HEMODYNAMIC DISORDERS, THROMBOEMBOLISM, AND SHOCK 2

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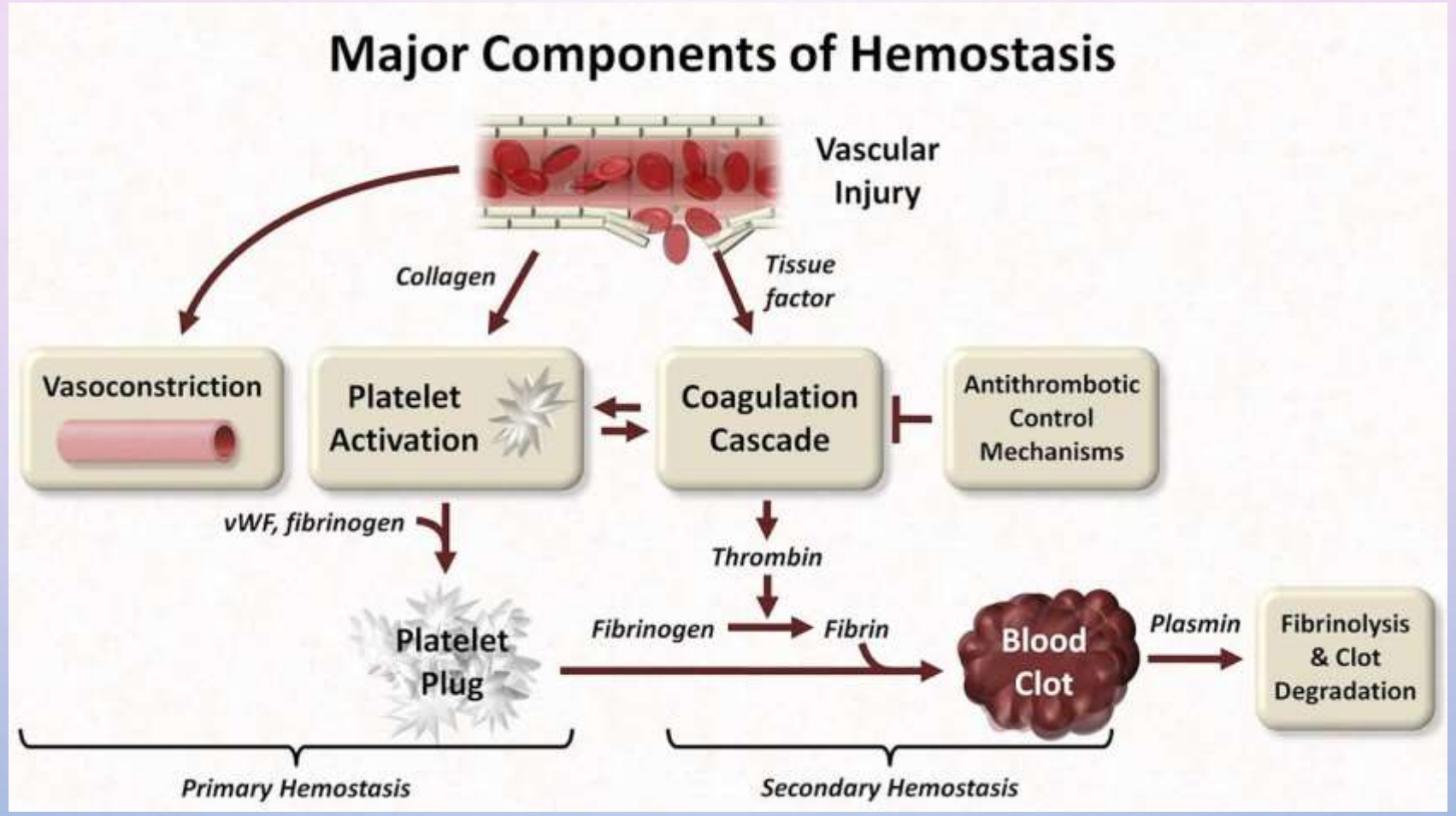
HEMOSTASIS AND THROMBOSIS

- 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.

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.

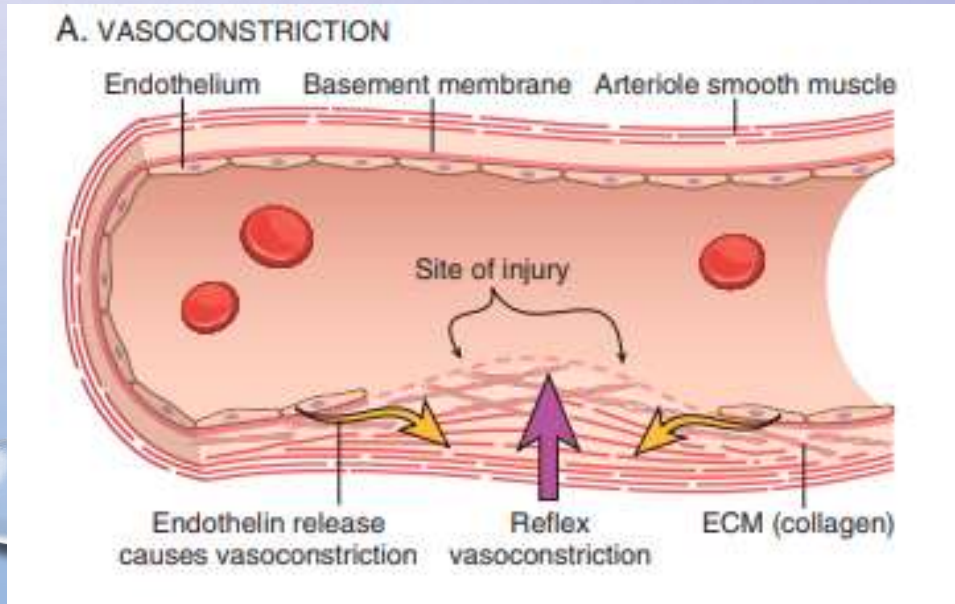

Major Components of Hemostasis
Vascular Injury
Collagen
Tissue factor
Vasoconstriction
Platelet Activation
Coagulation Cascade
Antithrombotic Control Mechanisms
vWF, fibrinogen
Thrombin
Platelet Plug
Fibrinogen
Fibrin
Blood Clot
Plasmin
Fibrinolysis & Clot Degradation
Primary Hemostasis
Secondary Hemostasis

MAJOR COMPONENT OF HEMOSTASIS

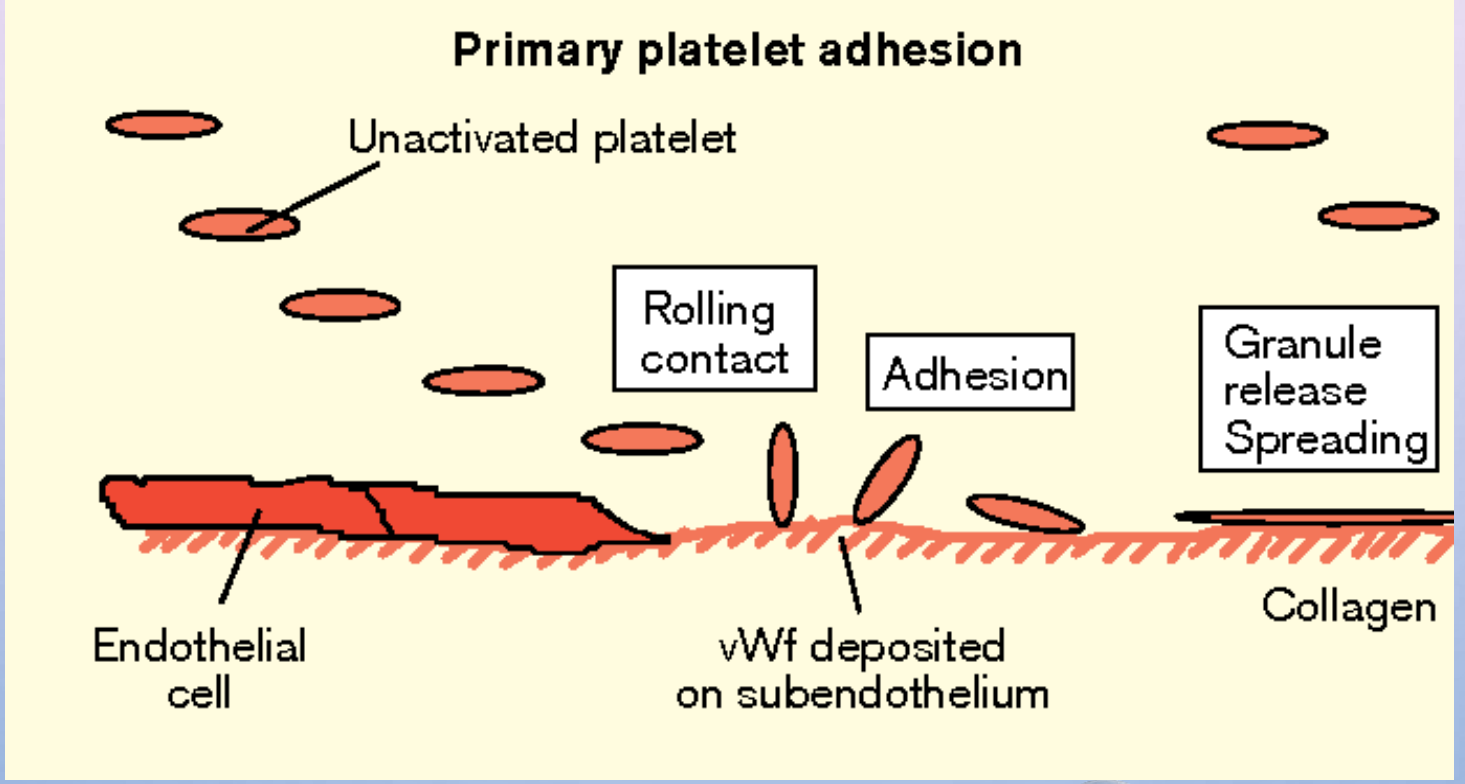
1. platelates
2. Clotting factors
3. Endothelium

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.

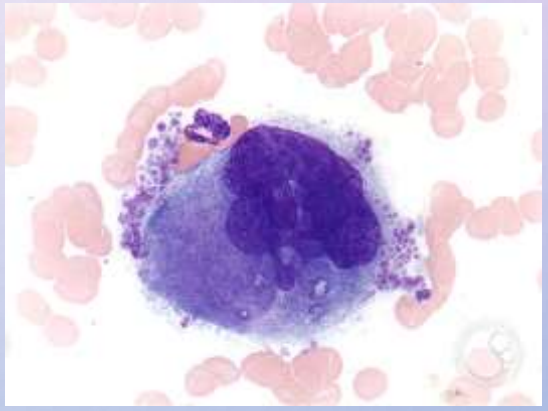


- **2. PLATELET ACTIVATION**
- THE FORMATION OF THE PLATELET PLUG.



- PLATELETS

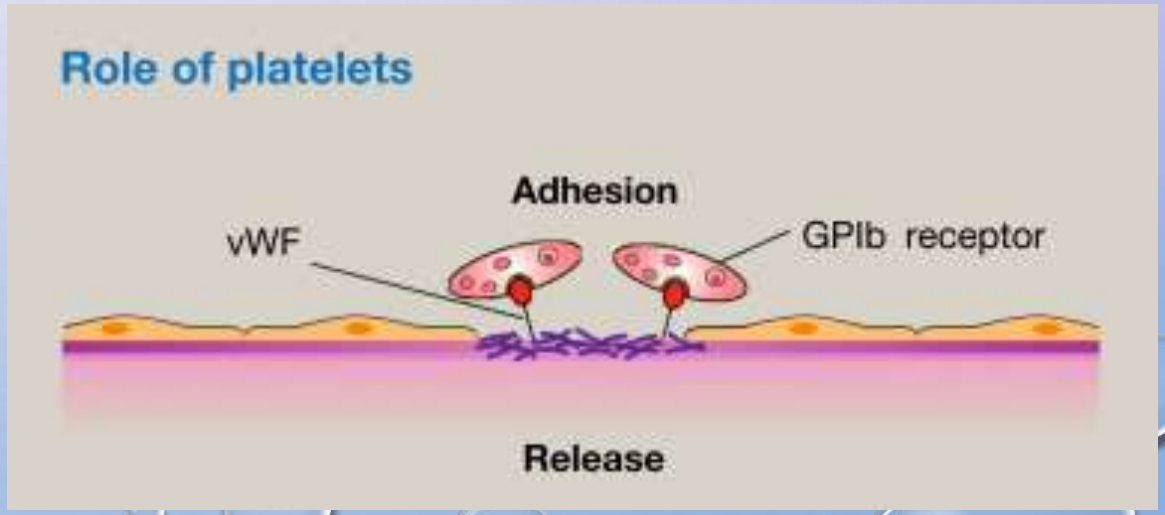
- platelets play a critical role in hemostasis by forming the primary plug that initially seals vascular defects and by providing a surface that binds and concentrates activated coagulation factors.
- platelets are disc-shaped anucleate cell fragments that are shed from megakaryocytes in the bone marrow into the bloodstream.



- Their function depends on several factors including:
- Glycoprotein receptors.
- A contractile cytoskeleton
- Awo types of cytoplasmic granules.
- α-granules have the adhesion molecule p-selectin, and contain proteins involved in coagulation.
- dense (or δ) granules contain ADP and 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

- B. SECRETION OF GRANULE CONTENTS, e.g:

✓ THROMBIN: ACTIVATES PLATELETS

✓ ADP: CREATE AN ADDITIONAL ROUNDS OF PLATELET ACTIVATION.

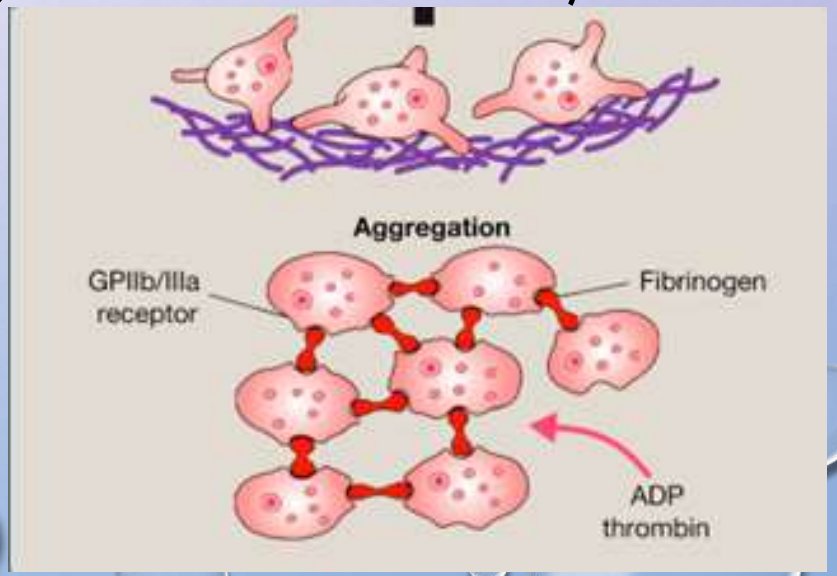
✓ THROMBOXANE A2 (TXA2): A POTENT INDUCER OF PLATELET AGGREGATION.

- 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.

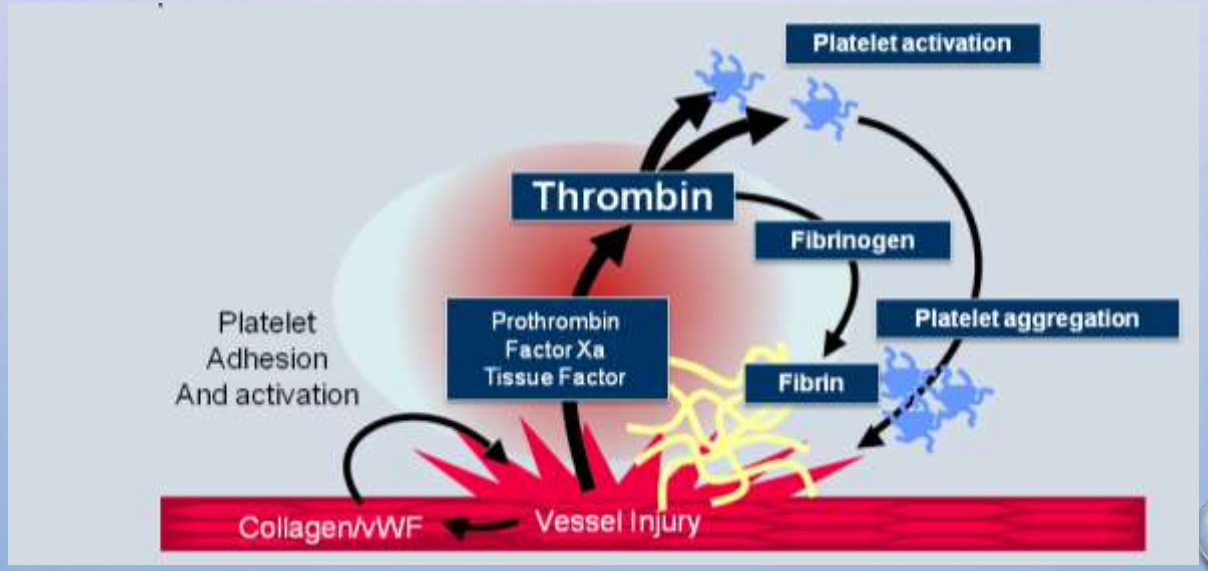
✓fibrinogen cause reversible aggregation

✓thrombin cause irreversible aggregation (converts fibrinogen into insoluble fibrin).

✓cytoskeleton cause contraction of the plug.



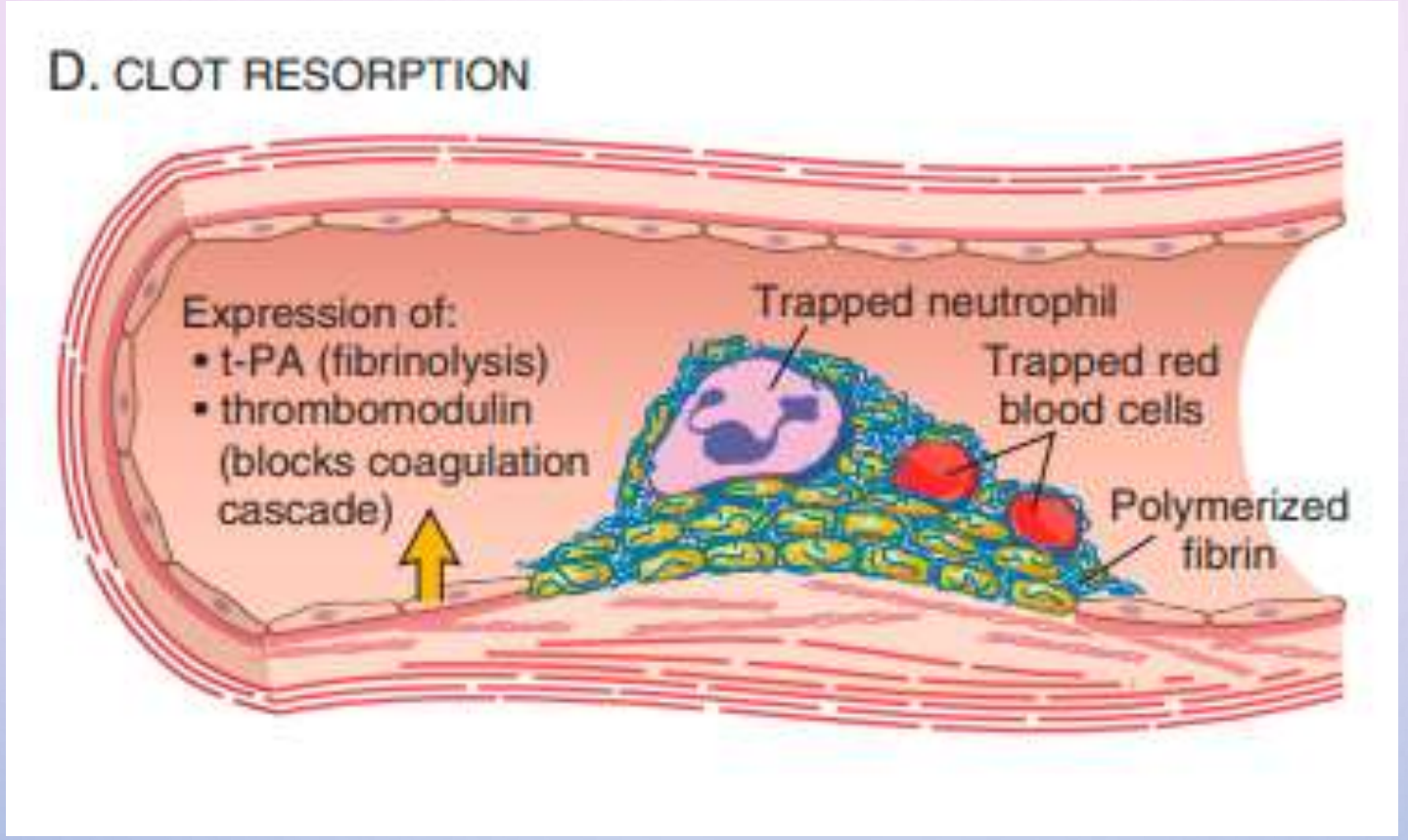
- II .SECONDARY HEMOSTASIS:
- DEPOSITION OF FIBRIN.
- VASCULAR INJURY EXPOSES TISSUE FACTOR AT THE SITE OF INJURY.
- TISSUE FACTOR BINDS AND ACTIVATES FACTOR VII , SETTING IN MOTION A CASCADE OF REACTIONS THAT CULIMINATES IN THROMBIN GENERATION.



- 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

- 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

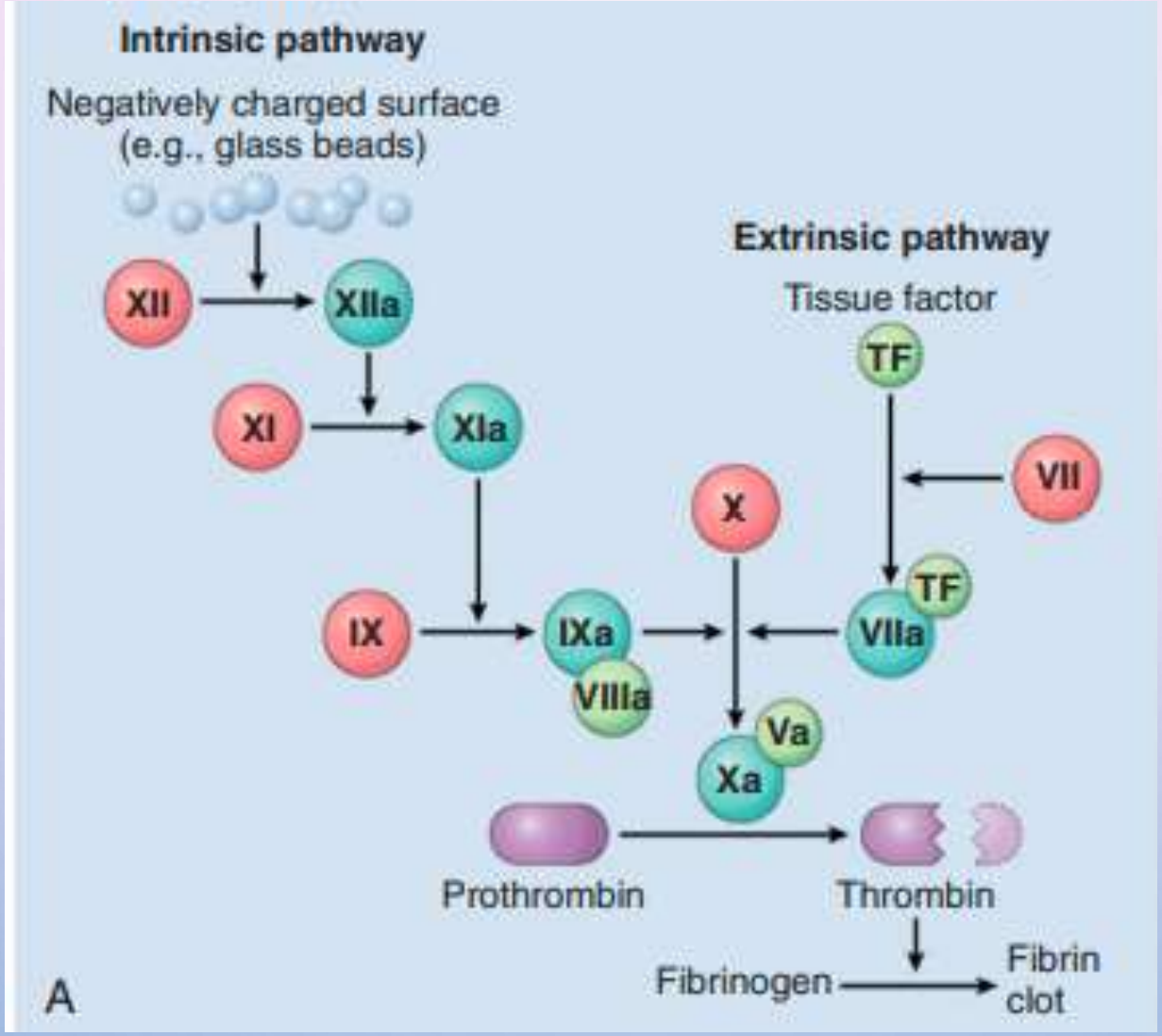
COAGULATION CASCADE

- 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


Intrinsic pathway
Negatively charged surface
(e.g., glass beads)
XII
XIIa
XI
XIa
IX
IXa
VIIIa
Extrinsic pathway
Tissue factor
TF
VII
X
TF
VIIa
Va
Xa
Prothrombin
Thrombin
Fibrinogen
Fibrin
clot
A

PT

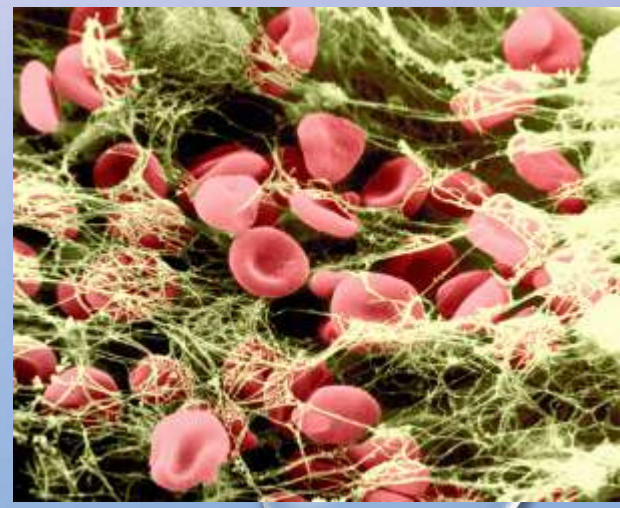
vitamin K antagonists

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.

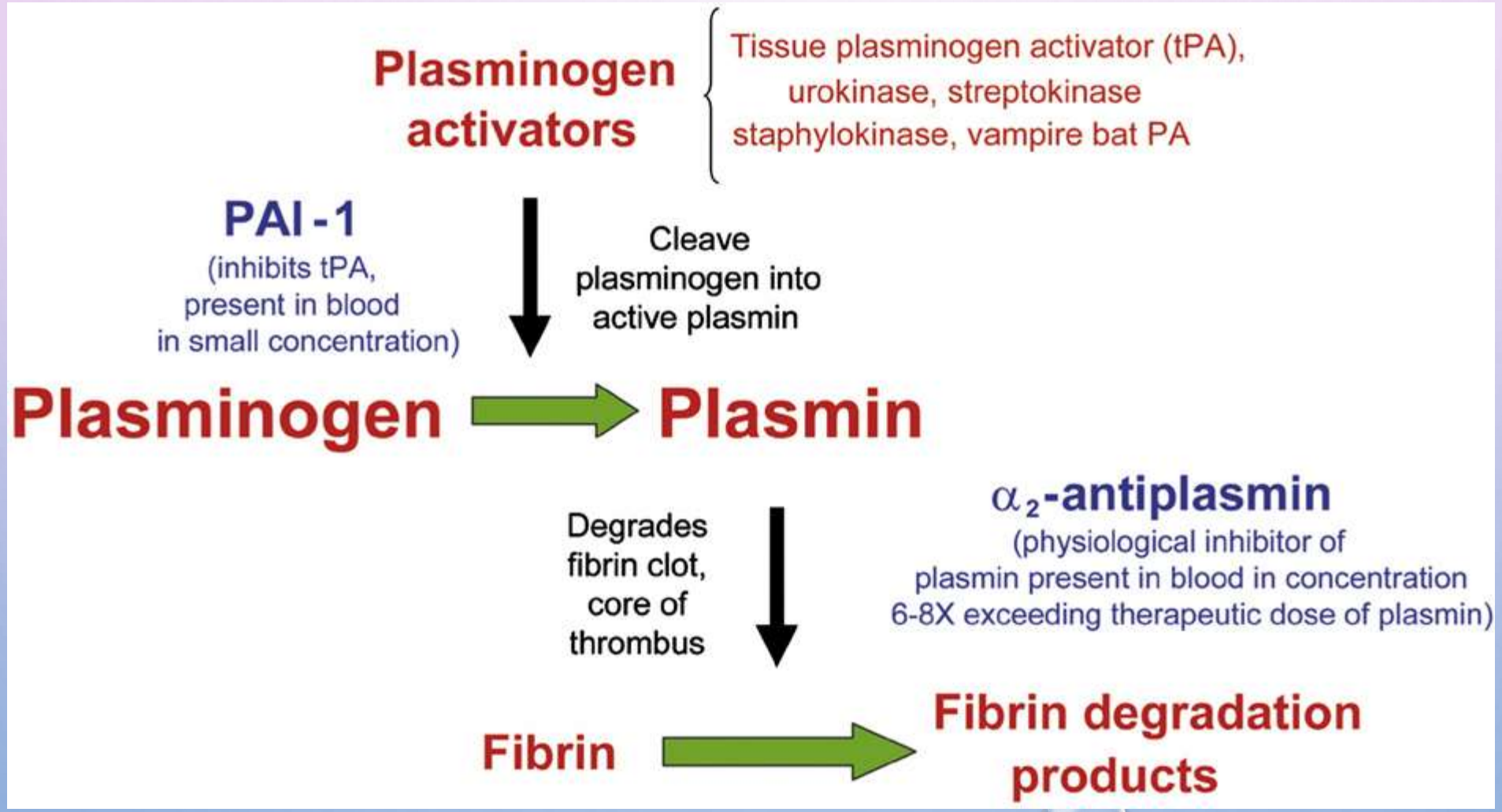


FACTORS THAT LIMIT COAGULATION.

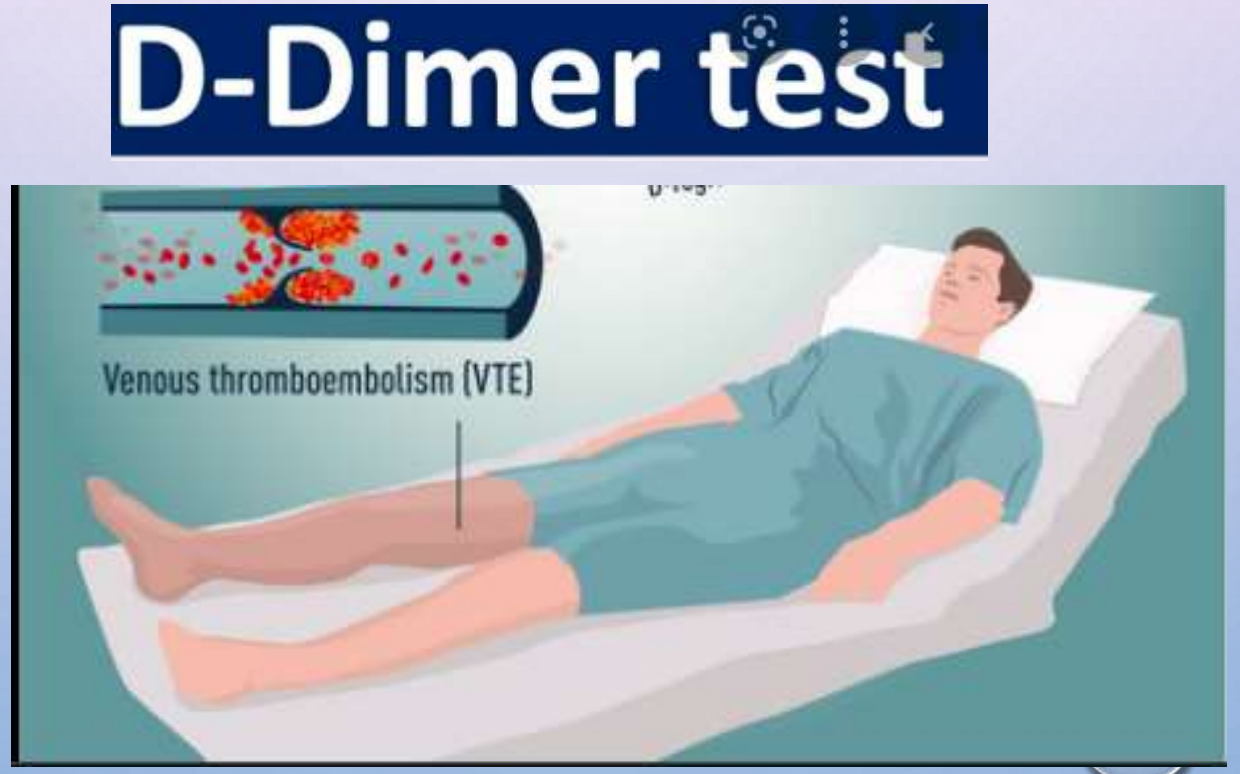
- COAGULATION MUST BE RESTRICTED TO THE SITE OF VASCULAR INJURY TO PREVENT DANGEROUS CONSEQUENCES THROUGH:

- 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:
- 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:

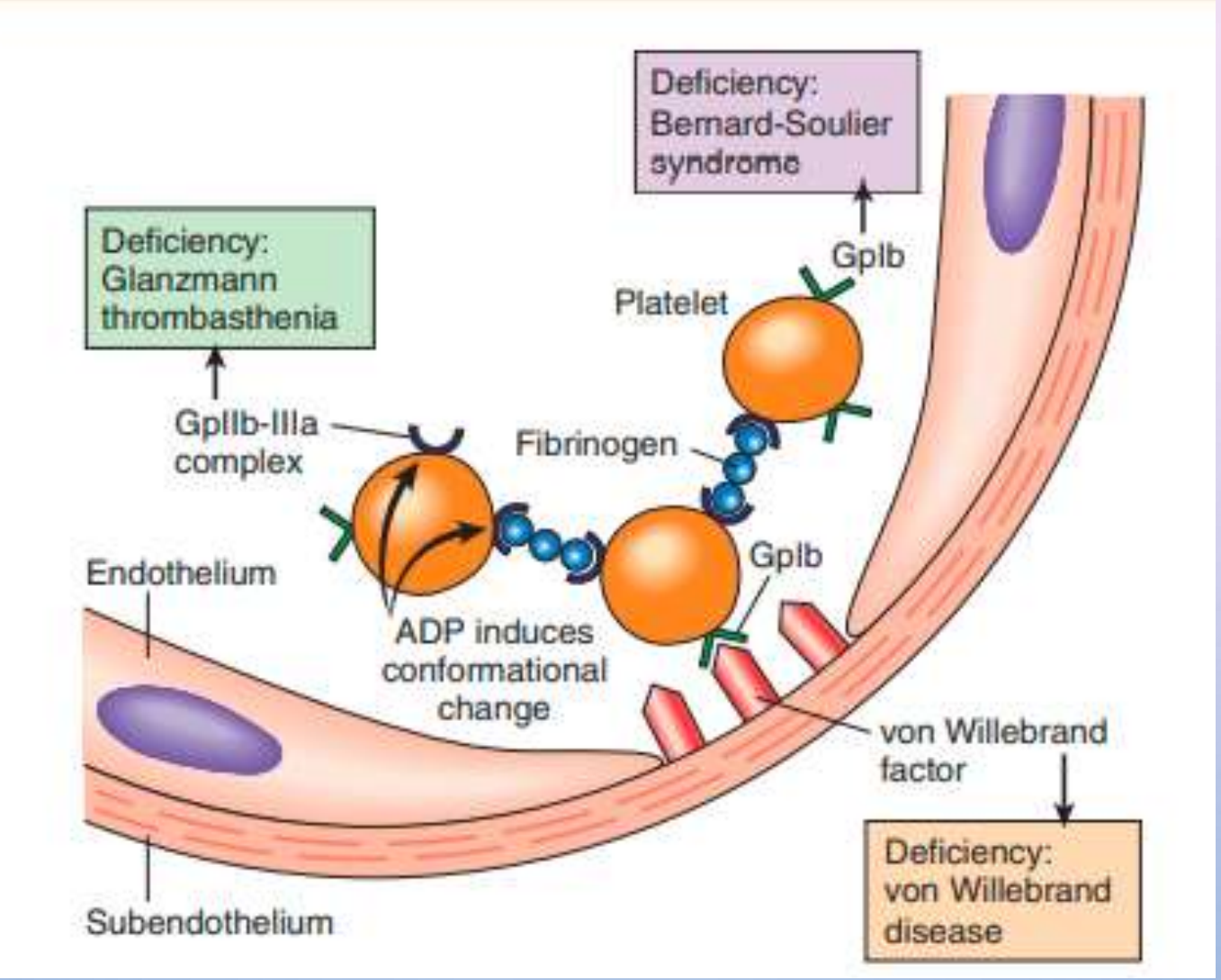
✓ SERVE AS A BARRIER THAT SHIELDS PLATELETS FROM SUBENDOTHELIAL VWF AND COLLAGEN.

✓ 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.


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