HEMODYNAMIC DISORDERS, THROMBOEMBOLISM, AND SHOCK 2

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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.

pathologic state

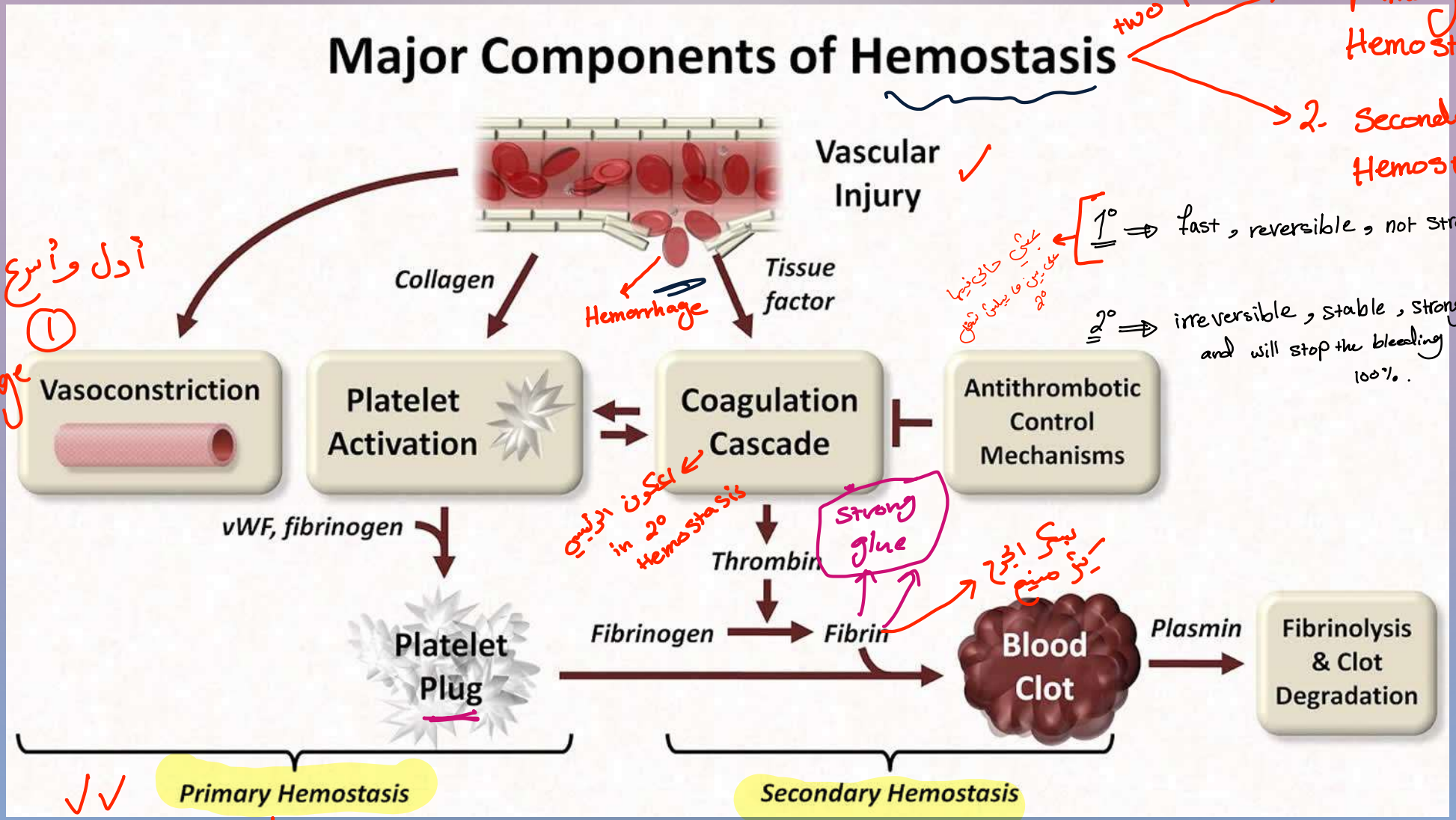
+ تكون clot وانا مش
حاجباني.

NORMAL HEMOSTASIS

1+2 +3 ← parameters ← بيطلعوا على 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



two phases
1- Primary Hemostasis.
2- Secondary Hemostasis.

1° ⇒ fast, reversible, not strong.

2° ⇒ irreversible, stable, strong and will stop the bleeding 100%.

1- Vasoconstriction
2- Platelet activation

MAJOR COMPONENT OF HEMOSTASIS

1. platelates
2. Clotting factors
3. Endothelium

THE GENERAL SEQUENCE OF EVENTS LEADING TO HEMOSTASIS AT A SITE OF VASCULAR INJURY INCLUDE:

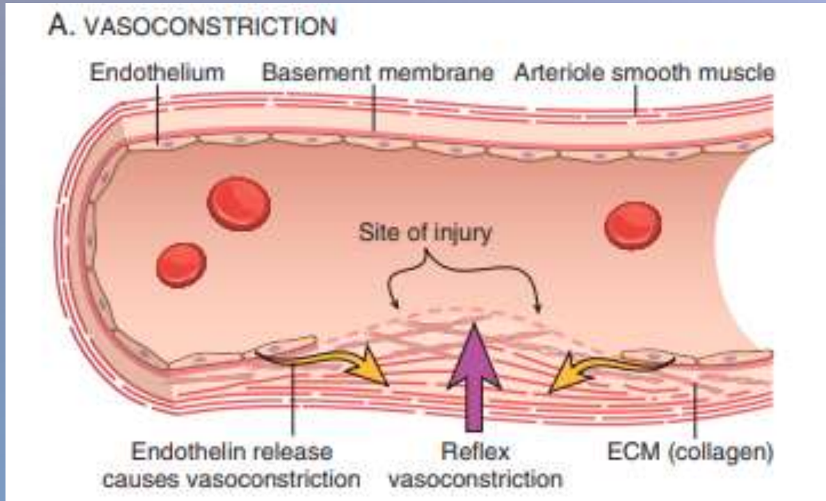
I . PRIMARY HEMOSTASIS

- 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.

VWF → Von Willebrand factor.

أقل ال Blood flow الواصل للمنطقة ← أسرع شي + first step

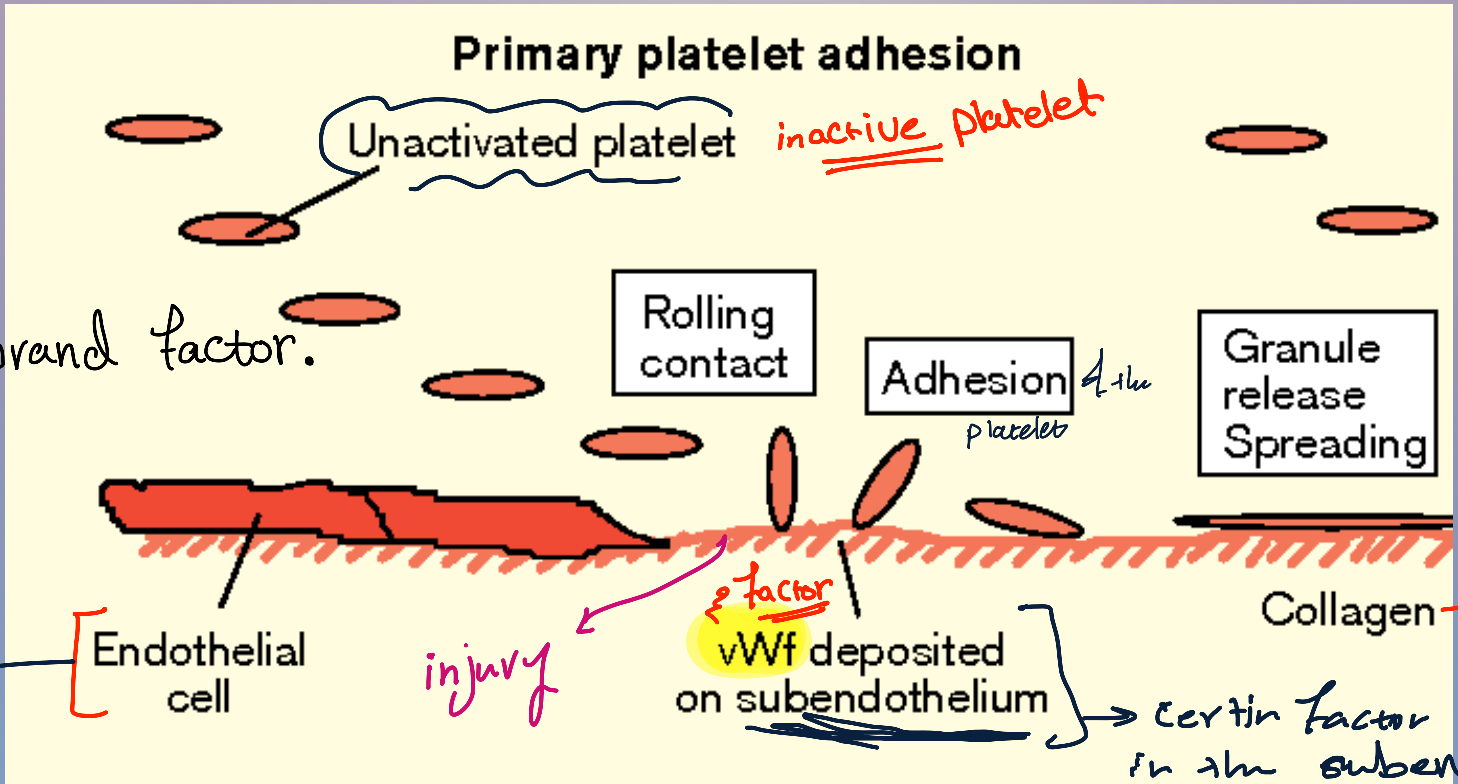
VWF → Von Willebrand factor.



- 2. PLATELET ACTIVATION

- THE FORMATION OF THE PLATELET PLUG.

VWF → Von Willebrand factor.



Collagen → بتشبك ال platelet بال collagen

vWf deposited on subendothelium → certin factor in the subendothelium (VWF)

Endothelial cell ← على شان تكون ال platelet inactive لازم يظل ال Endothelial cell intact (زابطا)

إذا فقدنا → subendothelium space فيه factor → هذا ال factor إذا شاف ال platelet → رح تكون و تعمل clot → activated

- PLATELETS

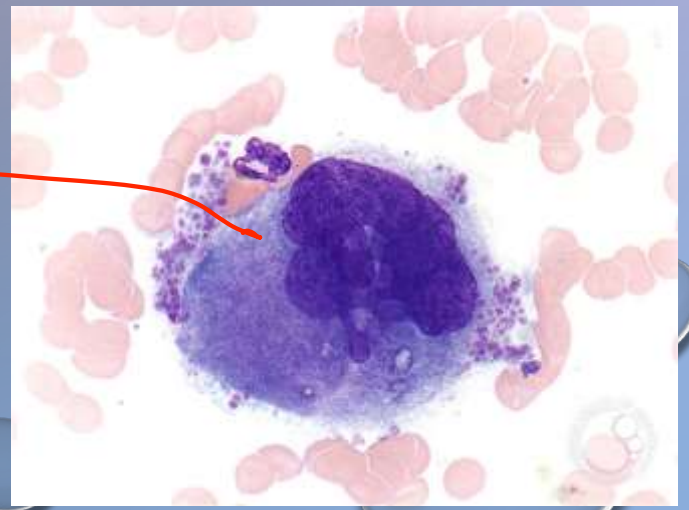
بتصلح / تغلق

- 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.

Megs

(Megakaryocyte)

الخلية المسئولة عن انتاج الـ platelet



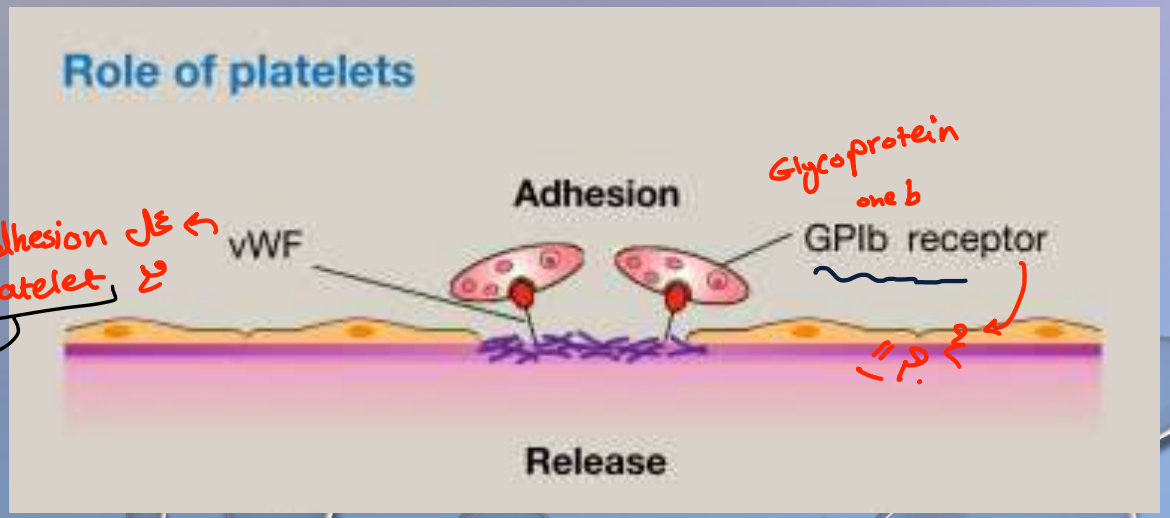
VWF → von Willebrand factor.

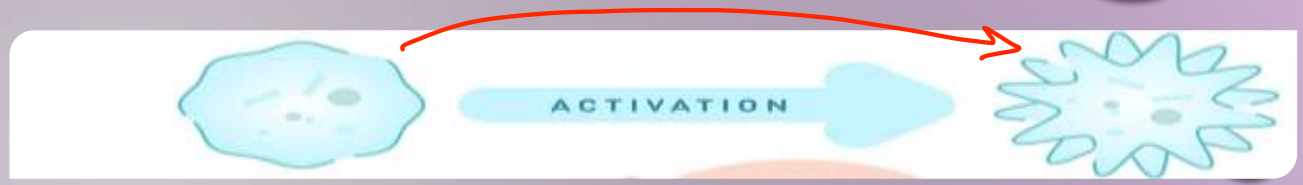
PLATELETS UNDERGO A SEQUENCE OF REACTIONS AFTER A TRAUMATIC VASCULAR INJURY THAT CULMINATE IN THE FORMATION OF A PLATELET PLUG

- 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.

VWF → Von Willeb

VWF → Von Willebrand factor.



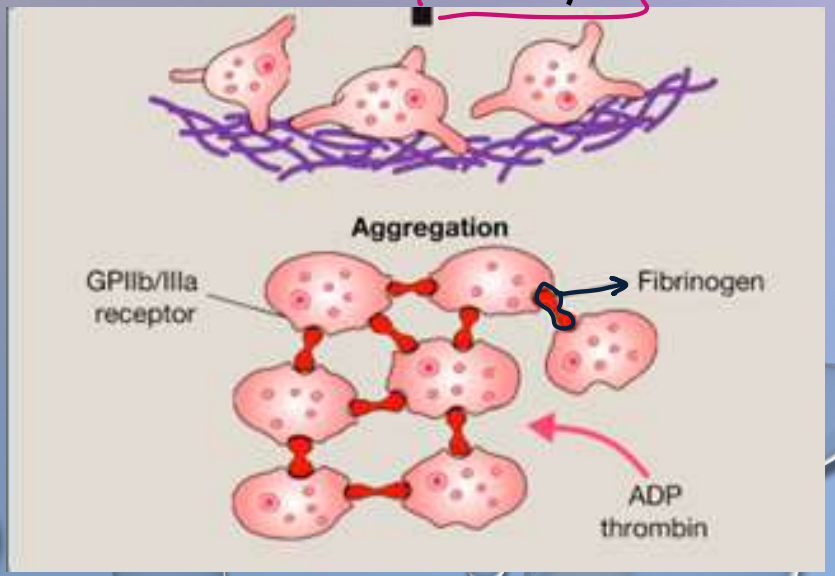


- **2.PLATELET ACTIVATION.**
  - A. CHANGES IN SHAPE from smooth discs to "spiky "with greatly increased surface area.
  - alterations in glycoprotein iib/iiia that increase its affinity for fibrinogen
  - the translocation of negatively charged phospholipids to the platelet surface
  - B. SECRETION OF GRANULE CONTENTS, e.g:
    1. ✓ THROMBIN: activates platelets
    2. ✓ ADP: create an additional rounds of platelet activation.
    3. ✓ THROMBOXANE A2 (TXA2): a potent inducer of platelet aggregation.

- 3. PLATELET AGGREGATION FOLLOWS THEIR ACTIVATION.

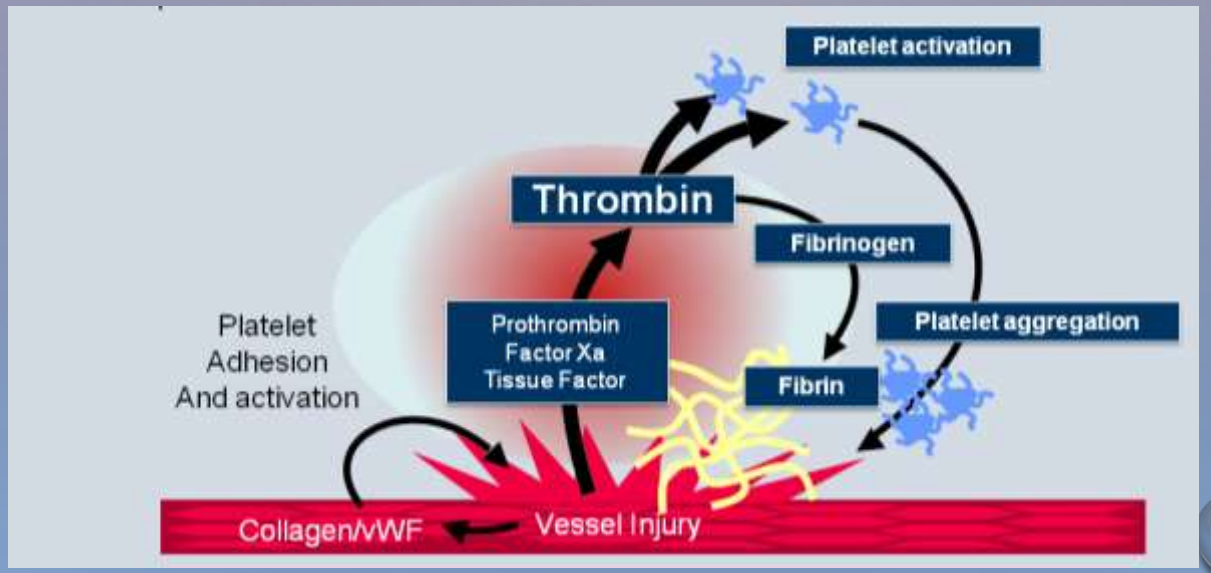
- The conformational change in glycoprotein iib/iiia allows binding of fibrinogen that forms bridges between adjacent platelets, leading to their aggregation.

- ✓ 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 CULIMINATES IN THROMBIN GENERATION.

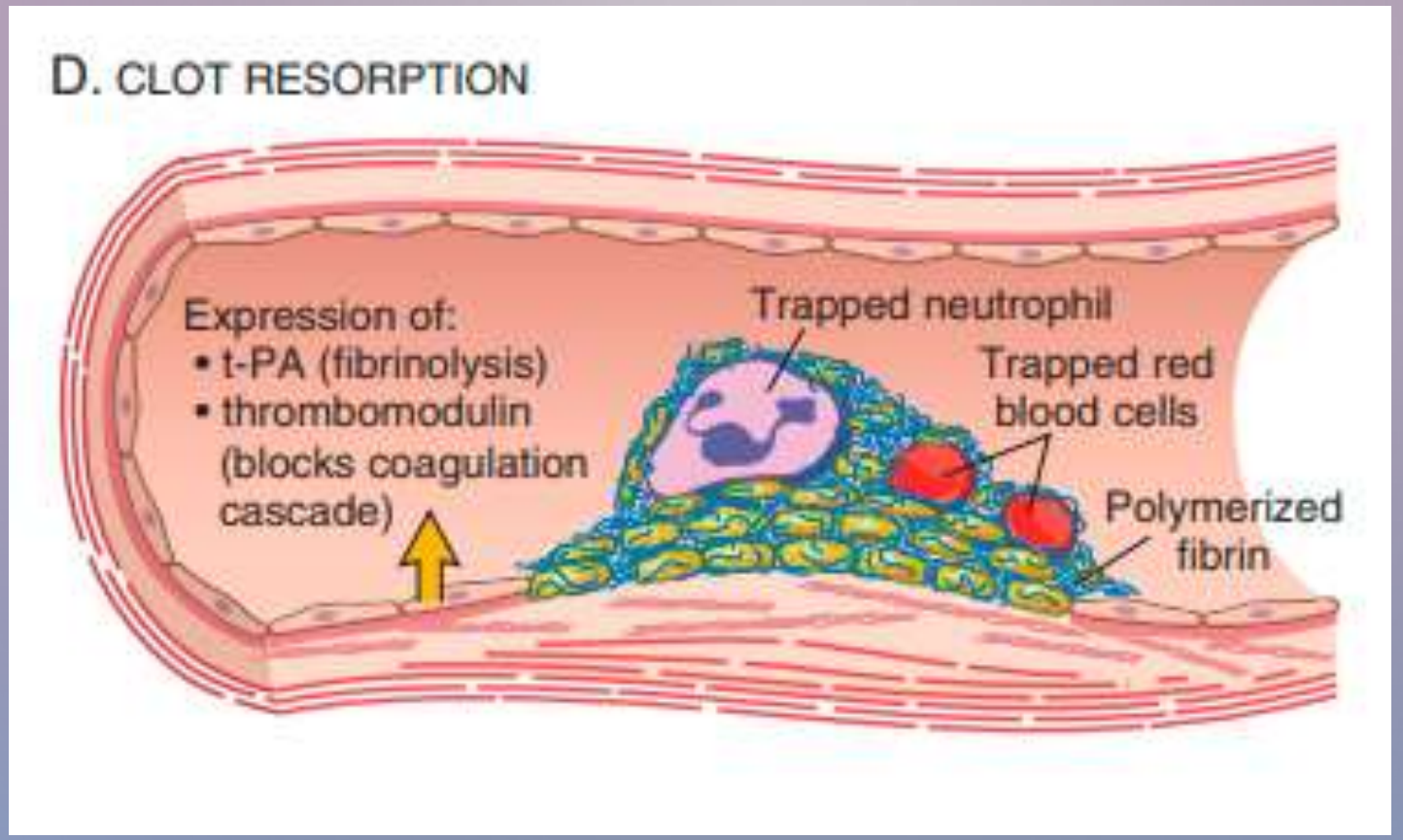


- III. CLOT STABILIZATION AND RESORPTION:
- polymerized fibrin and platelet aggregates undergo contraction to form a solid, permanent plug that prevents further hemorrhage.

- 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

يراقب عملية clot formation , بمنع تكونها في غير مكان site of injury

- at this stage, counterregulatory 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
Expression of:
• t-PA (fibrinolysis)
• thrombomodulin (blocks coagulation cascade)
Trapped neutrophil
Trapped red blood cells
Polymerized fibrin

COAGULATION CASCADE

- the coagulation cascade is a series of amplifying enzymatic reactions that lead to the deposition of an insoluble fibrin clot.

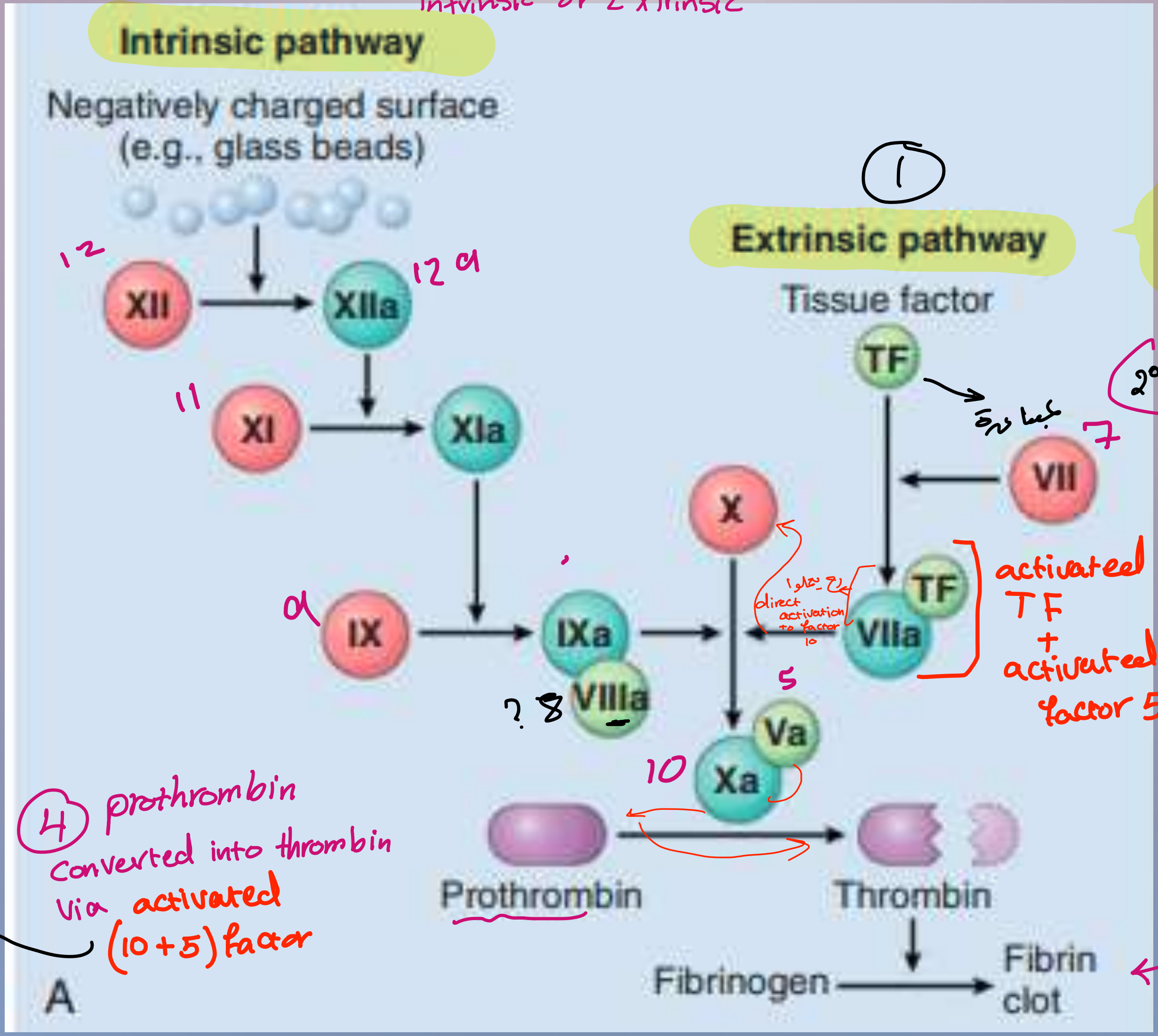
- each reaction step involves an enzyme (an activated coagulation factor), a substrate (an inactive proenzyme form of a coagulation factor), and a cofactor (a reaction accelerator).

- these components are assembled on a negatively charged phospholipid surface, which is provided by activated platelets. assembly of reaction complexes also depends on calcium

PTT

PT

② معرفة نوع factor
intrinsic or Extrinsic



* يحدث ال bleeding
إذا لم يتكون clot ....
ليش ما تكون clot ؟!
إذا هناك مشكلة بال 1° أو 2° Hemostasis

من الحالة = العرفة لي 1° ← platelets
بروح بطلب فحص platelet count in CVC
على فرض طلعت الامور كلو تمام بطلب فحص خاص بال 2°

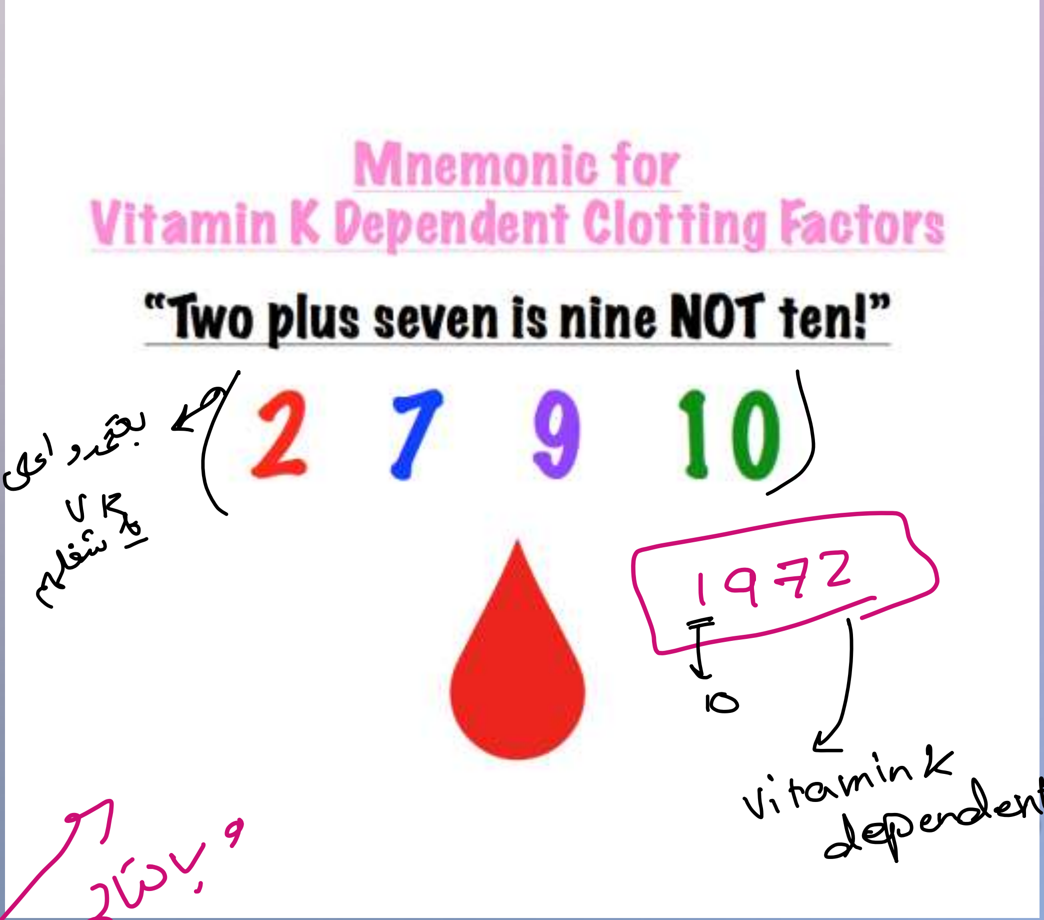
* 2° ⇐ بطلب certin test بقيس ال factors الموجودة بال intrinsic + Extrinsic pathway
* فحص التجلط PTT ← intrinsic pathway
* PT ← بقيس Extrinsic pathway

① in 2° Hemostasis I need fibrin
② fibrin comes from fibringen through thrombin
③ thrombin come from prothrombin

وبالتالي بنقدر نحكي انه ال Coagulation cascade فيه 2 branch

Extrinsic pathway ↓ بدايته Tissue factor في subendothelial space

Intrinsic pathway ↓ بدايته مع factor 12 ← 11 ← 9 ← 10



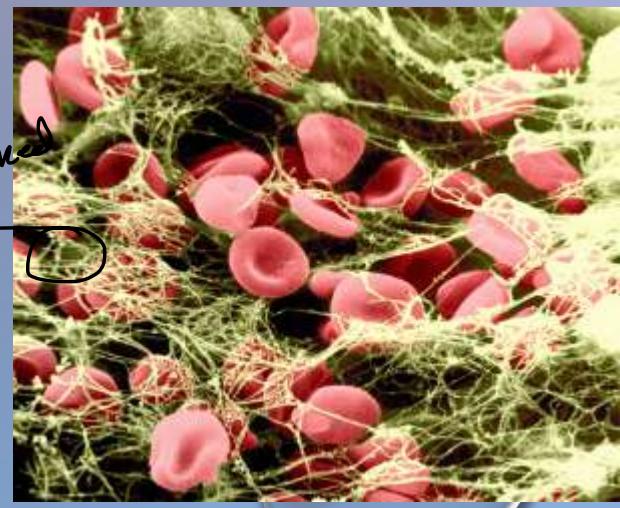
vitamin K antagonists

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.

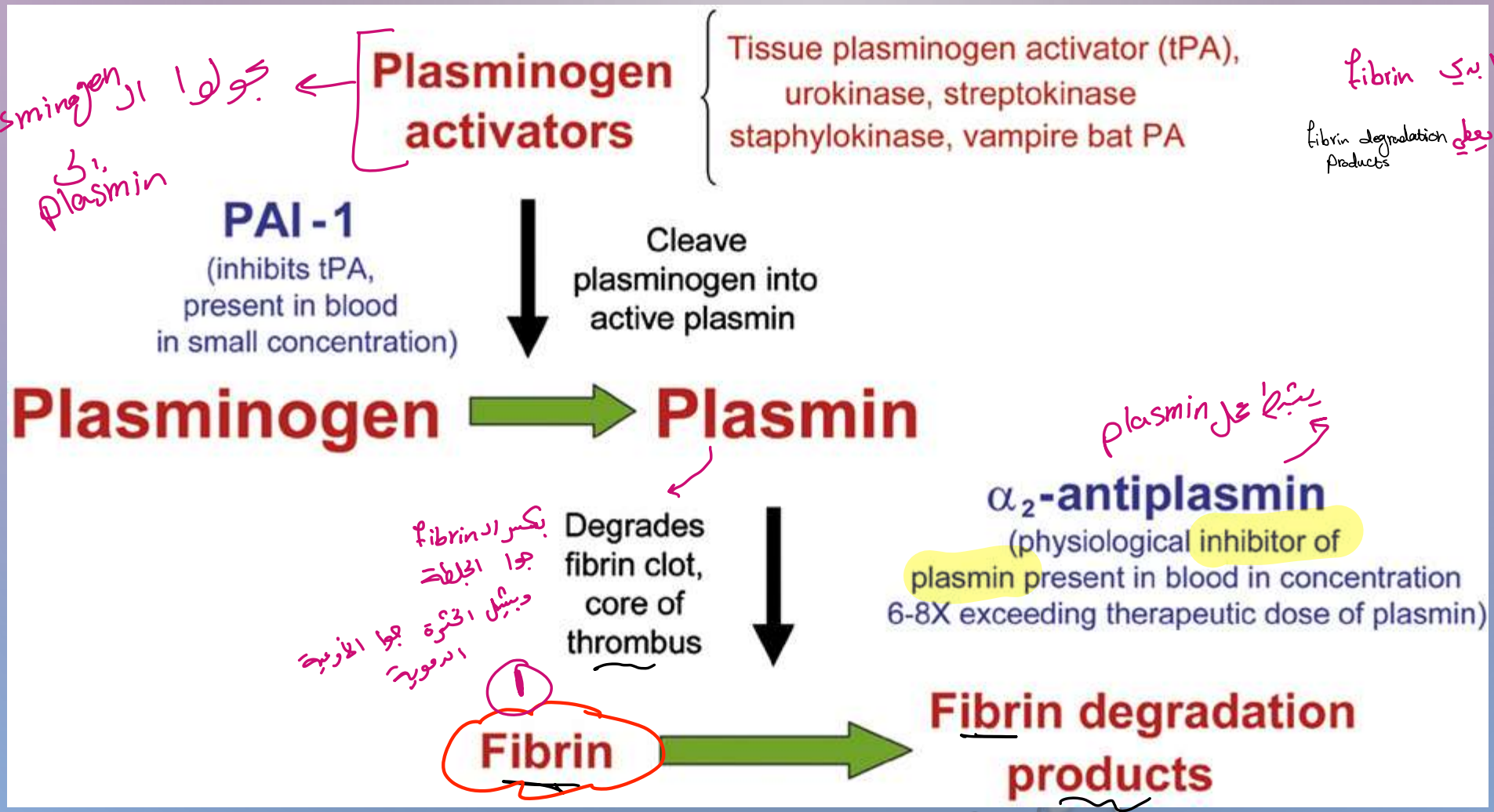


FACTORS THAT LIMIT COAGULATION.

- 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: most effective
- 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

D-Dimer
(fibrin degradation product)

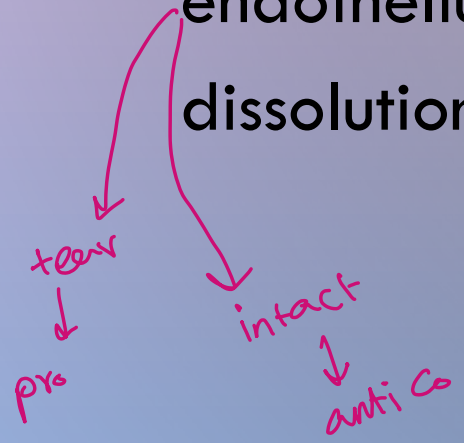
D-Dimer test

إذا كان عندي
يعني اعرفين كان فيه
تكسر وانحطام fibrin
بكمية كبيرة D-Dimer

رجله اليمين متورمة وحمرا وساخنة
وعندي thrombus

ENDOTHELIUM

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



+ Mechanisims help endothelium to act as anticoagulant:

- 1.PLATELET INHIBITORY EFFECTS:

✓ serve as a barrier that shields platelets from subendothelial vwf and collagen.

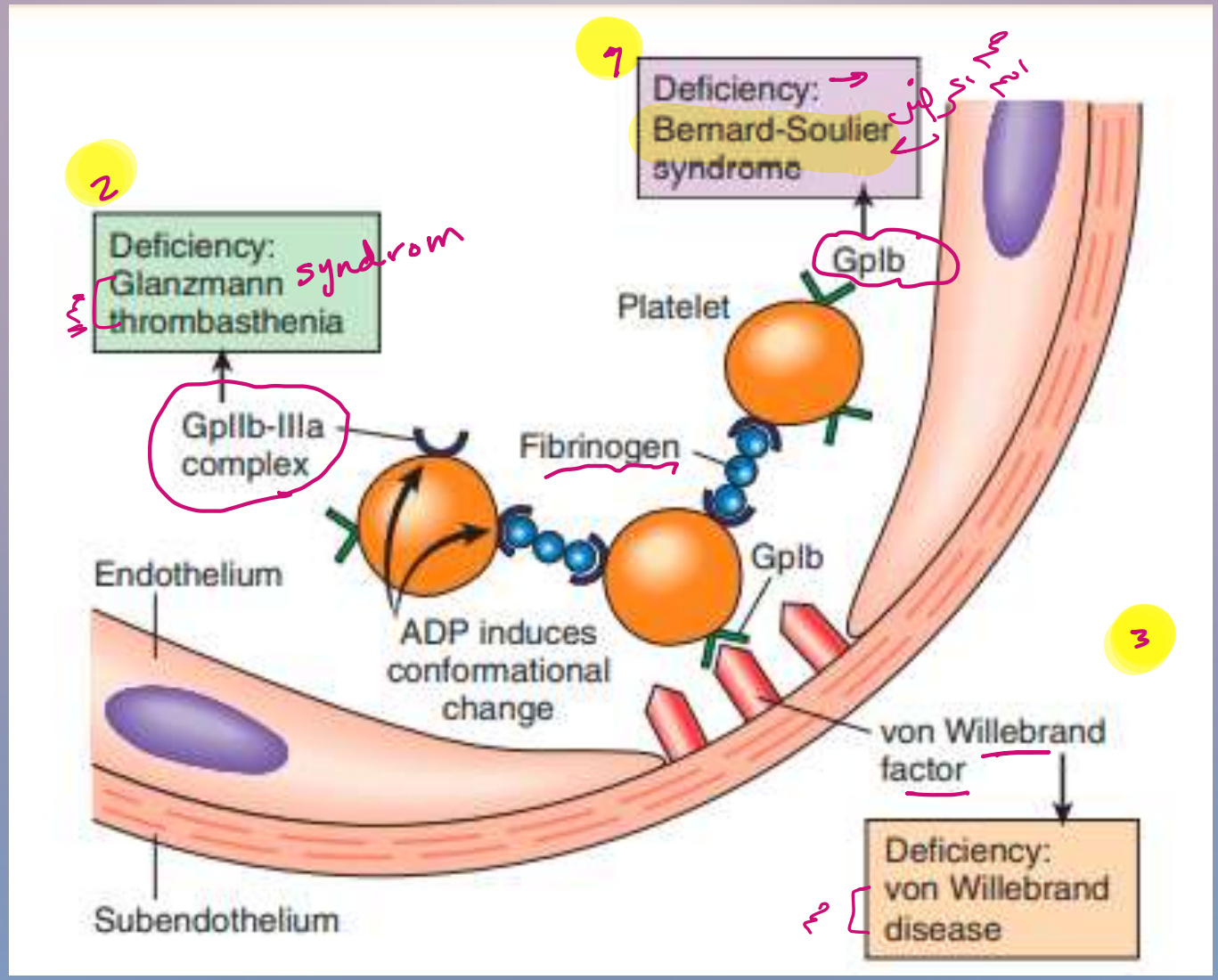
✓ releases a number of factors that inhibit platelet activation and aggregation. among the most important are prostacyclin (pgi2), nitric oxide (no).

✓ 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.


1
Deficiency:
Bernard-Soulier
syndrome
2
Deficiency:
Glanzmann
thrombasthenia
GpIb
Platelet
GpIIb-IIIa
complex
Fibrinogen
GpIb
Endothelium
ADP induces
conformational
change
3
von Willebrand
factor
Deficiency:
von Willebrand
disease
Subendothelium