

Hemodynamic Disorders, Thromboembolism, and Shock

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HEMOSTASIS AND THROMBOSIS

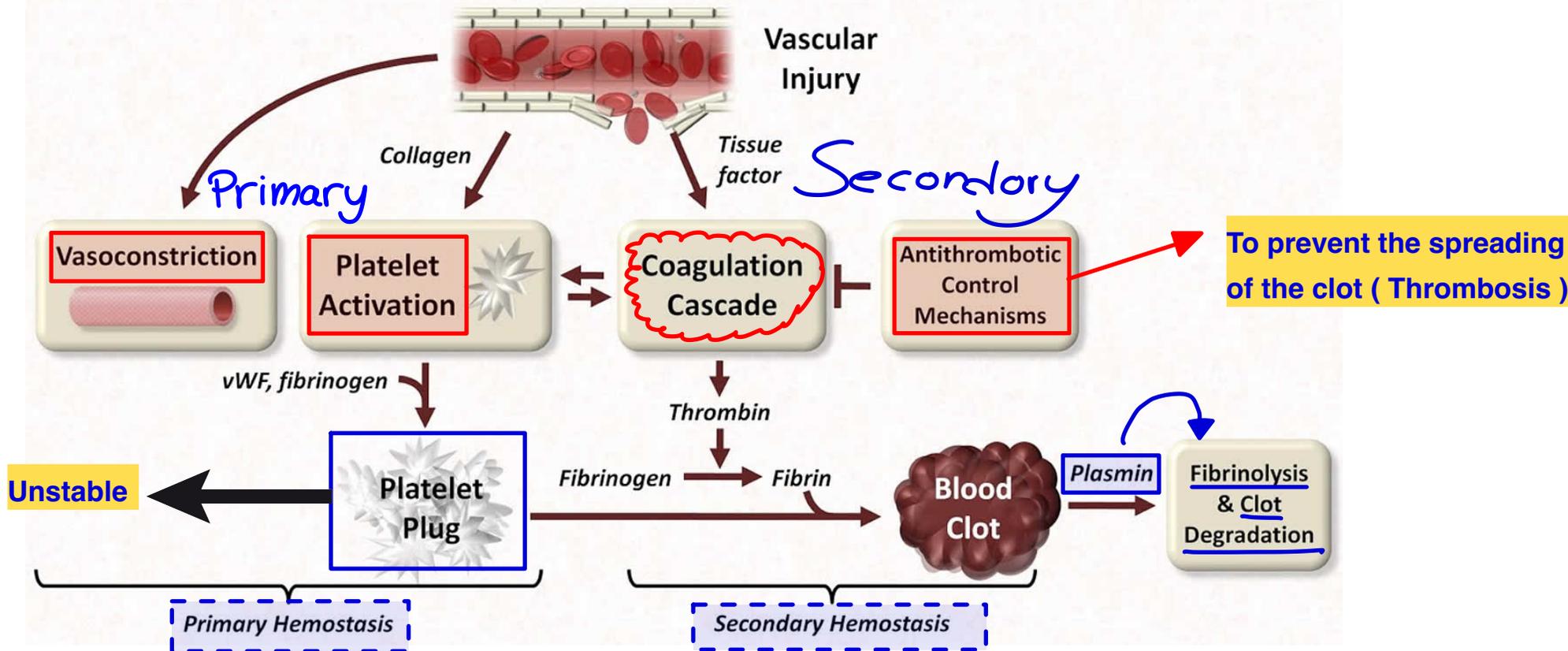
- Normal hemostasis comprises a series of regulated processes that culminate in the formation of a **blood clot** that **limits bleeding** from an **injured vessel**.
- The **pathologic counterpart** of hemostasis is **thrombosis**, the formation of **blood clot (thrombus)** within non-traumatized, **intact vessels**.

It occur for non injured blood vessels

Normal Hemostasis

- Hemostasis is process involving platelets, clotting factors, and endothelium that occurs at the site of vascular injury and culminates in the formation of a blood clot, which serves to prevent or limit the extent of bleeding.

Major Components of Hemostasis



Major component of hemostasis

1. platelets

2. Clotting factors

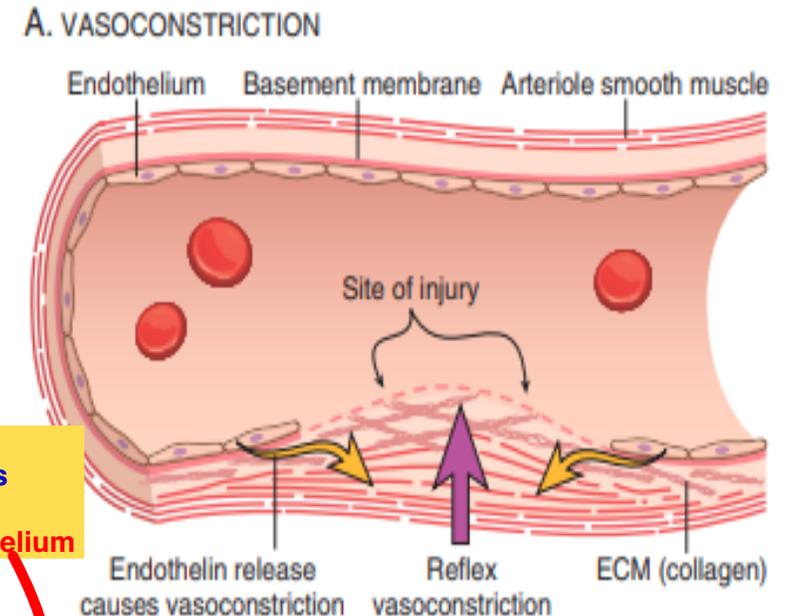
3. Endothelium

The general sequence of events leading to hemostasis at a site of vascular injury
INCLUDE:

I. Primary hemostasis

• 1. Arteriolar vasoconstriction :

- occurs immediately and markedly reduces blood flow to the injured area.
- it is mediated by reflex neurogenic mechanisms.
- it is augmented by endothelin a potent endothelium-derived vasoconstrictor.
- this effect is transient, however, bleeding would resume if not followed by activation of platelets and coagulation factors



It's hormone-like Substance that is Secreted from damaged endothelium

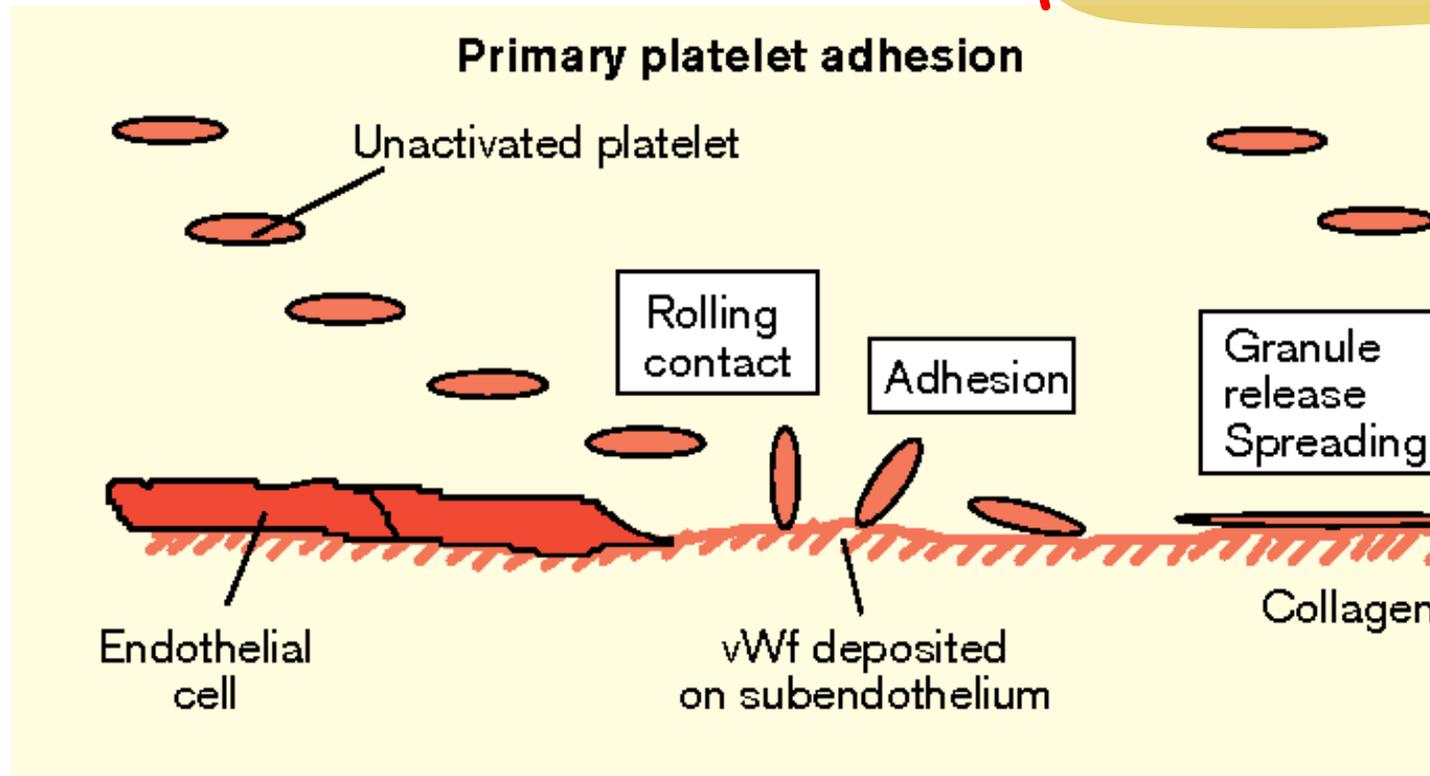
This effect won't last long
It's must be followed with platelets activation

- 2. platelet activation

- The formation of the platelet plug.

Platelets are circulating in the blood when injury happens to the endothelium the sub-endothelium expose the vWf which the platelets have the ability for adhesion with it, which forms :

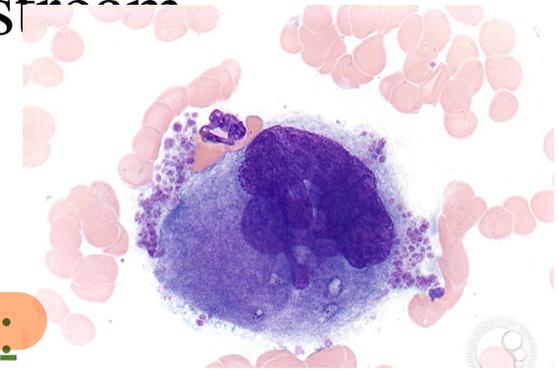
platelets Plug



- Platelets

- platelets play a critical role in hemostasis by forming the **primary plug** that **initially seals vascular defects** and by **providing a surface that binds and concentrates activated coagulation factors**.

- platelets are **disc-shaped anucleate cell fragments** that are **shed** from **megakaryocytes** in the bone marrow into the bloodstream.



- Their function depends on several factors including:

- Glycoprotein receptors.

- A contractile cytoskeleton

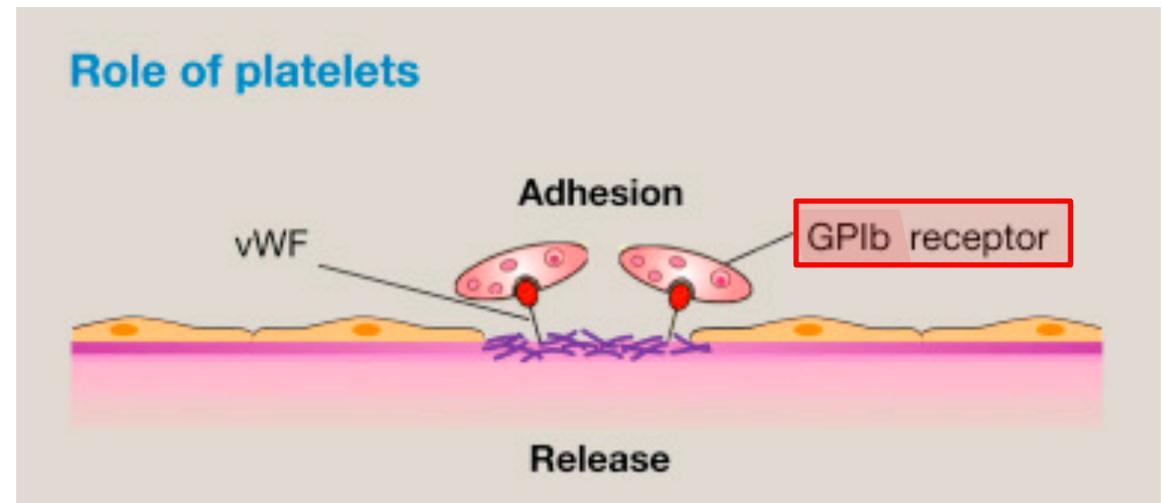
- Two types of cytoplasmic granules.

- **α -granules** have the adhesion molecule **p-selectin**, and **contain proteins involved in coagulation**.

- **dense (or δ) granules** contain **ADP, ATP, ionized calcium, serotonin, and epinephrine**.

platelets undergo a sequence of reactions After a traumatic vascular injury that culminate in the formation of a platelet plug

- 1. Platelet adhesion:
- is mediated via interactions with vwf which acts as a bridge between the platelet surface receptor glycoprotein ib (gpib) and exposed collagen.





- **2. platelet activation.**

- **A. changes in shape** from smooth discs to spiky “sea urchins” with greatly increased surface area.

- alterations in glycoprotein **iib/iiia** that increase its affinity for **fibrinogen**

- the translocation of **negatively charged phospholipids** to the platelet surface

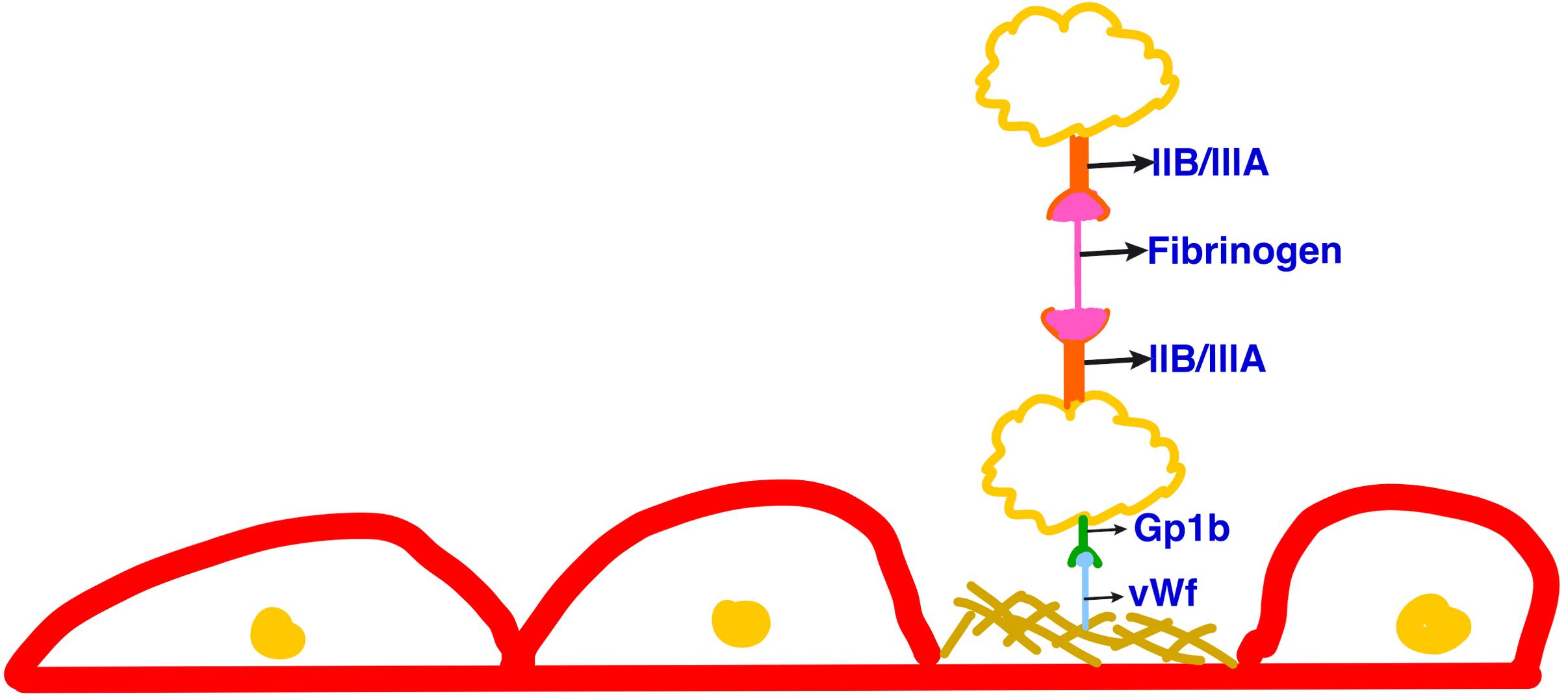
IIB/IIIA act as a cross-linker between two platelets through Fibrinogen
It also promotes platelets aggregation

- **B. Secretion of granule contents, e.g:**

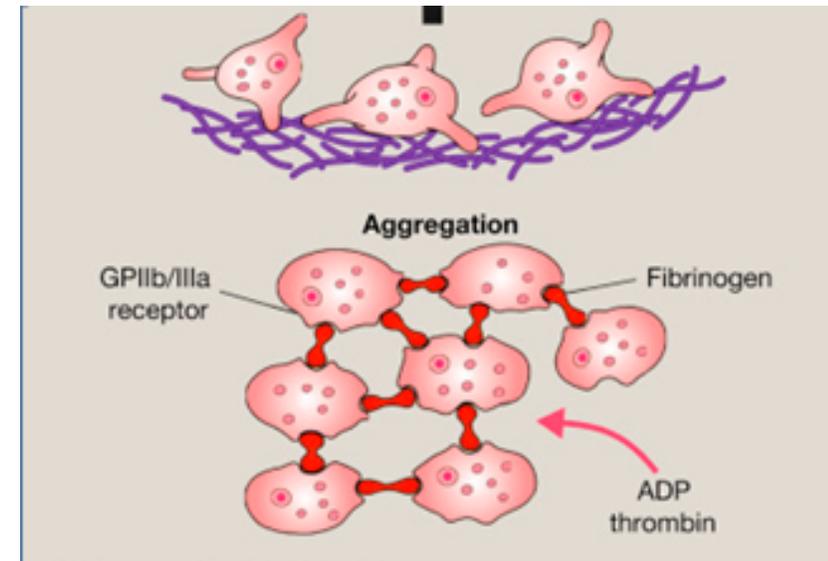
- **Thrombin:** activates platelets

- **ADP:** create an additional rounds of platelet activation.

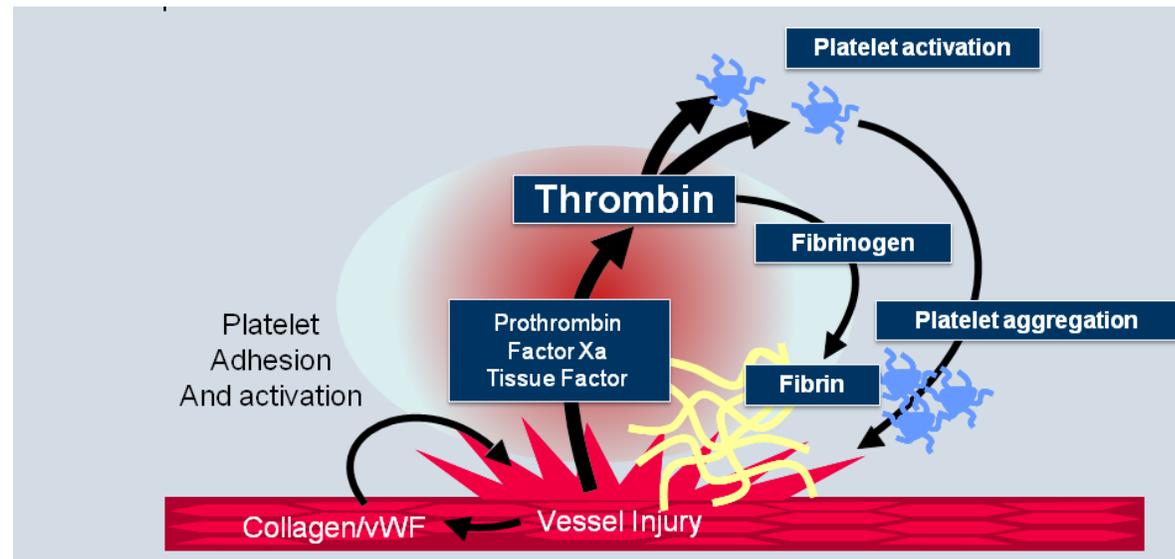
- **thromboxane A2 (TXA2):** a potent inducer of platelet aggregation.



- 3. Platelet aggregation follows their activation.
- The conformational change in glycoprotein iib/iiia allows binding of fibrinogen that forms bridges between adjacent platelets, leading to their aggregation.
- fibrinogen cause reversible aggregation
- thrombin cause irreversible aggregation (converts fibrinogen into insoluble fibrin).
- cytoskeleton cause contraction of the plug.

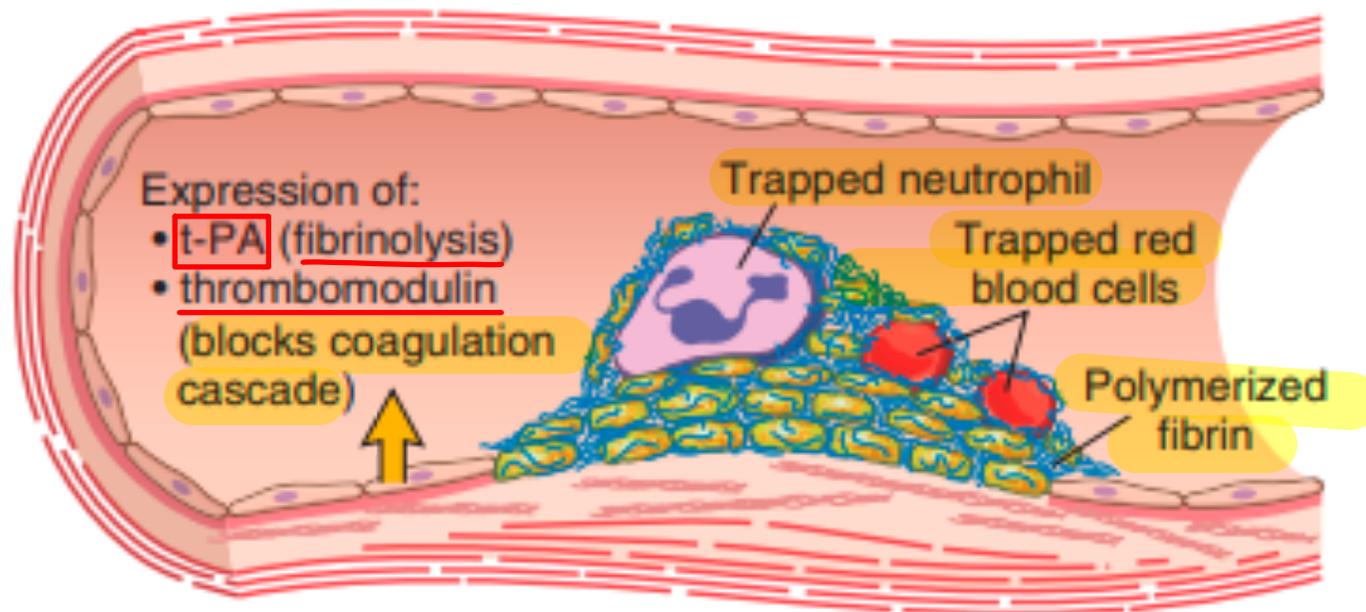


- II. Secondary hemostasis:
- deposition of fibrin.
- Vascular injury exposes tissue factor at the site of injury.
- Tissue factor binds and activates factor VII, setting in motion a cascade of reactions that culminates in thrombin generation.



- III. Clot stabilization and resorption:
- Polymerized fibrin and platelet aggregates undergo contraction to form a solid, permanent plug that prevents further hemorrhage.
- Entrapped red cells and leukocytes are also found in hemostatic plugs, in part due to adherence of leukocytes to P-selectin expressed on activated platelet
- 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, and eventually lead to clot resorption and tissue repair.

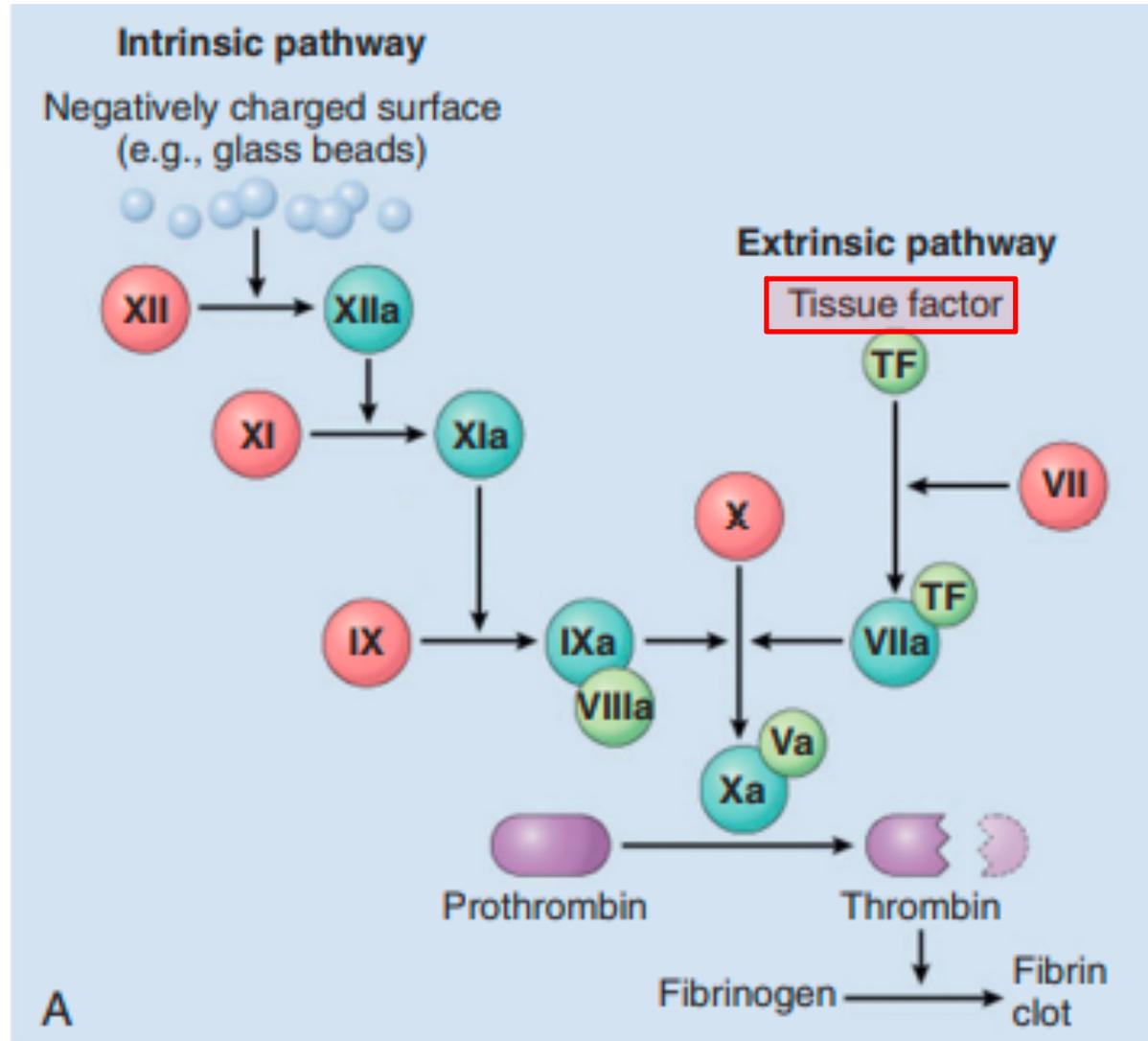
D. CLOT RESORPTION



Coagulation Cascade

- the coagulation cascade is a series of amplifying enzymatic reactions that lead to the deposition of an insoluble fibrin clot.
- each reaction step involves an enzyme (an activated coagulation factor), a substrate (an inactive proenzyme form of a coagulation factor), and a cofactor (a reaction accelerator).
- these components are assembled on a negatively charged phospholipid surface, which is provided by activated platelets. assembly of reaction complexes also depends on calcium

PT
T



PT



Mnemonic for
Vitamin K Dependent Clotting Factors

"Two plus seven is nine NOT ten!"

2 7 9 10



vitamin K antagonists

WEPT 1972



Coagulation cascade has traditionally been divided into the extrinsic and intrinsic pathways

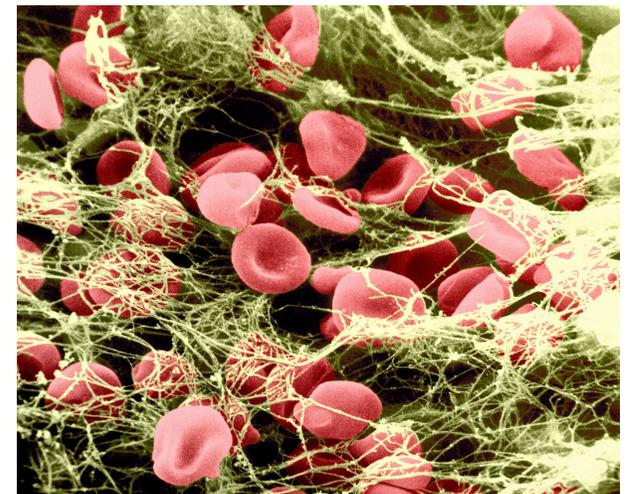
- 1. The prothrombin time (PT)
- assay assesses the function of the proteins in the extrinsic pathway (factors VII, X, V, II (prothrombin), and fibrinogen).
- The partial thromboplastin time (PTT)
- assay screens the function of the proteins in the intrinsic pathway (factors XII, XI, IX, VIII, X, V, II, and fibrinogen).

Among thrombin's most important activities are the following:

- 1. Conversion of fibrinogen into crosslinked fibrin.
- Thrombin directly converts soluble fibrinogen into fibrin monomers that polymerize into an insoluble fibril.
- 2. Platelet activation.
- 4. Anti-coagulant effects.
- encountering normal endothelium, thrombin changes from a procoagulant to an anticoagulant.



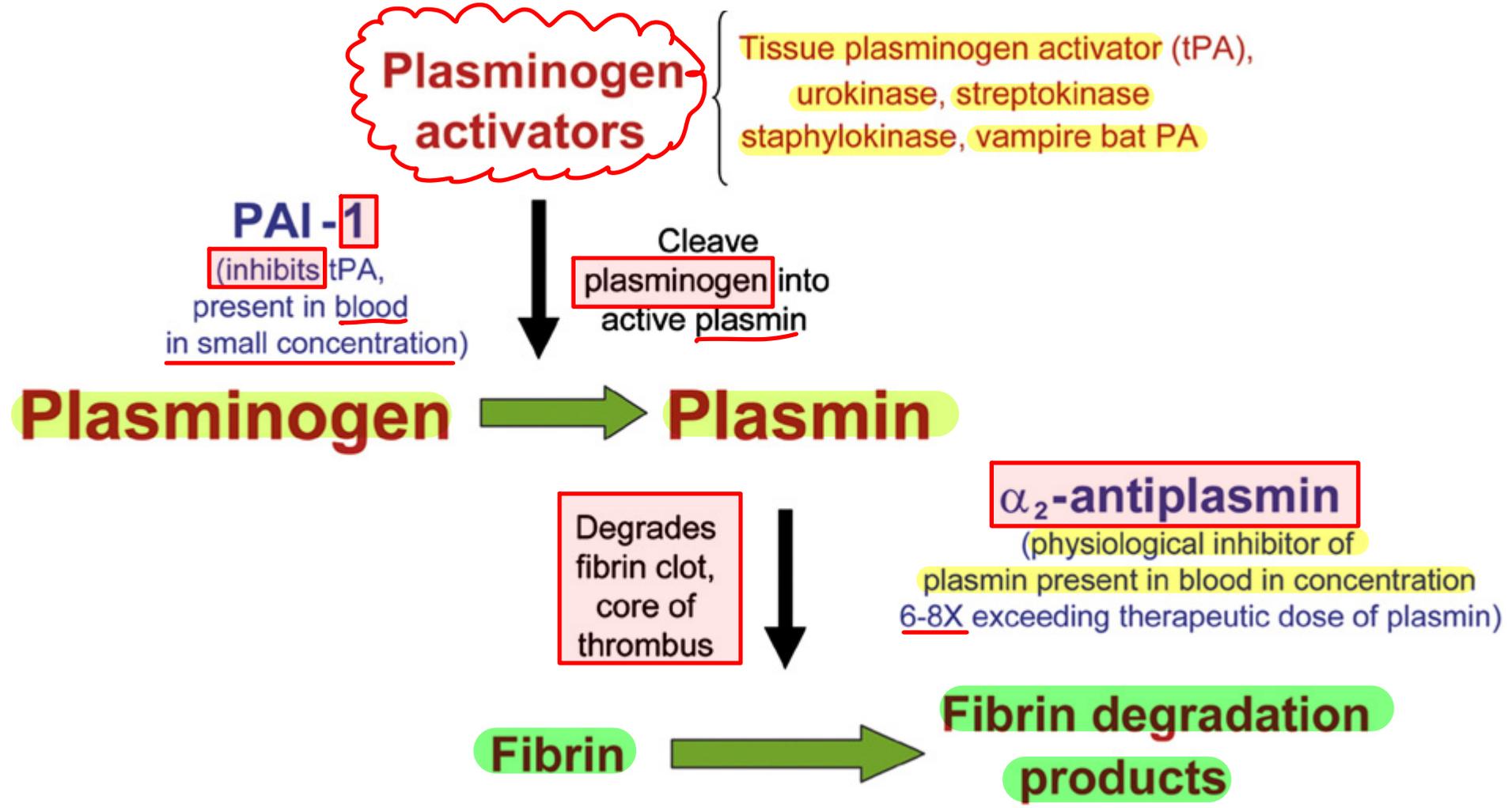
Thrombomodulin



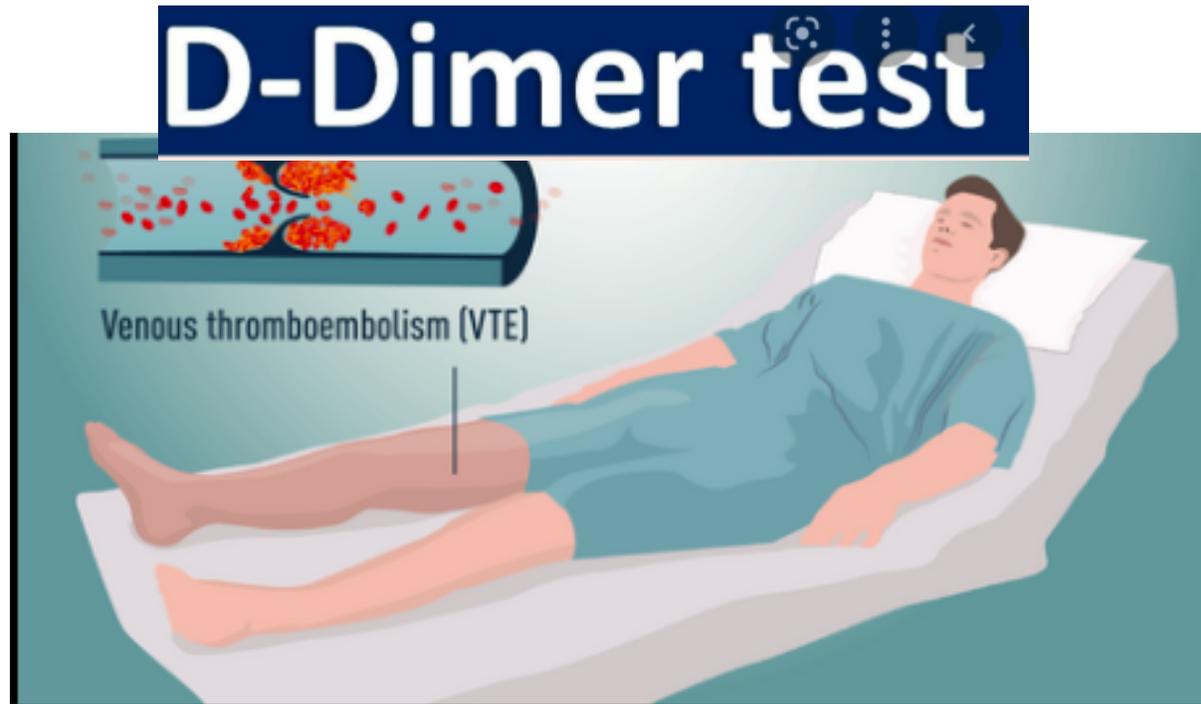
Factors That Limit Coagulation.

- coagulation must be restricted to the site of vascular injury to prevent dangerous consequences through:
- 1. simple dilution:
- blood flowing at the site of injury washes out activated coagulation factors, which are rapidly removed by the liver.
- 2. requirement for negatively charged phospholipids
- 3. fibrinolytic cascade:
- through the enzymatic activity of plasmin, which breaks down fibrin and interferes with its polymerization.

fibrinolytic cascade



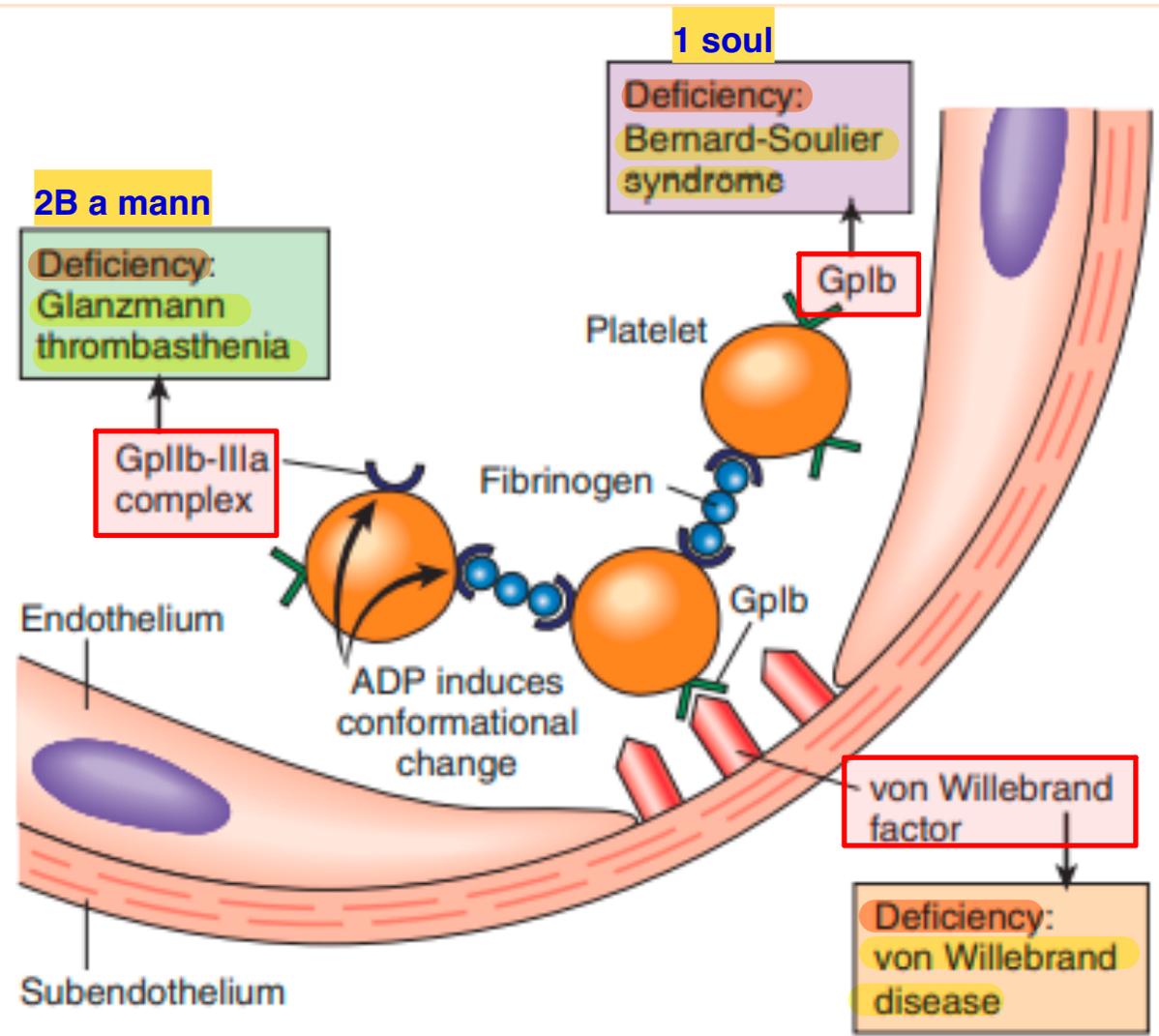
- An elevated level of breakdown products of fibrinogen (D-dimers) are a useful clinical markers of several thrombotic states



Endothelium

- The balance between the anticoagulant and procoagulant activities of endothelium often determines whether clot formation, propagation, or dissolution occurs.

- 1. Platelet inhibitory effects:
- serve as a barrier that shields platelets from subendothelial vWF and collagen.
- releases a number of factors that inhibit platelet activation and aggregation. Among the most important are prostacyclin (PGI₂), nitric oxide (NO).
- endothelial cells bind and alter the activity of thrombin, which is one of the most potent activators of platelets.
- 2. Anticoagulant effects.
- Normal endothelium shields coagulation factors from tissue factor in vessel walls and expresses multiple factors that actively oppose coagulation:
- most notably thrombomodulin, endothelial protein C receptor, heparin-like molecules, and tissue factor pathway inhibitor.



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