It is essential for life and deranged in many disorders, divided in two main groups:**

1. **Hemorrhagic** *disorders*: excessive bleeding, hemostatic mechanisms are either blunted or insufficient to prevent abnormal blood loss.
2. **Thrombotic** *disorders:* blood clots (called *thrombi*) form within intact (**non-traumatized)** blood vessels or within the chambers of the heart.


Endothelium
Platelets
Clotting factors
Clotting
Hemostasis
Bleeding
Balance

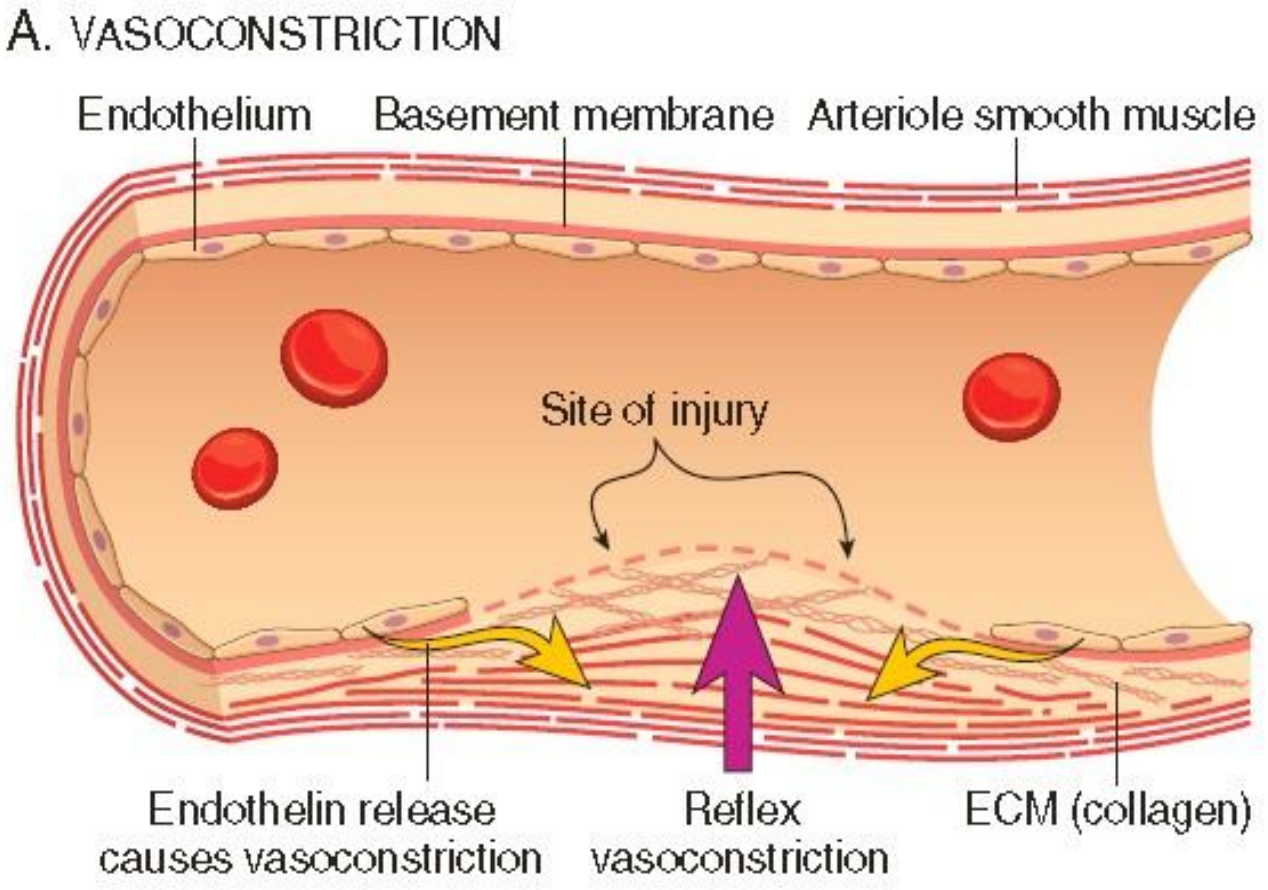
# The general sequence of events leading to hemostasis..

- *Arteriolar vasoconstriction*
- *Primary hemostasis: the formation of the platelet plug*
- *Secondary hemostasis: deposition of fibrin*
- Clot stabilization and resorption

# *Arteriolar vasoconstriction*

- Occurs immediately & **markedly reduces** blood flow to the injured area .
- mediated by: **reflex neurogenic mechanisms** & augmented by the **local secretion of factors such as *endothelin*.**

- **Endothelin** a potent endothelium-derived vasoconstrictor.
- This effect is transient → bleeding would resume if not for activation of platelets & coagulation factors.

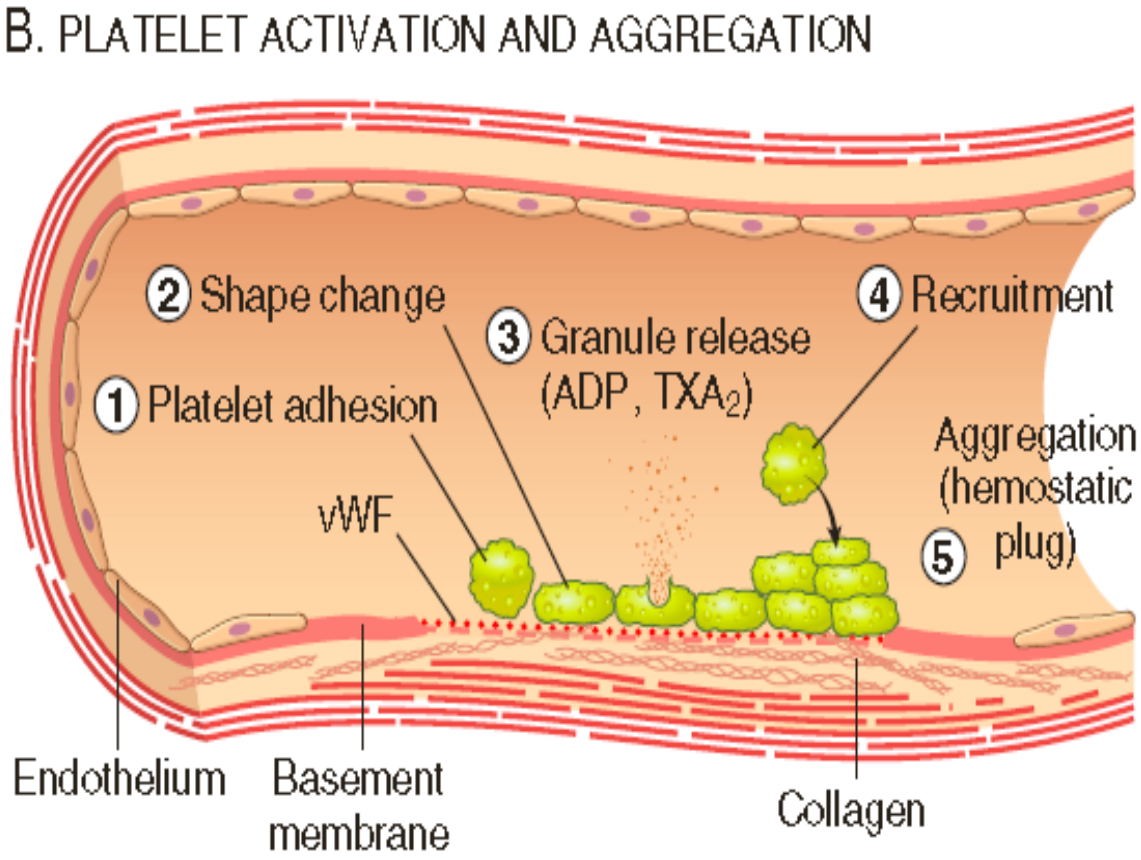


# *Primary hemostasis: the formation of the platelet plug*

- Disruption of the endothelium exposes subendothelial **von Willebrand factor (vWF)** & **collagen**.
- Which Promote platelet adherence & activation →

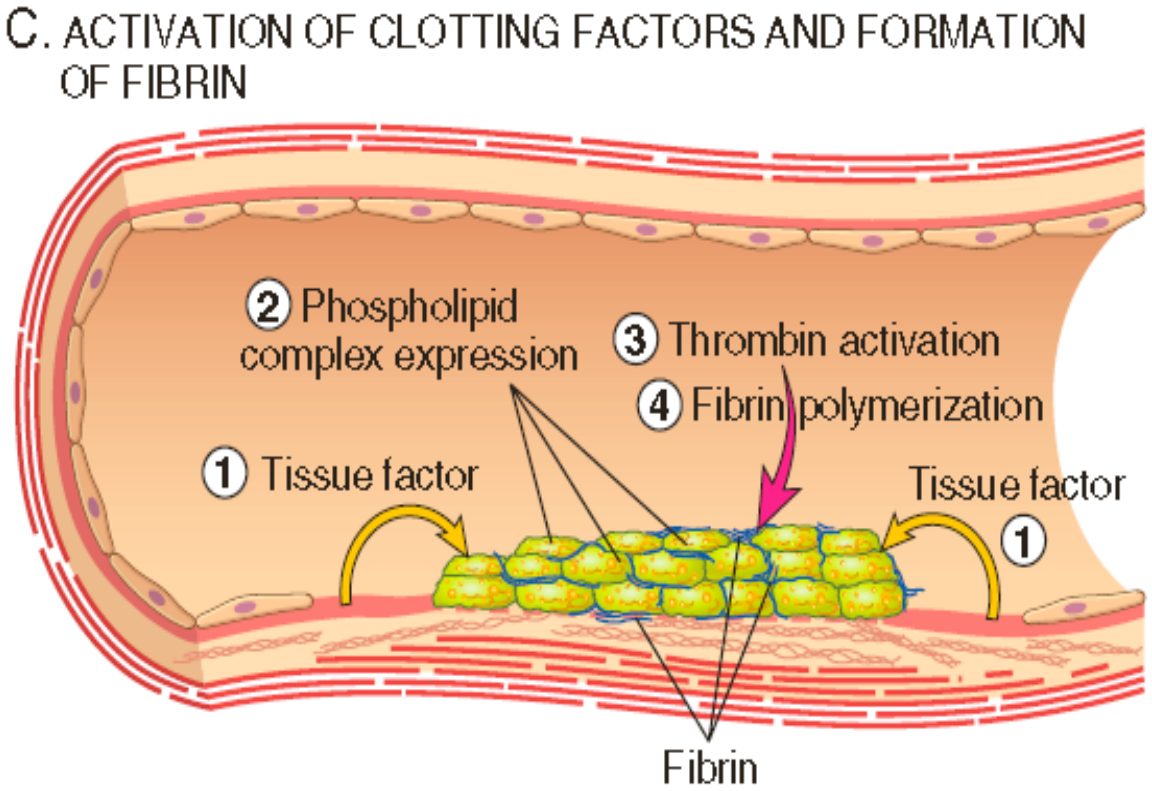
1. A dramatic shape change (small rounded discs → flat plates with spiky protrusions that **markedly increased surface area)**.
2. The release of secretory granules.

- **secretory granules products** recruit additional platelets in minutes → *aggregate* to form **a *primary hemostatic plug***



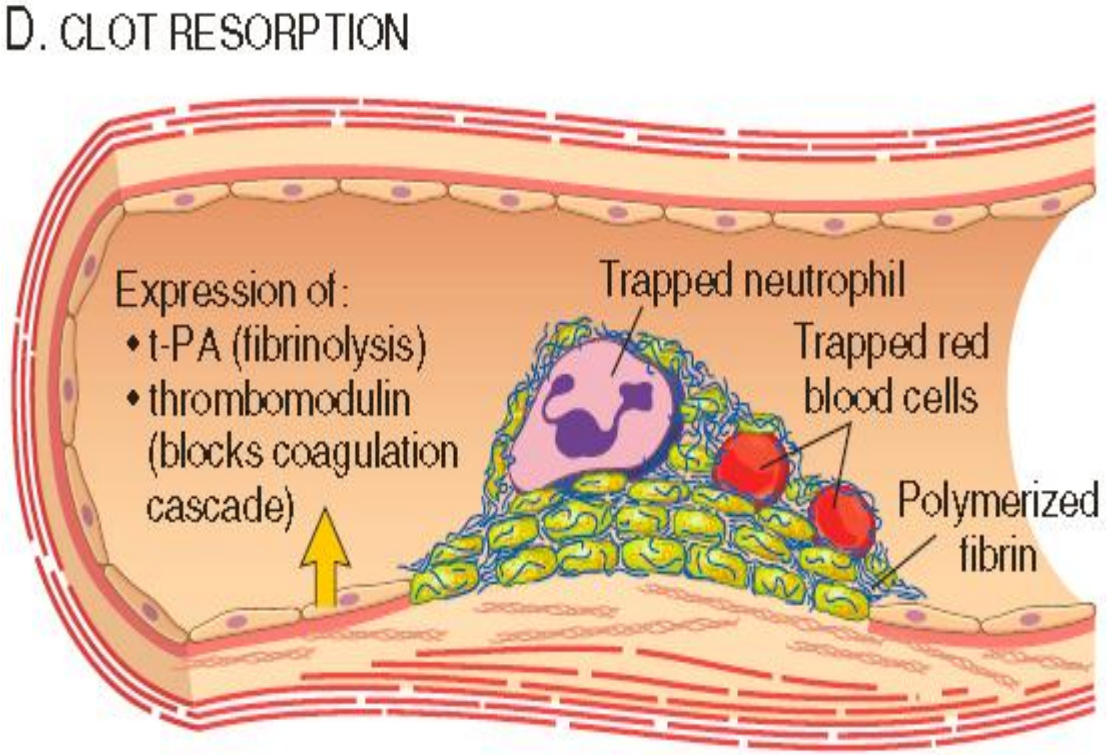
# Secondary hemostasis: Deposition of fibrin.

- Vascular injury also exposes **tissue factor** at the site of injury.
- **Tissue factor** is a membrane-bound procoagulant glycoprotein , normally expressed by subendothelial cells in the vessel wall (smooth muscle cells & fibroblasts).
- It binds & activates **factor VII** → a cascade of reactions → **thrombin** generation → Thrombin cleaves circulating fibrinogen → insoluble fibrin → creating a fibrin meshwork
- **Fibrin is a potent activator of platelets, leading to additional platelet aggregation**
- These events create **the initial platelet plug.**



# Clot stabilization & resorption

- Polymerized fibrin & platelet aggregates undergo contraction to form a solid, *permanent plug* that prevents further hemorrhage.
- At this stage, **counter regulatory mechanisms (e.g., *tissue plasminogen activator, t-PA made by endothelial cells*)** are set into motion that **limit clotting** to the site of injury.
- This mechanisms eventually lead to clot resorption & tissue repair.

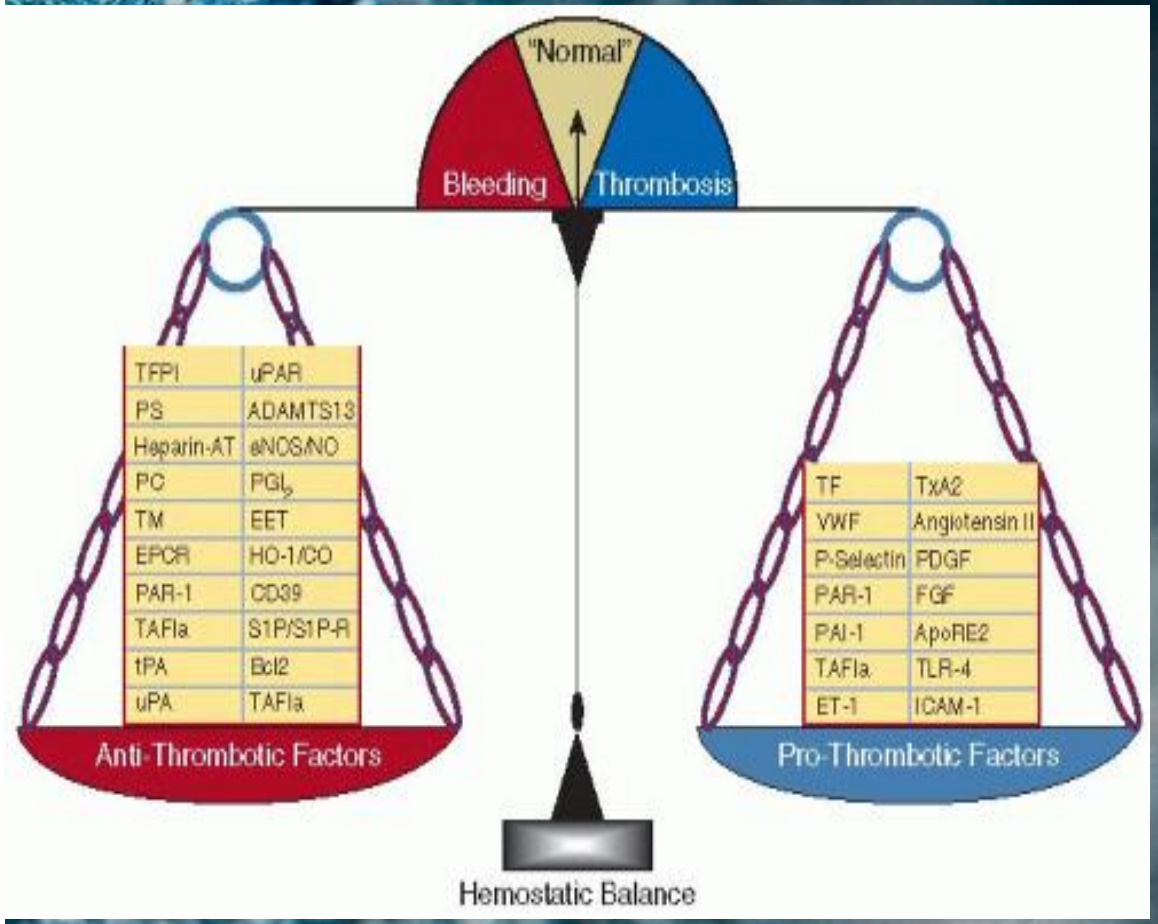


- ✓ Endothelial cells are central regulators of hemostasis; **balance between anti-thrombic & prothrombotic** activities of endothelium determines whether thrombus formation, propagation, or dissolution occurs.

- ✓ **Normal** endothelial cells express a variety of anticoagulant factors that inhibit platelet aggregation & coagulation, & promote fibrinolysis.

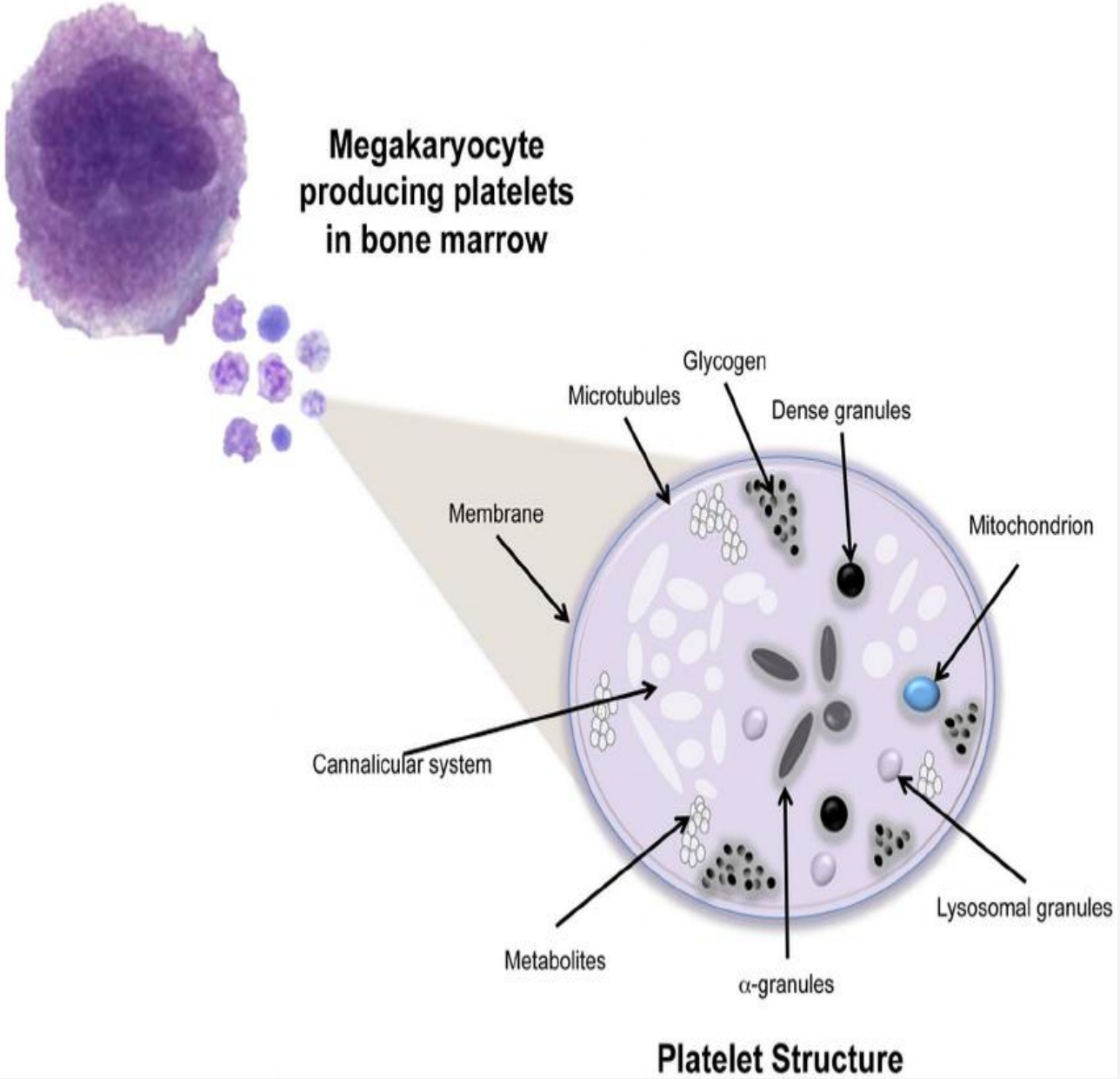
- ✓ Trauma, microbial pathogens, hemodynamic forces, & a number of pro-inflammatory mediators shift the balance, & endothelial cells acquire numerous *procoagulant* activities.

- ✓ **Endothelium** modulates the functions of **platelets** and can trigger **coagulation**.

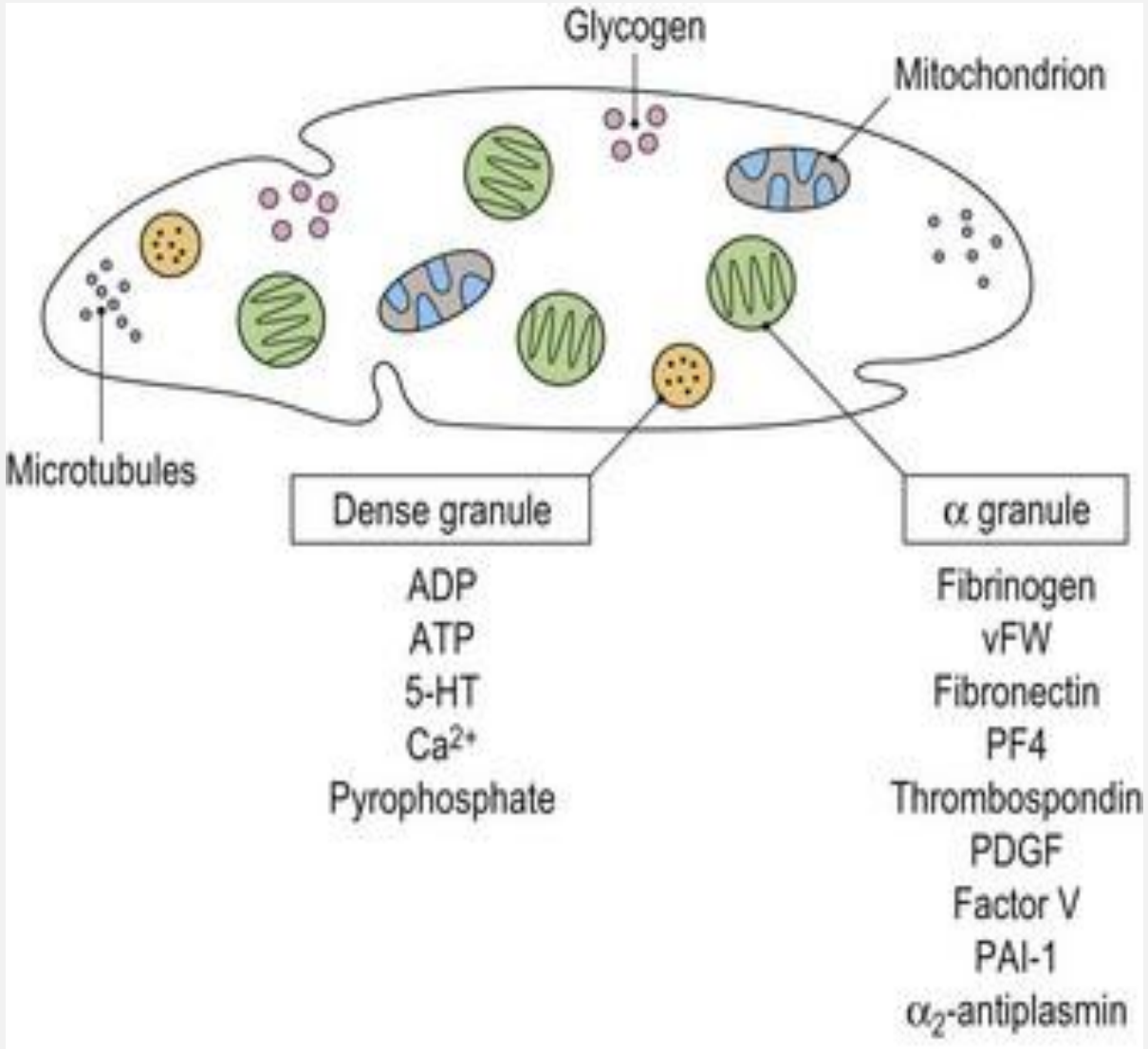


# Platelets

Critical role in hemostasis by (1) forming the primary plug → initially seals vascular defects & (2) providing a surface that binds &concentrates activated coagulation factors.



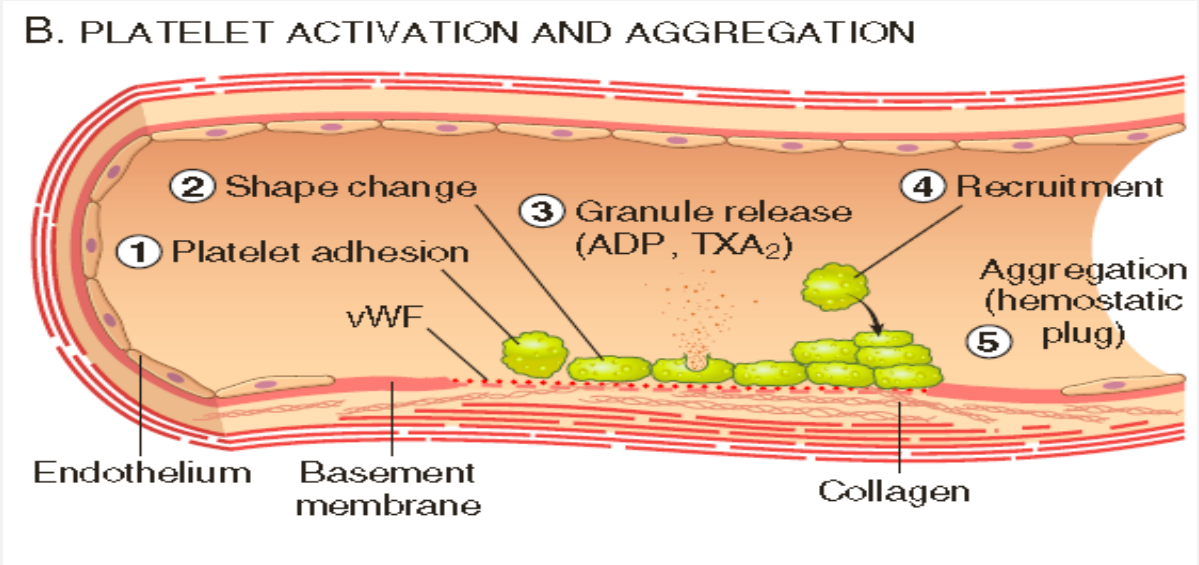

- Platelets are disc-shaped anucleate cell fragments
- Shed from megakaryocytes in bone marrow to the blood.
- Their function depends on several glycoprotein receptors, a contractile cytoskeleton, & two types of Cytoplasmic granules:

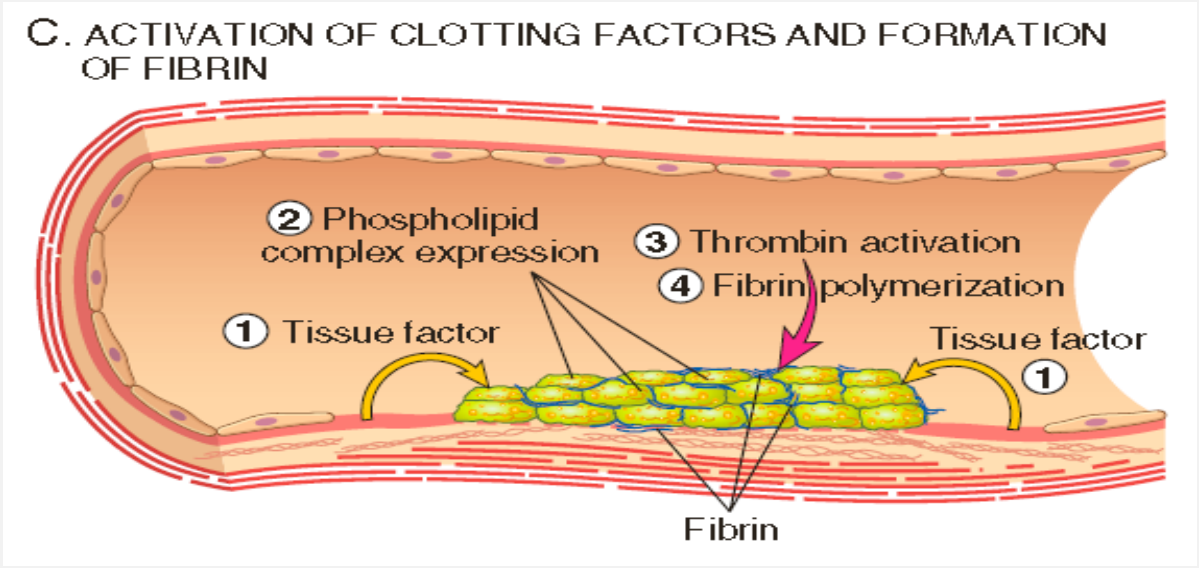



1. ***a-Granules:*** Adhesion molecule P-selectin on their membranes. Contian coagulation proteins (fibrinogen, coagulation factor V, & vWF), also wound healing proteins (fibronectin, platelet factor 4,platelet-derived growth factor (PDGF), transforming growth factor-β).
2. ***Dense (δ) granules:*** Contain ADP, ATP, $Ca_{+2}$, serotonin , & epinephrine.

After a traumatic vascular injury → platelets encounter vWF & collagen → Four events in the formation of a platelet plug:

- ✓Platelet adhesion
- ✓Platelet activation
- ✓Platelet aggregation
- ✓Fibrin formation & support of local coagulation

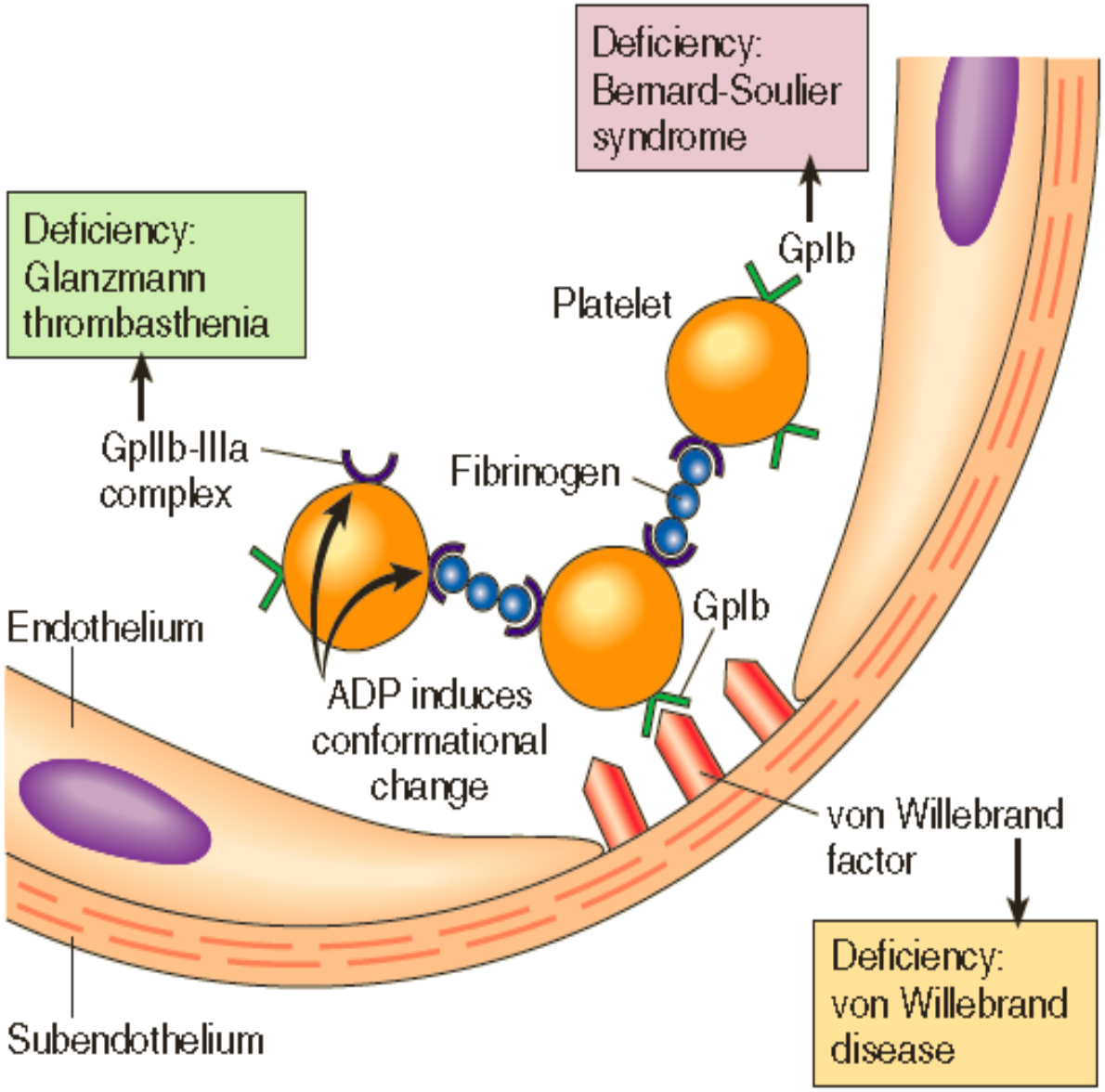


# Platelet adhesion

Is mediated mainly via interactions with **vWF** → acts as a bridge between the platelet surface receptor **glycoprotein Ib (GpIb) and exposed collagen.**

Genetic deficiencies of vWF (vonWillebrand disease) or GpIb (Bernard-Soulier syndrome) result in bleeding disorders.



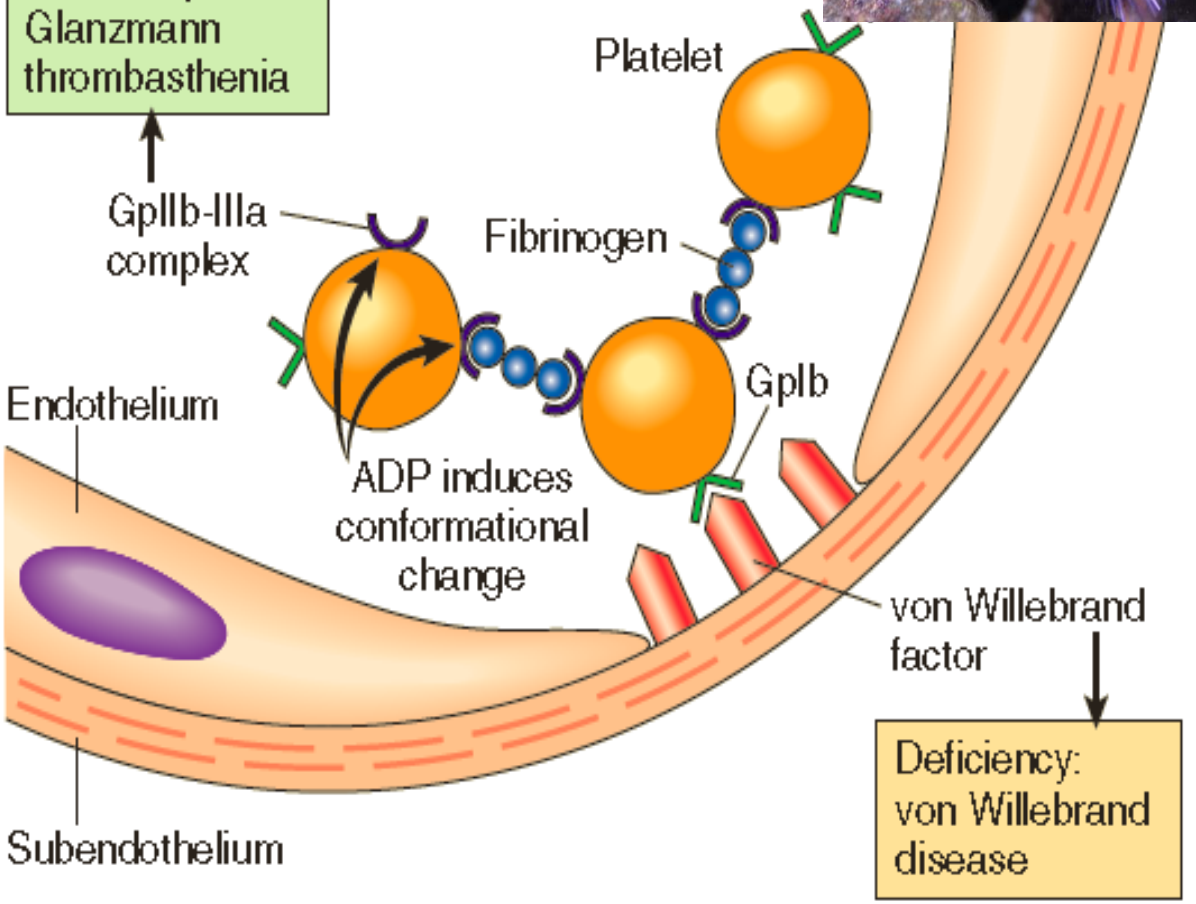
# Platelet activation

+ Platelets rapidly change shape following adhesion → from smooth discs to spiky "sea urchins" → greatly increased surface area.

+ alterations in glycoprotein IIb/IIIa that increase its affinity for fibrinogen,

+ the translocation of negatively charged phospholipids (particularly phosphatidylserine) to the platelet surface. (bind calcium & serve as sites for the assembly of coagulation factor complexes).

+ Secretion (release reaction) of granule contents occurs with changes in shape; these two events referred to together as platelet activation



# Platelet activation

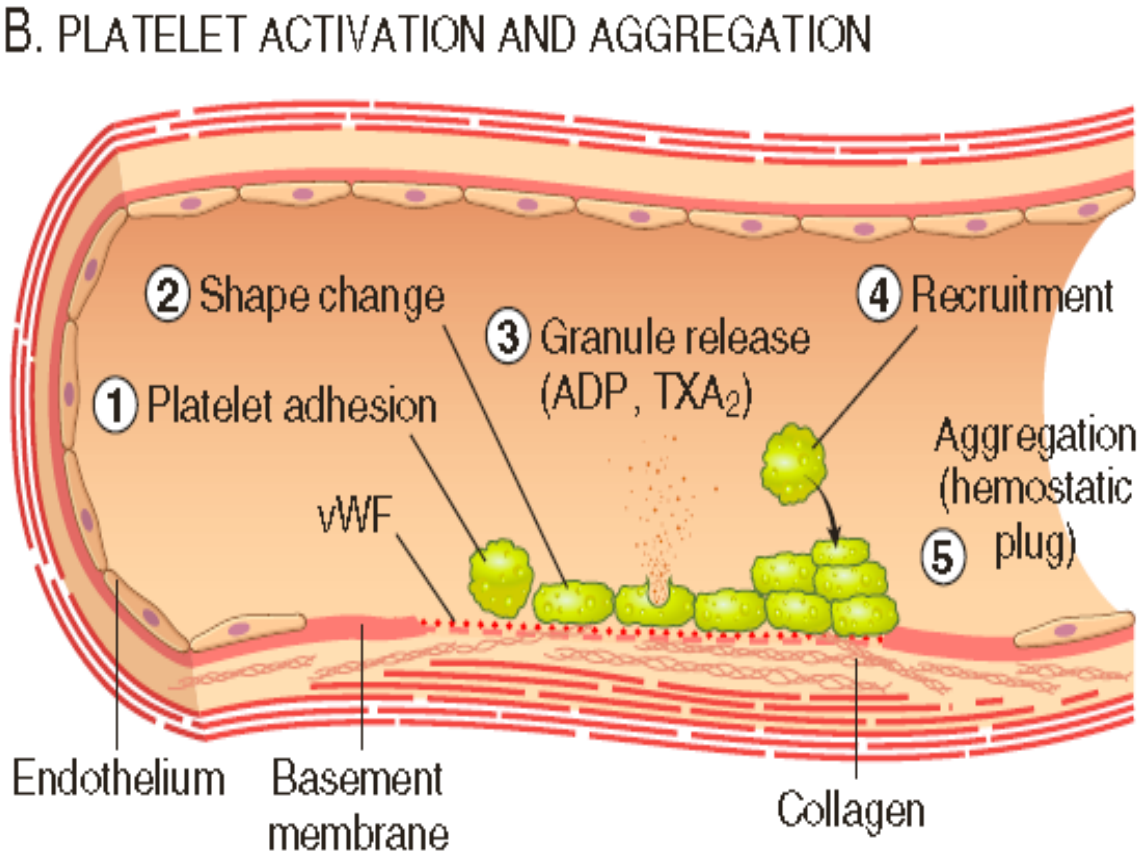
Platelet activation triggered by a number of factors:

+ Thrombin activates platelets through protease-activated receptor (PAR)

+ ADP causes additional rounds of platelet activation (**recruitment**).

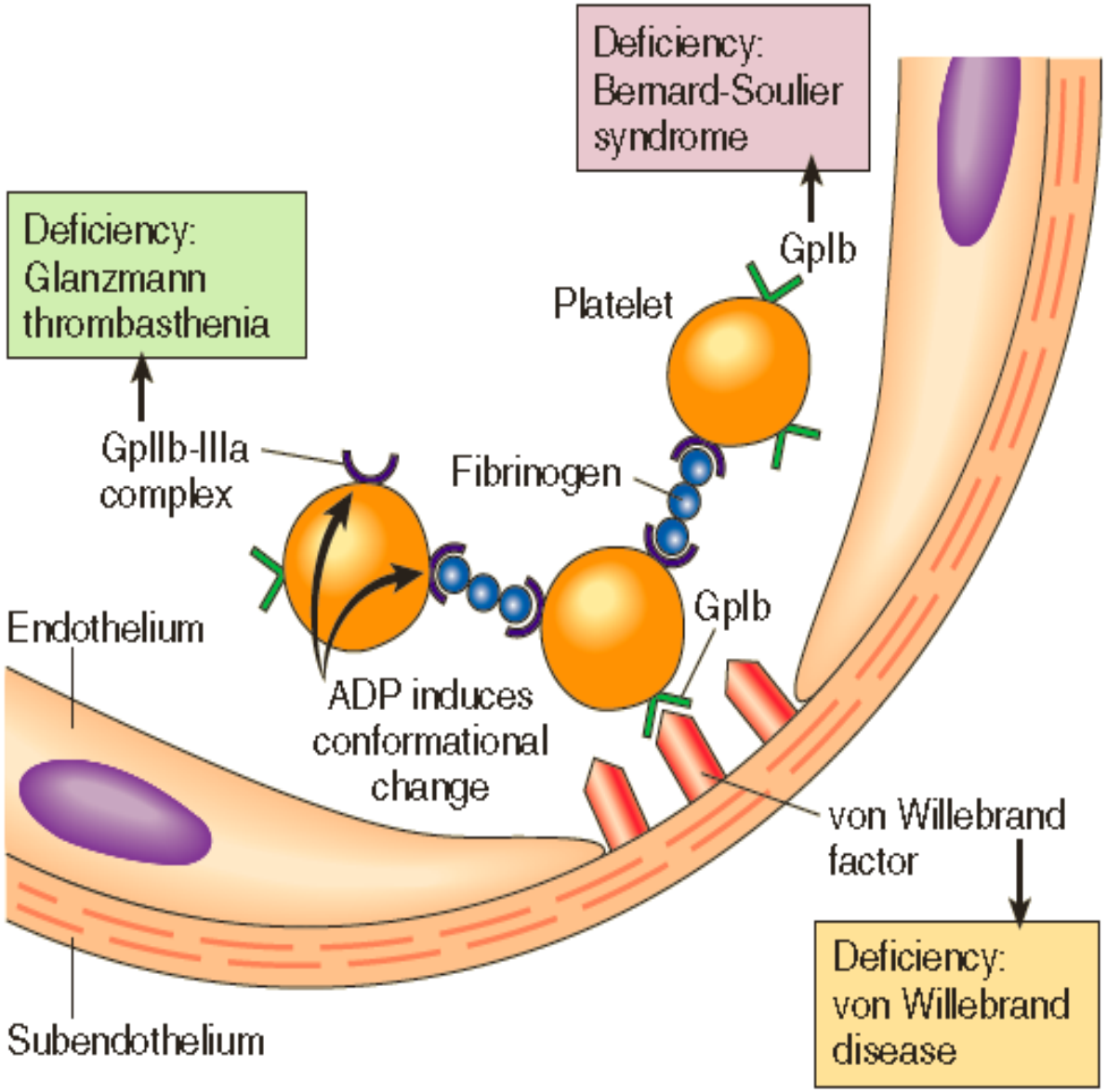
+ Activated platelets also produce the prostaglandin thromboxane A2 (TXA2), a potent inducer of platelet aggregation.

+Aspirin inhibits platelet aggregation & produces a mild bleeding defect by inhibiting cyclooxygenase, a platelet enzyme that is required for TXA2 synthesis.

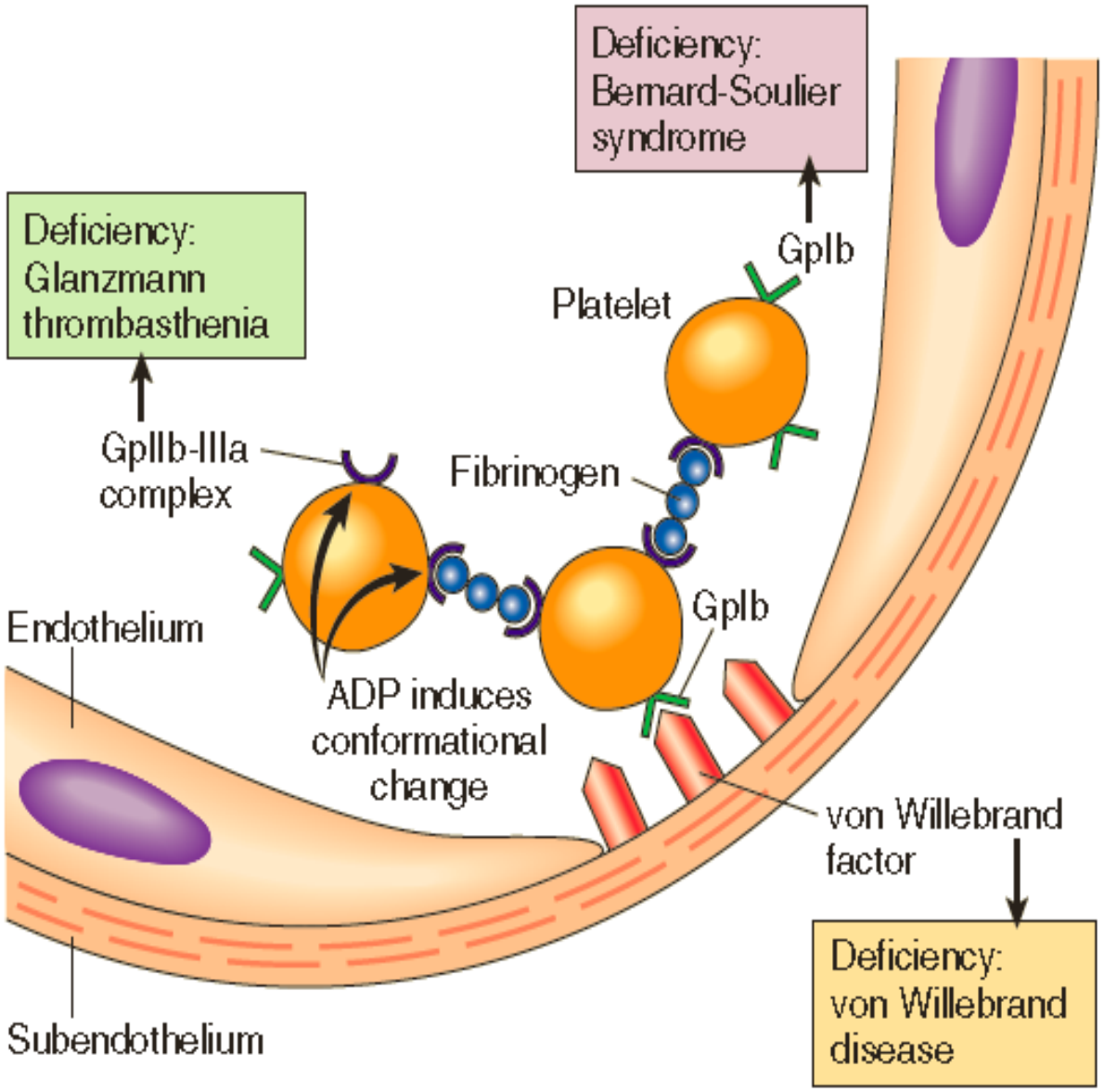


# Platelet aggregation

- Conformational change in glycoprotein IIb/IIIa occurs with platelet activation allows binding of fibrinogen
- Fibrinogen, a large bivalent plasma polypeptide that forms bridges between adjacent platelets → aggregation.
- Inherited deficiency of GpIIb-IIIa results in a bleeding disorder called Glanzmann thrombasthenia.



- The initial wave of aggregation is reversible, but concurrent activation of thrombin stabilizes the platelet plug → causing further platelet activation & aggregation & by promoting irreversible *platelet contraction*.
- **Platelet contraction** is dependent on the cytoskeleton & consolidates the aggregated platelets.
- In parallel, thrombin also converts fibrinogen into insoluble fibrin, cementing the platelets in place & creating the definitive secondary hemostatic plug.




Please recruit more platelets!
It gets too hectic here.
iRELIEF

# Thank You!