Pathophysiology-Blood Coagulation

Faculty of Pharmaceutical Sciences

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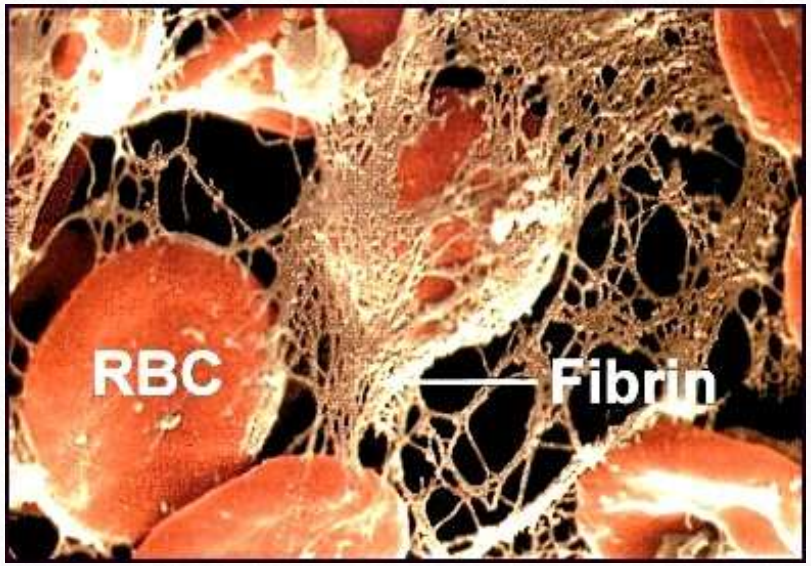
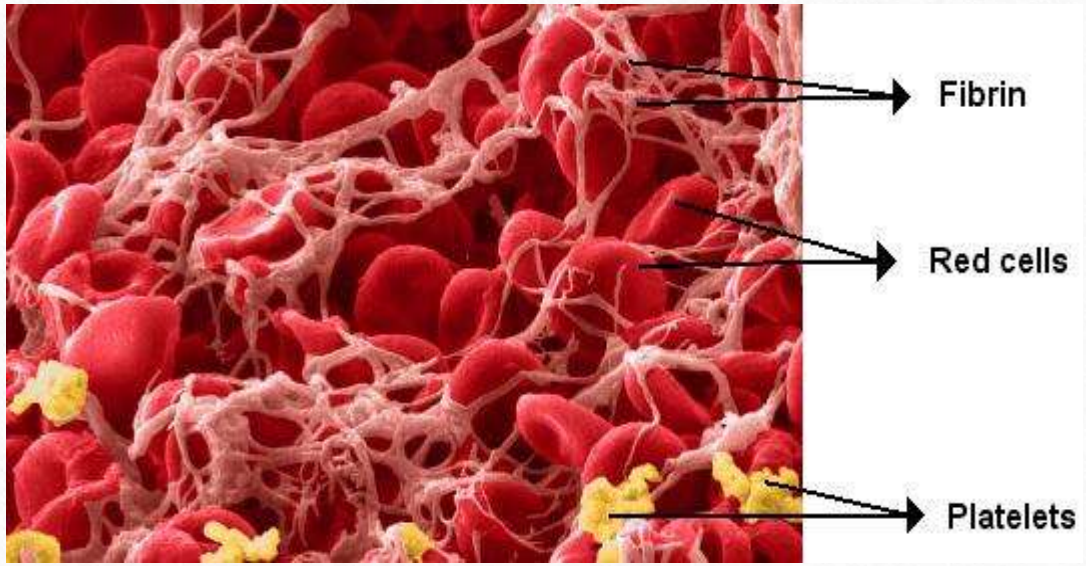
HAEMOSTASIS





Haemostasis

* The term ***haemostasis*** means prevention of blood loss.

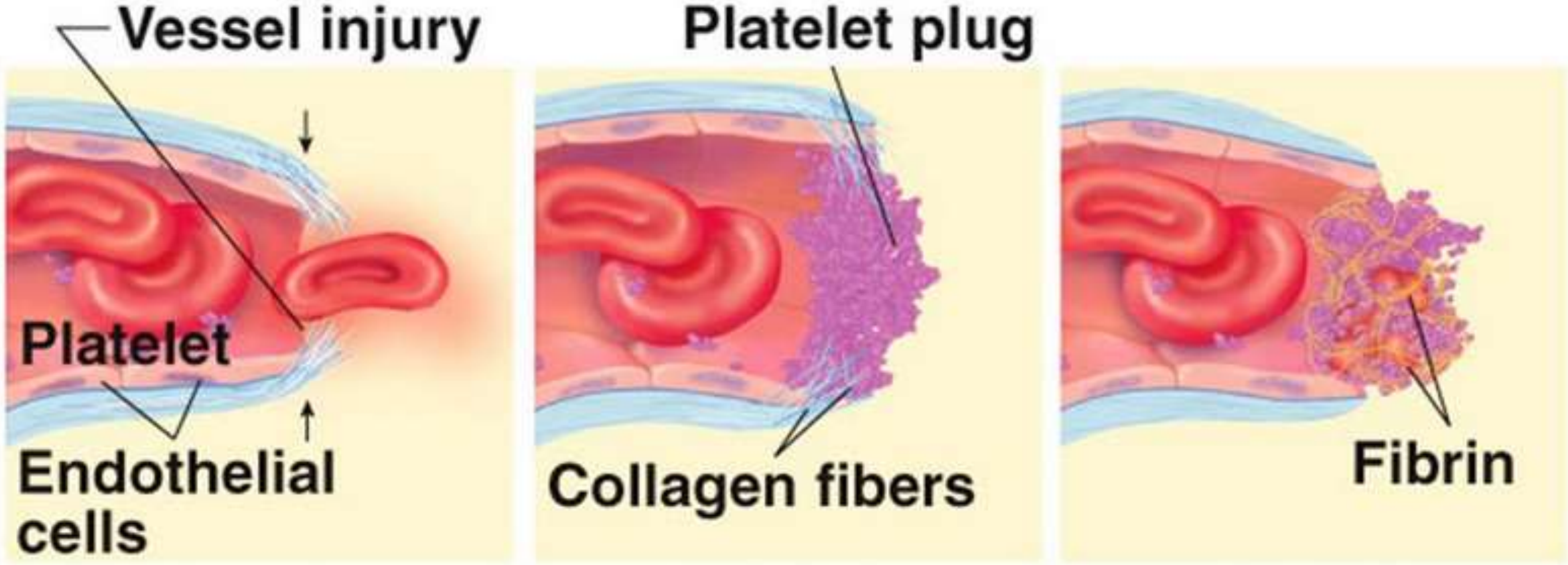
* **Haemostasis** is the process of forming clots in the walls of damaged blood vessels and preventing blood loss while maintaining blood in a fluid state within the vascular system.

إيقاف النزيف وفي الوقت نفسه الحفاظ على التدفق الطبيعي للدم

Mechanism

Haemostasis involves 4 main steps:

1. Vascular spasm. (تشنج) → vasoconstriction
2. Platelets reaction. → adhesion
3. Formation of the platelet plug. → aggregation
3. Blood coagulation. → coagulation cascade


Vessel injury
Platelet
Endothelial cells
Vascular spasm
(a)
Platelet plug
Collagen fibers
Platelet plug formation
(b)
Fibrin
Blood clotting
(c)

I-Vascular spasm → Vasoconstriction

- A vasospasm is the narrowing of the arteries caused by a persistent (مستمر) contraction of the blood vessels, which is known as vasoconstriction.

- Reduces the flow of blood from an injured vessel. → by reduces diameter

Cause: → (Vascular spasm) أسباب حدوث

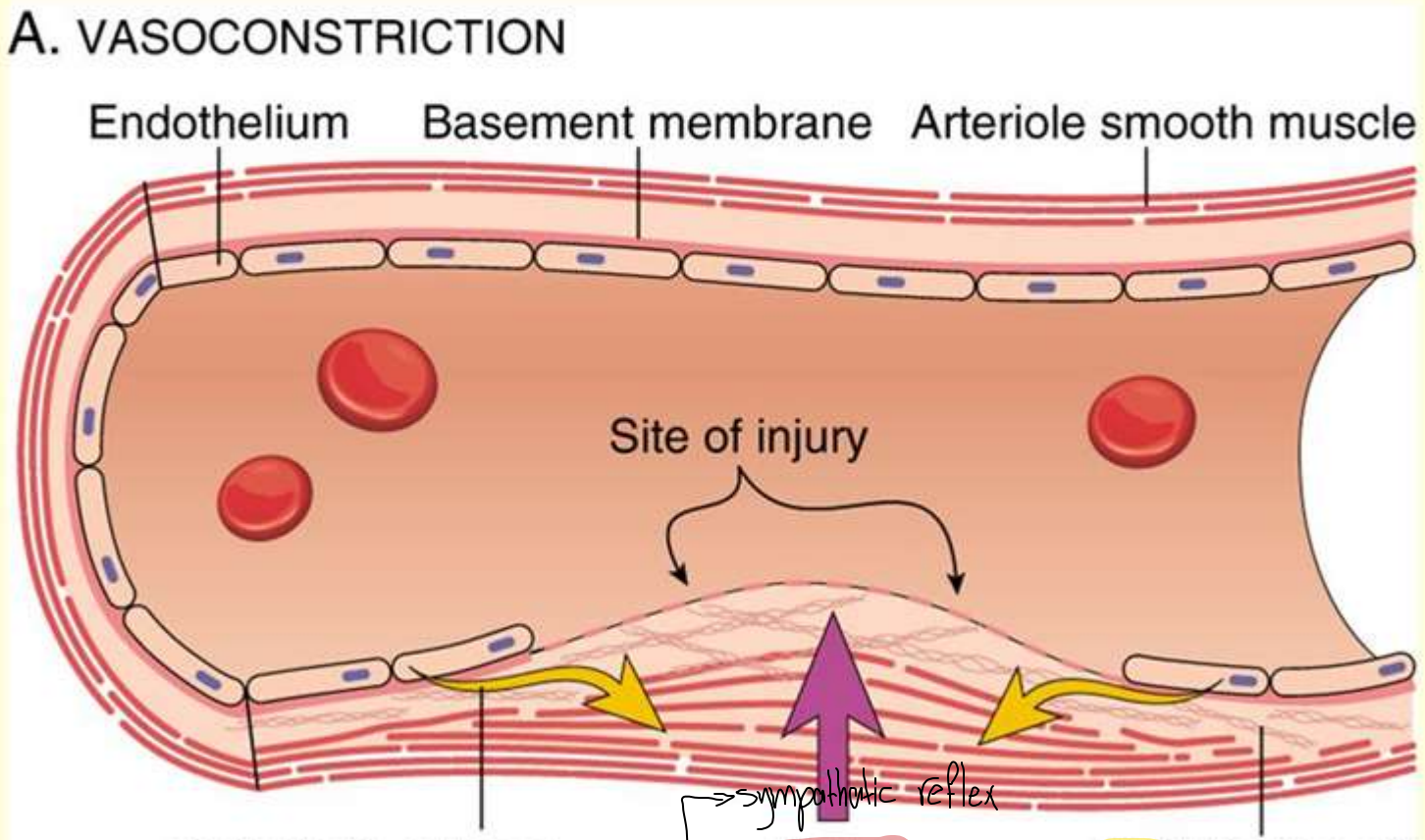
1- Sympathetic reflex. ⇒ (sympathetic) ← يرسل إشارات تحفز smooth muscle على الانقباض ← الوعاء الدموي يرسل إشارات إلى

2- Release of vasoconstrictors (TXA$_2$ and serotonin) from platelets that adhere to the walls of damaged vessels.

← تروميكسان

← يحفز على انقباض الوعاء الدموي المتضرر

Vascular spasm



↳ From endothelial cell causes vascular spasm by bind with receptor on endothelium

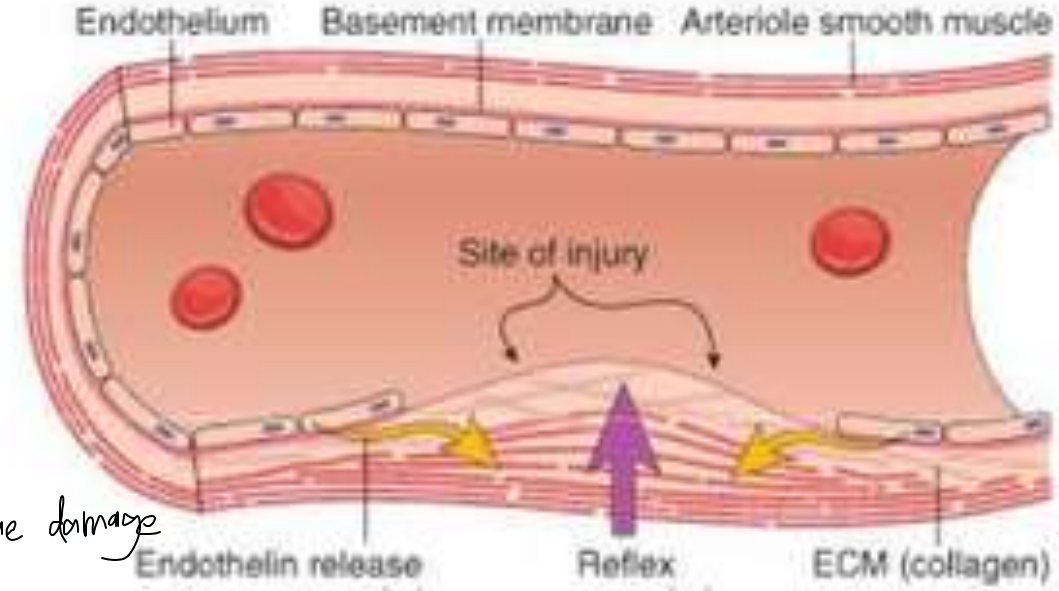
بسبب تمزق endothelium يؤدي إلى انكشاف collagen على السطح

platlet يلتصق بال

1. Vascular spasm

- Trauma to the vessel wall results in smooth muscle contraction
- Contraction caused by
  - Local myogenic spasm
  - Factors released from the injured vessel wall (endothelin and serotonin)
  - Nervous reflexes

↳ from tissue damage and platlet



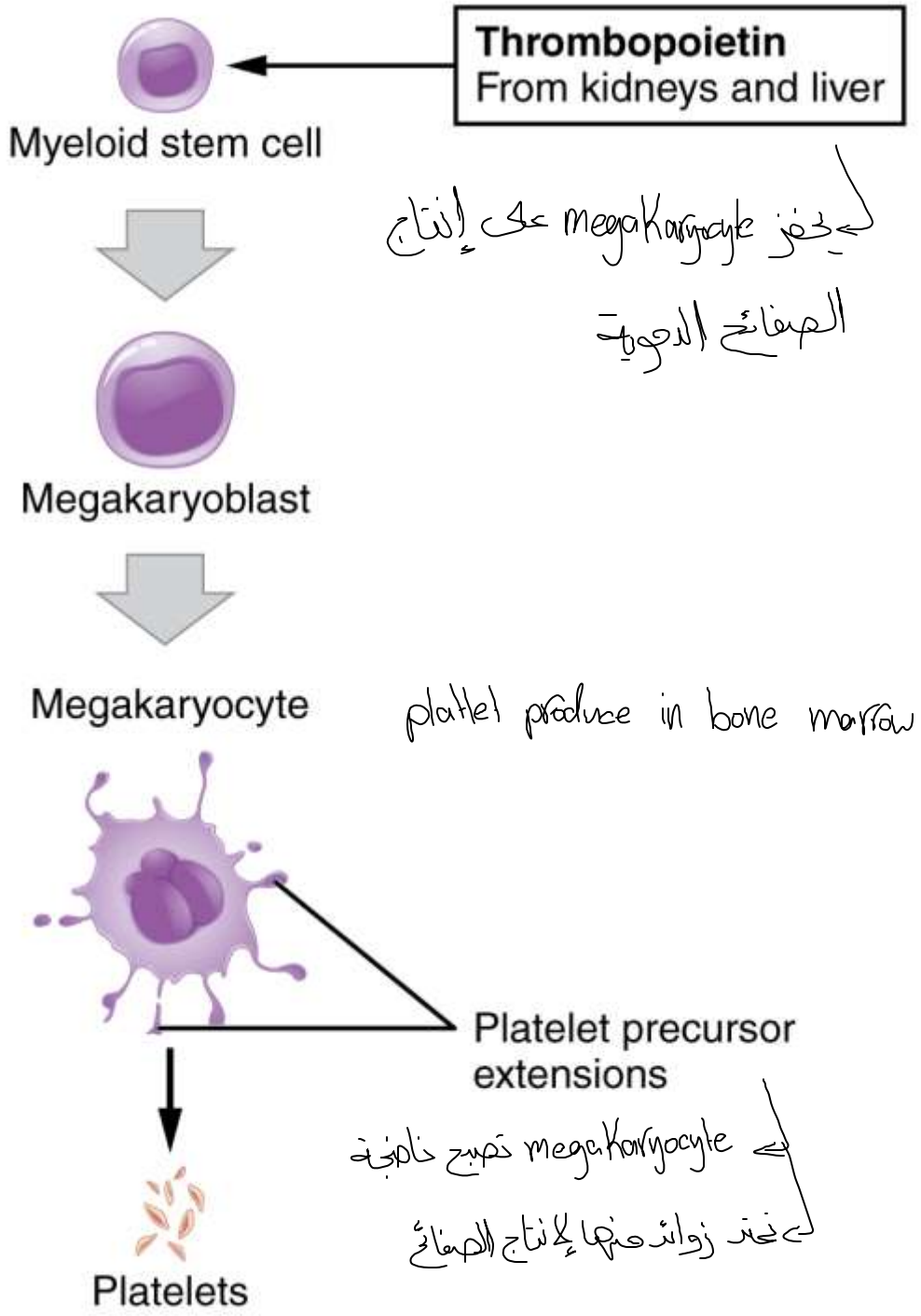
سنأثر مؤقت

Vasoconstriction is a transient effect and cannot cause long term cessation of bleeding

II- Platelet plug formation

Mechanism:

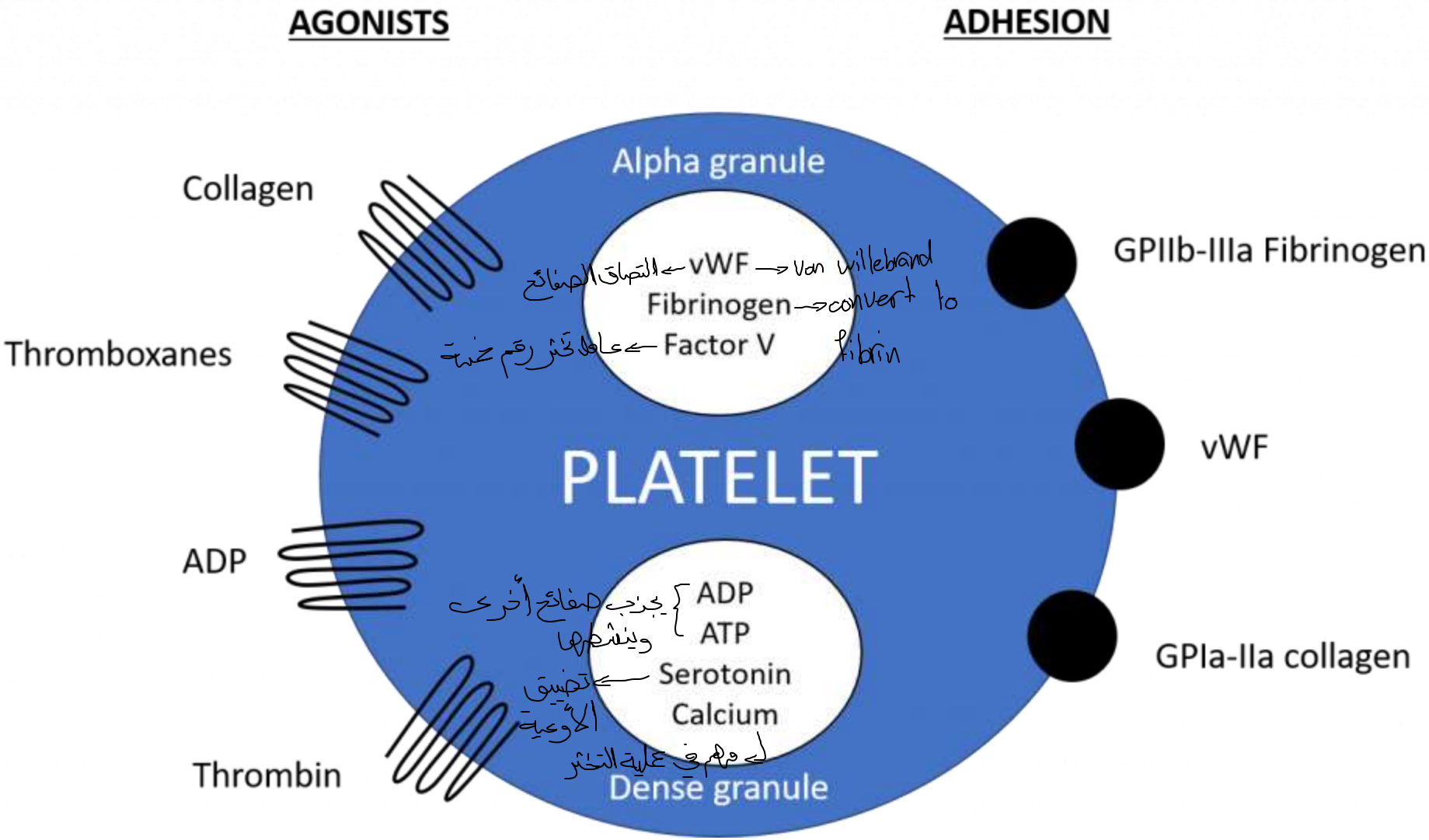
- **Platelet adherence.** → platlet adhesion with collagen
- **Platelet activation.** → after adhesion → produce thromboxin and ADP
- **Platelet aggregation.** → temporary platlet plug → primary platlet plug



يحفز megaKaryocyte على إنتاج الصفائح الدموية

platlet produce in bone marrow

megaKaryocyte تصبح خلايا
تمتد زوائد منها لإنتاج الصفائح


AGONISTS
ADHESION
Collagen
Thromboxanes
ADP
Thrombin
Alpha granule
vWF → van willebrand
التصاق الصفائح
Fibrinogen → convert to fibrin
Factor V
عامل تخثر رقم خمسة
PLATELET
ADP
ATP
يجذب صفائح أخرى وينشطها
Serotonin
تضيق الأوعية
Calcium
لها دور في عملية التخثر
Dense granule
GPIIb-IIIa Fibrinogen
vWF
GPIa-IIa collagen

Platelets

- Produced in the bone marrow by fragmentation of the cytoplasm of megakaryocytes (1000-5000/cell).
- 1/3 of marrow output of platelets is trapped in spleen (splenectomy?)
- Normal count: 150,000-400,000/µL (250,000)
- Life span 7-10 days.
- Removed from circulation by tissue macrophage system mainly in spleen.
- Thrombopoietin: major regulator of platelet production (produced by liver and kidney).
- It increases no. & rate of maturation of megakaryocytes.

Functional characteristics of platelets

- **The cell membrane of platelets contains:**
  - A coat of glycoprotein (receptors) that cause adherence to injured endothelial cells and exposed collagen.

    الكشوف
  - Phospholipids that play an important role in blood clotting.

- # Their cytoplasm :

  - **Contains:**

    - ✓ Contractile proteins (actin & myosin).
    - ✓ Dense granules, which contain substances that are secreted in response to platelet activation including serotonin & ADP.
    - ✓ α-granules, which contain secreted proteins e.g., platelet-derived growth factor (PDGF) which stimulates wound healing, fibrin stabilizing factor (factor XIII) and other clotting factors.

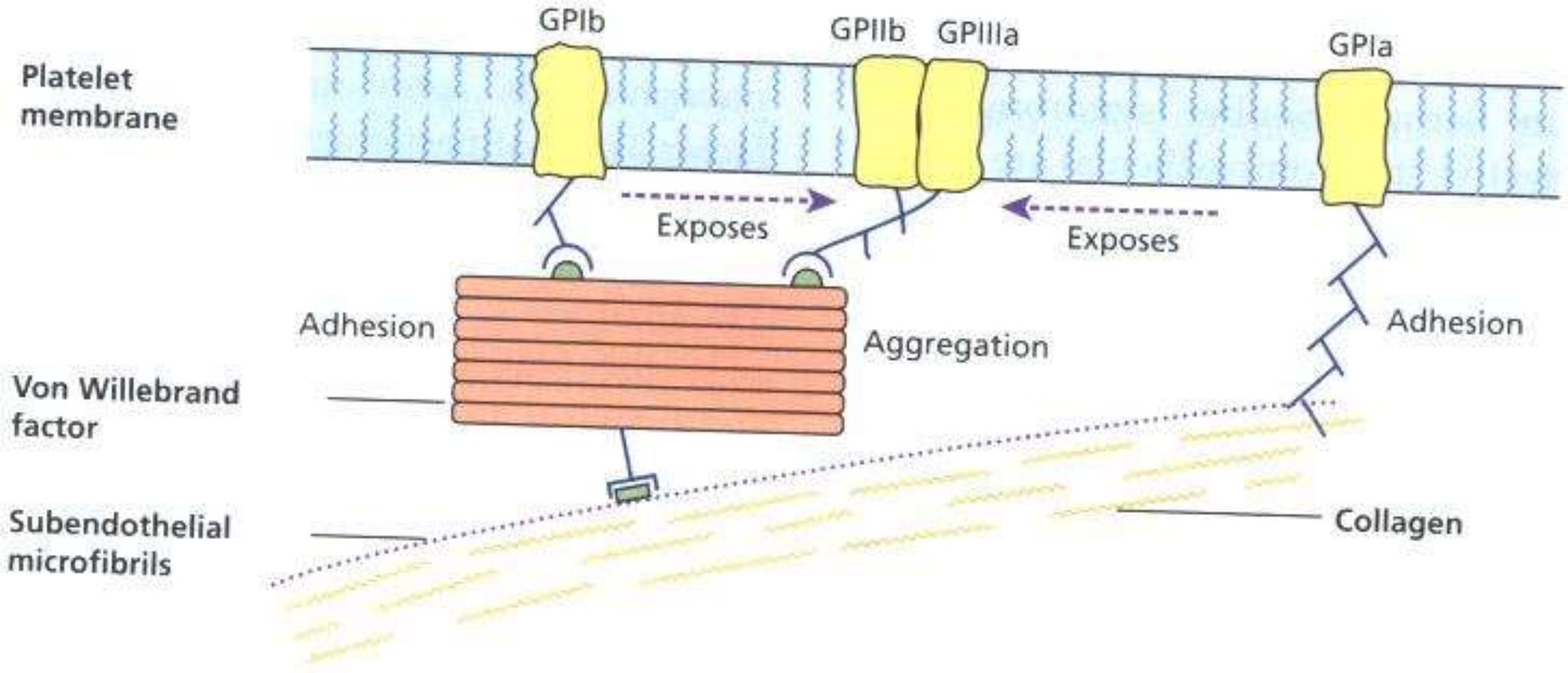
  - **Can store large quantities of Ca^{++}.**

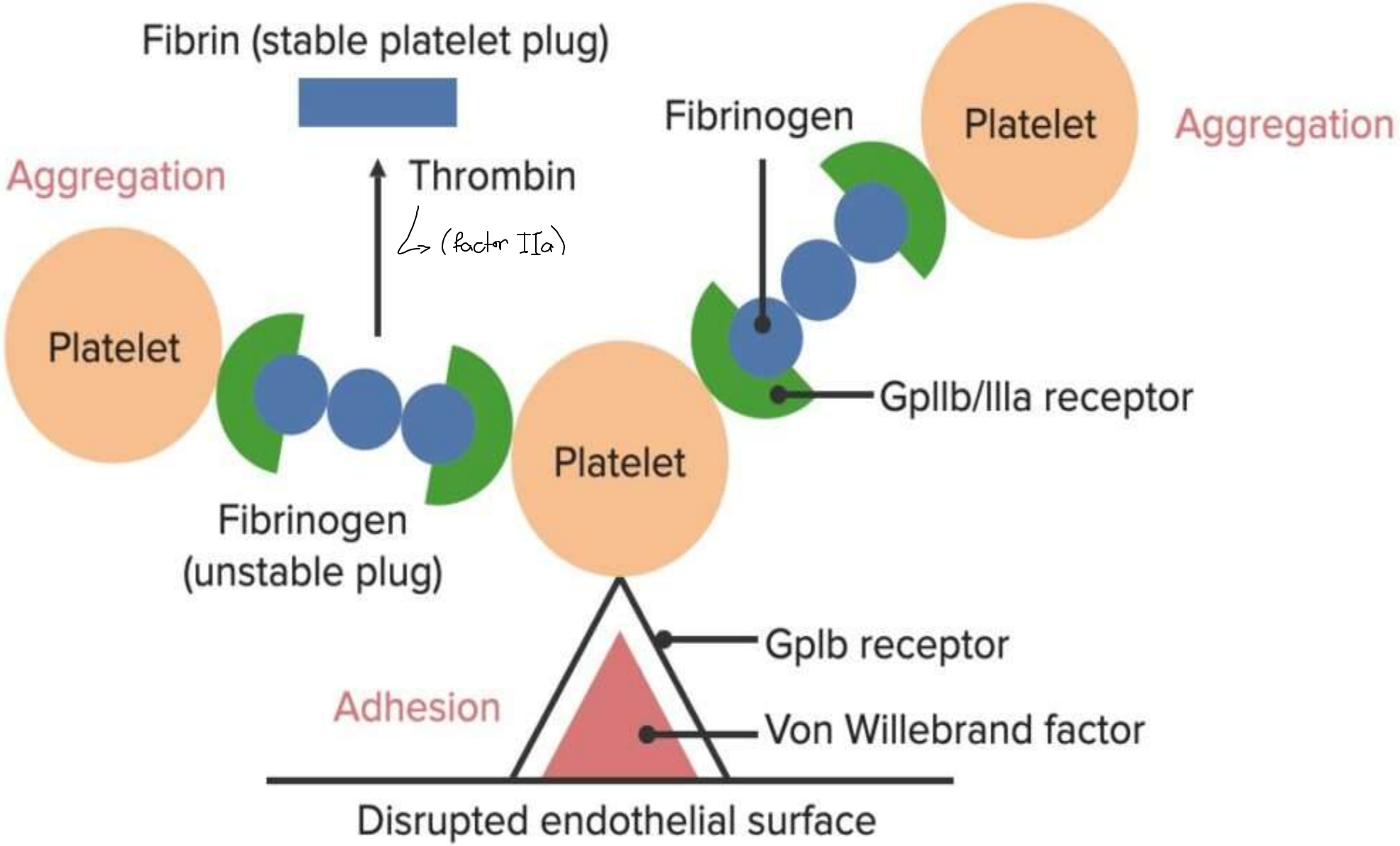
يحفز التئام الجروح

Mechanism of platelet plug formation

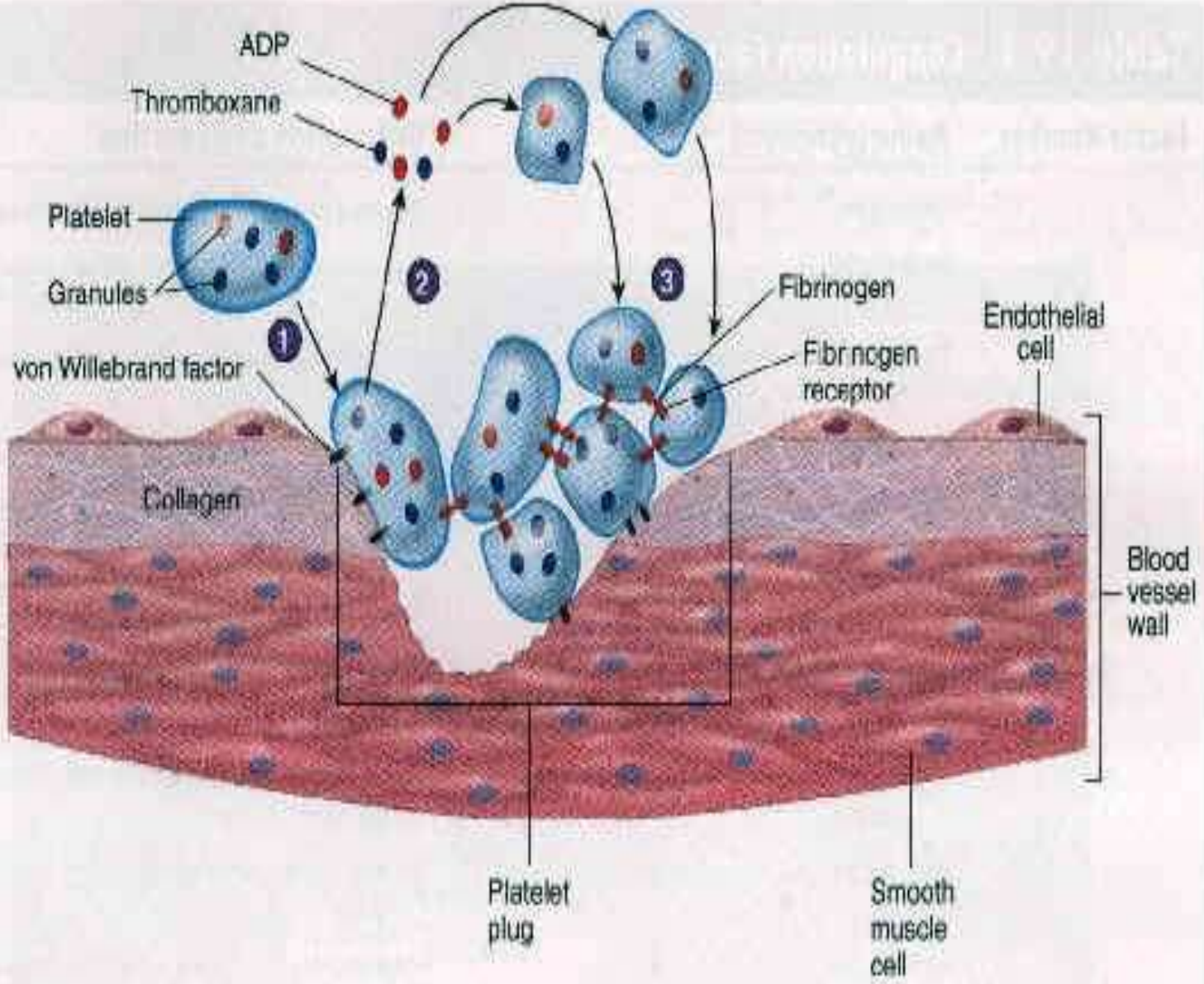
* ***Platelet adhesion:*** When a blood vessel wall is injured, platelets adhere to the exposed collagen and von Willebrand factor in the wall via platelet receptors → *Platelet activation*.

* ***Activated platelets*** release the contents of their granules including ADP and secrete TXA_2 → activating nearby platelets to produce further accumulation of more platelets *(platelet aggregation)* and forming a *platelet plug*.


Platelet membrane
GPIb
GPIIb
GPIIIa
GPIa
Exposes
Exposes
Adhesion
Aggregation
Adhesion
Von Willebrand factor
Subendothelial microfibrils
Collagen


Fibrin (stable platelet plug)
Aggregation
Thrombin
(factor IIa)
Fibrinogen
Platelet
Aggregation
Platelet
GpIIb/IIIa receptor
Platelet
Fibrinogen
(unstable plug)
GpIb receptor
Adhesion
Von Willebrand factor
Disrupted endothelial surface

1. Platele: adhesion occurs when von Willebrand factor connects collagen and platelets.
2. The platelet release reaction is the release of ADP, thromboxanes, and other chemicals that activate other platelets.
3. Platelet aggregation occurs when fibrinogen receptors on activated platelets bind to fibrinogen, connecting the platelets to one another. A platelet plug is formed by the accumulating mass of platelets.



Platelet Plug Formation

Blood Coagulation

- The clotting mechanism involves a cascade of reactions in which clotting factors are activated.
- Most of them are **plasma proteins** synthesized by the liver (vitamin K is needed for the synthesis of factor II, VII, IX and X).
- They are always present in the plasma in an inactive form.
- When activated they act as proteolytic enzymes which activate other inactive enzymes.
- Several of these steps require Ca^{++} and platelet phospholipid.

Table 18.1 The coagulation factors

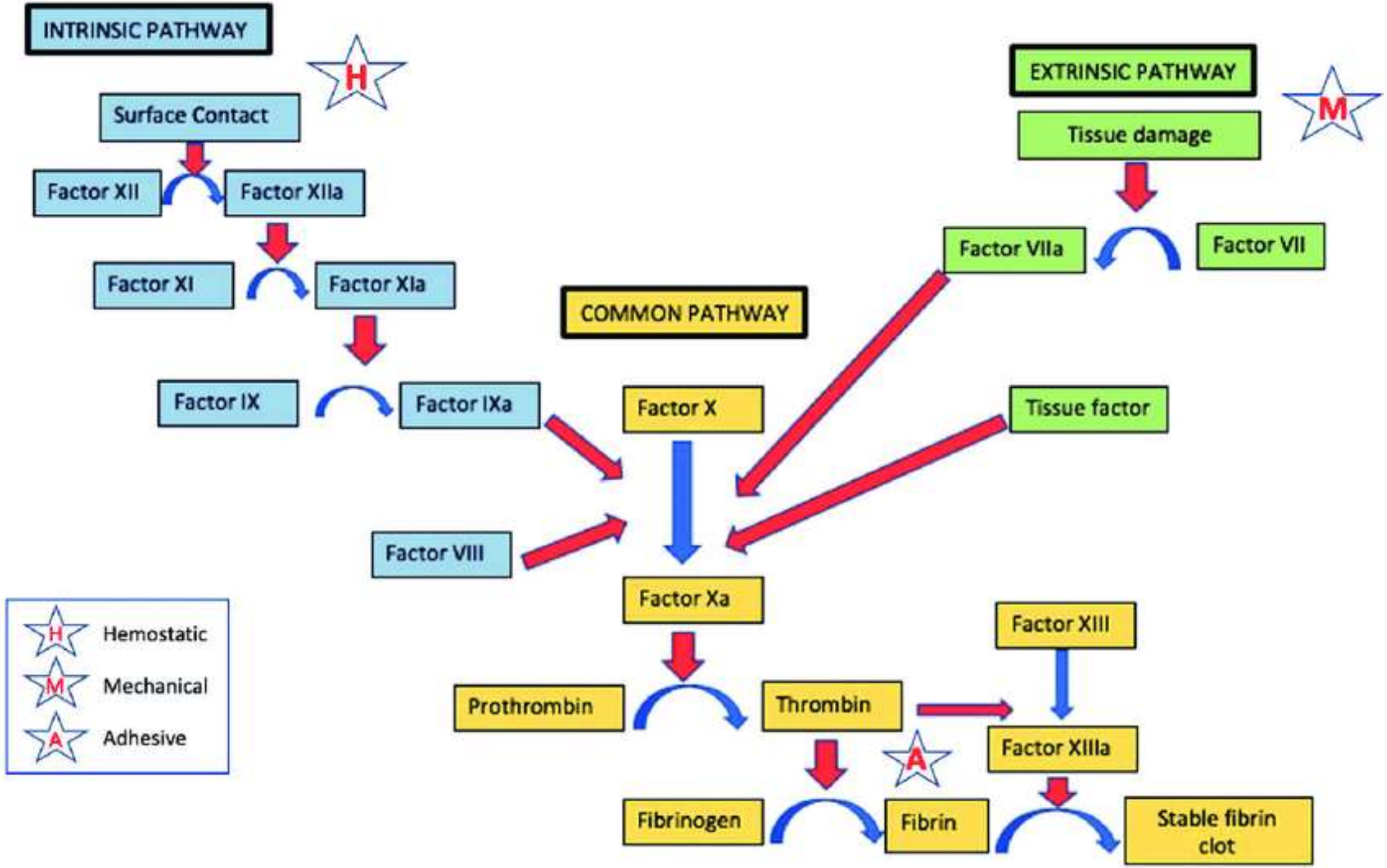
Factor number	Descriptive name
I	Fibrinogen
II	Prothrombin
III	Tissue factor
V	Labile factor
VII	Proconvertin
VIII	Antihaemophilic factor
IX	Christmas factor
X	Stuart–Prower factor
XI	Plasma thromboplastin antecedent
XII	Hageman (contact) factor
XIII	Fibrin-stabilizing factor
	Prekallikrein (Fletcher factor)
	HMWK (Fitzgerald factor)

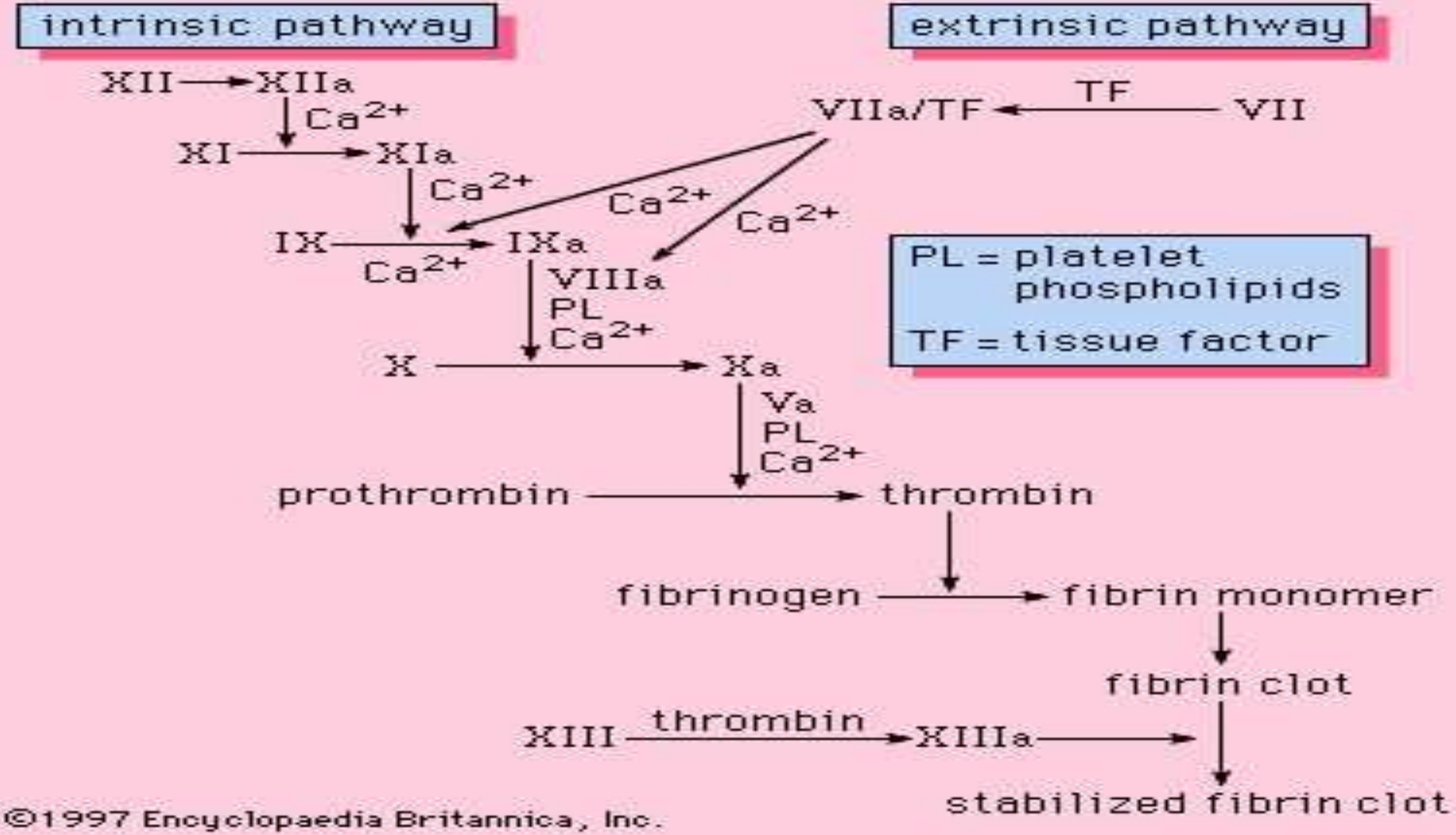
*Active without proteolytic modification.
HMWK, high molecular weight kininogen.

Name	Description	Function
Fibrinogen (Factor I)	MW = 340,000 Da; glycoprotein	Adhesive protein that forms the fibrin clot
Prothrombin (Factor II)	MW =72,000 Da; vitamin K-dependent serine protease	Activated form is main enzyme of coagulation
Tissue factor (Factor III)	MW = 37,000 Da; also known as thromboplastin	Lipoprotein initiator of extrinsic pathway
Calcium ions (Factor IV)	Necessity of Ca^{++} ions for coagulation reactions described in 19th century	Metal cation necessary for coagulation reactions
Labile factor (Factor V)	MW =330,000 Da	Cofactor for activation of prothrombin to thrombin
Proconvertin (Factor VII)	MW = 50,000 Da; vitamin K-dependent serine protease	With tissue factor, initiates extrinsic pathway
Antihemophilic factor (Factor VIII)	MW = 330,000 Da	Cofactor for intrinsic activation of factor X
Christmas factor (Factor IX)	MW = 55,000 Da; vitamin K-dependent serine protease	Activated form is enzyme for intrinsic activation of factor X
Stuart-prower factor (Factor X)	MW = 58,900 Da; vitamin K-dependent serine protease	Activated form is enzyme for final common pathway activation of prothrombin
Plasma thromboplastin antecedent (Factor X)	MW = 160,000 Da; serine protease	Activated form is intrinsic activator of factor IX
Hageman factor (Factor XII)	MW = 80,000 Da; serine protease	Factor that normally starts aPTT-based intrinsic pathway
Fibrin stabilizing factor (Factor XIII)	MW =320,000 Da	Transamidase that cross-links fibrin clot

Factor	Name	Pathway
I	Fibrinogen	Both
II	Prothrombin	Both
III	Tissue Factor	Extrinsic
IV	Calcium	Both
V	Proaccelerin	Both
VI	Accelerin	Both
VII	Proconvertin	Extrinsic
VIII	Antihemophiliac	Intrinsic
IX	Christmas Factor	Intrinsic
X	Stuart-Prower Factor	Both
XI	Plasmathromboplastin antecedent (PTA)	Intrinsic
XII	Hageman Factor	Intrinsic
XIII	Protransglutaminase	Both

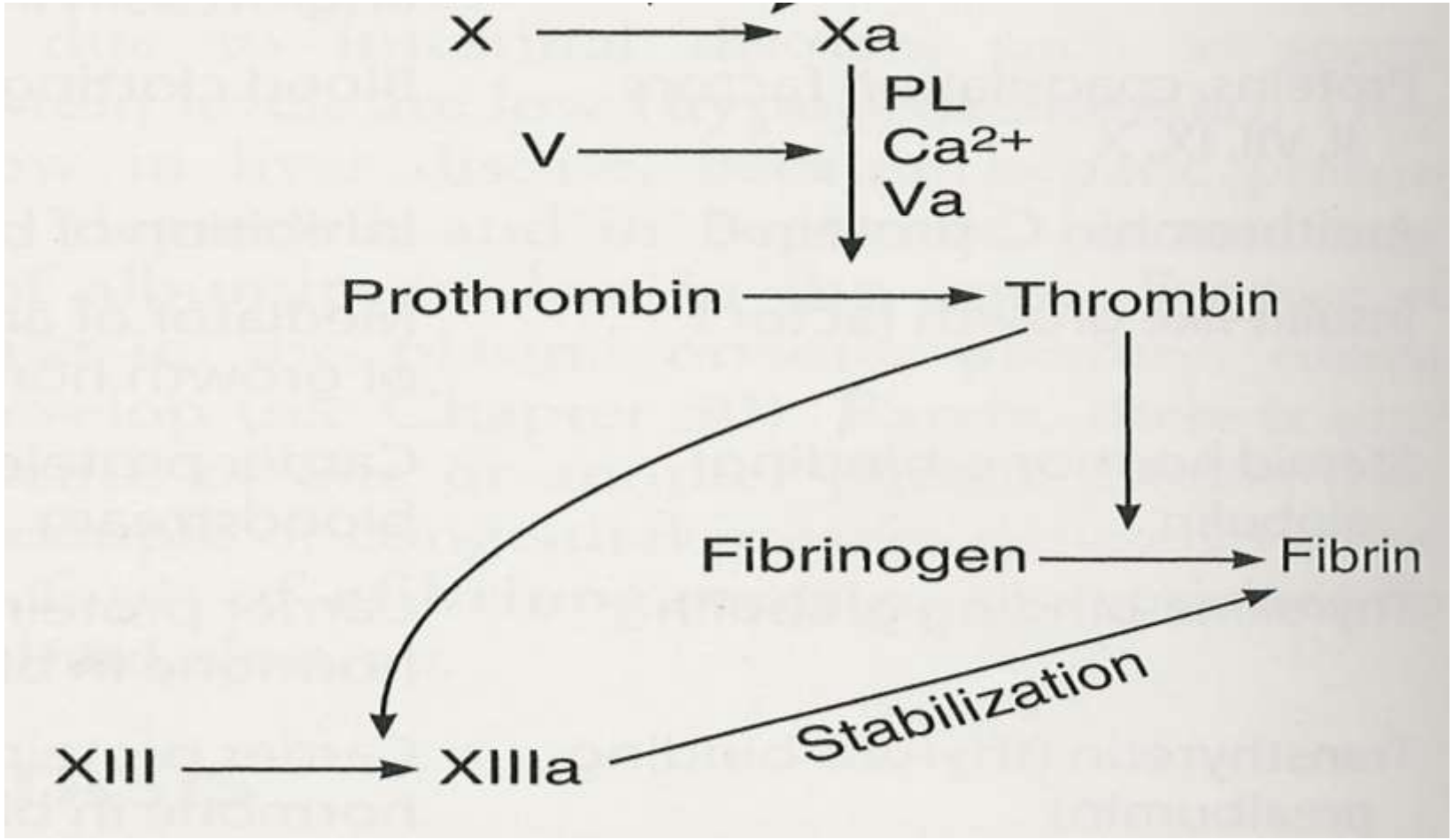
NUMBER*	NAME(S)	SOURCE	PATHWAY(S) OF ACTIVATION
I	Fibrinogen.	Liver.	Common.
II	Prothrombin.	Liver.	Common.
III	Tissue factor (thromboplastin).	Damaged tissues and activated platelets.	Extrinsic.
IV	Calcium ions (Ca^{2+}).	Diet, bones, and platelets.	All.
V	Proaccelerin, labile factor, or accelerator globulin (AcG).	Liver and platelets.	Extrinsic and intrinsic.
VII	Serum prothrombin conversion accelerator (SPCA), stable factor, or proconvertin.	Liver.	Extrinsic.
VIII	Antihemophilic factor (AHF), antihemophilic factor A, or antihemophilic globulin (AHG).	Liver.	Intrinsic.
IX	Christmas factor, plasma thromboplastin component (PTC), or antihemophilic factor B.	Liver.	Intrinsic.
X	Stuart factor, Prower factor, or thrombokinase.	Liver.	Extrinsic and intrinsic.
XI	Plasma thromboplastin antecedent (PTA) or antihemophilic factor C.	Liver.	Intrinsic.
XII	Hageman factor, glass factor, contact factor, or antihemophilic factor D.	Liver.	Intrinsic.


INTRINSIC PATHWAY
H
Surface Contact
Factor XII
Factor XIIa
Factor XI
Factor XIa
Factor IX
Factor IXa
EXTRINSIC PATHWAY
M
Tissue damage
Factor VIIa
Factor VII
COMMON PATHWAY
Factor X
Tissue factor
Factor VIII
Factor Xa
Factor XIII
Prothrombin
Thrombin
A
Factor XIIIa
Fibrinogen
Fibrin
Stable fibrin clot
H Hemostatic
M Mechanical
A Adhesive



Blood Coagulation

- The ultimate step in clot formation is the conversion of fibrinogen → fibrin.



Factor X can be activated by reactions in either of 2 systems:

An Intrinsic system.

An Extrinsic system

Intrinsic pathway

تكون بطيئة نسبيًا ←

→ require calcium and platlet phospholipid

يكون تالف endothelial cell ← وأليات الكولاجين تتلامس مع الدم ثم يتم

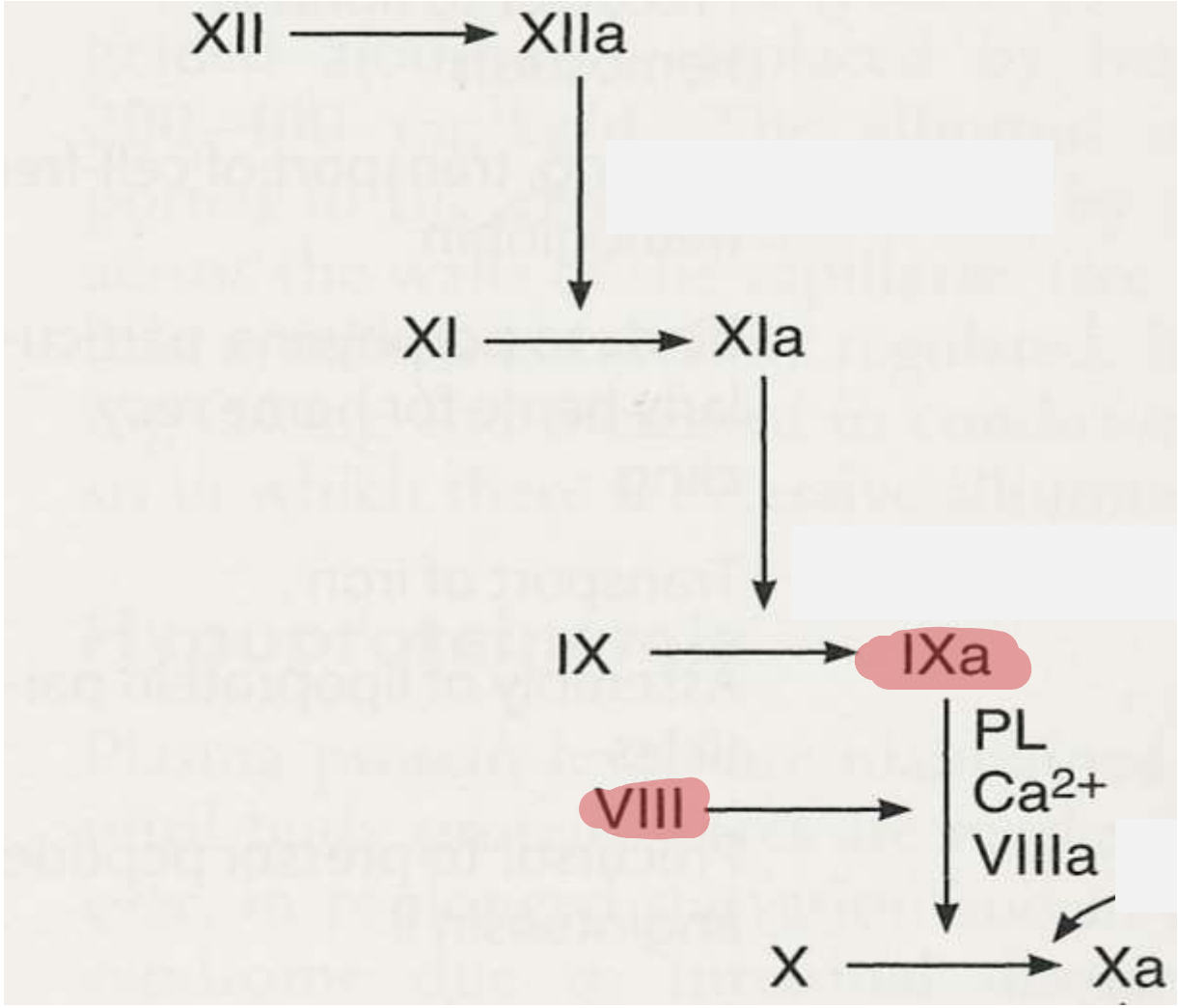
- The initial reaction is the conversion of inactive factor XII to active factor XIIa.

- Factor XII is activated in vitro by exposing blood to foreign surface (glass test tube).

- Activation in vivo occurs when blood is exposed to collagen fibers underlying the endothelium in the blood vessels.

أسفل

INTRINSIC SYSTEM



Extrinsic pathway

يعتمد على عوامل من خارج الدم خصوصًا من الأنسجة التالفة

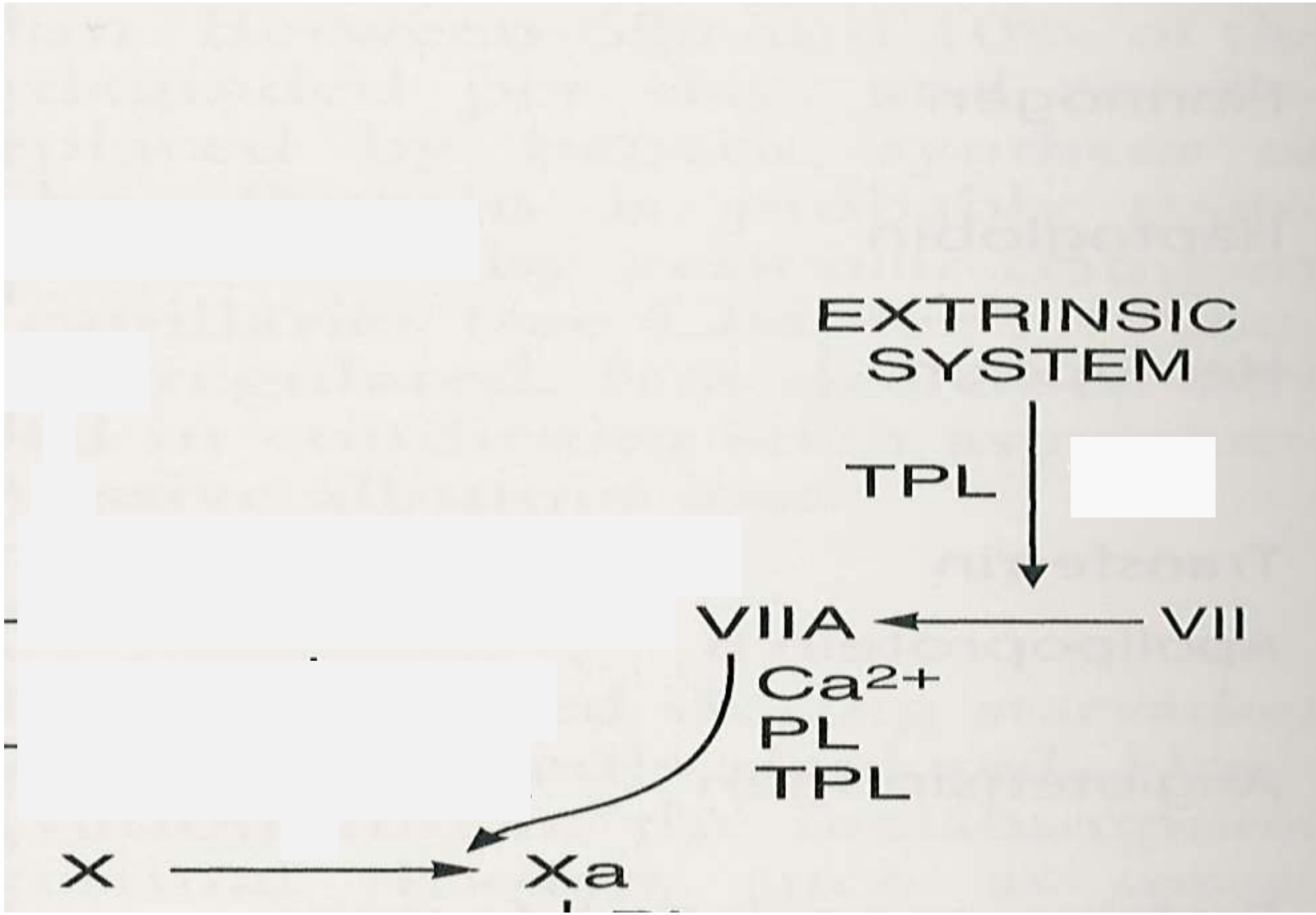
- Requires contact with tissue factors external to blood.

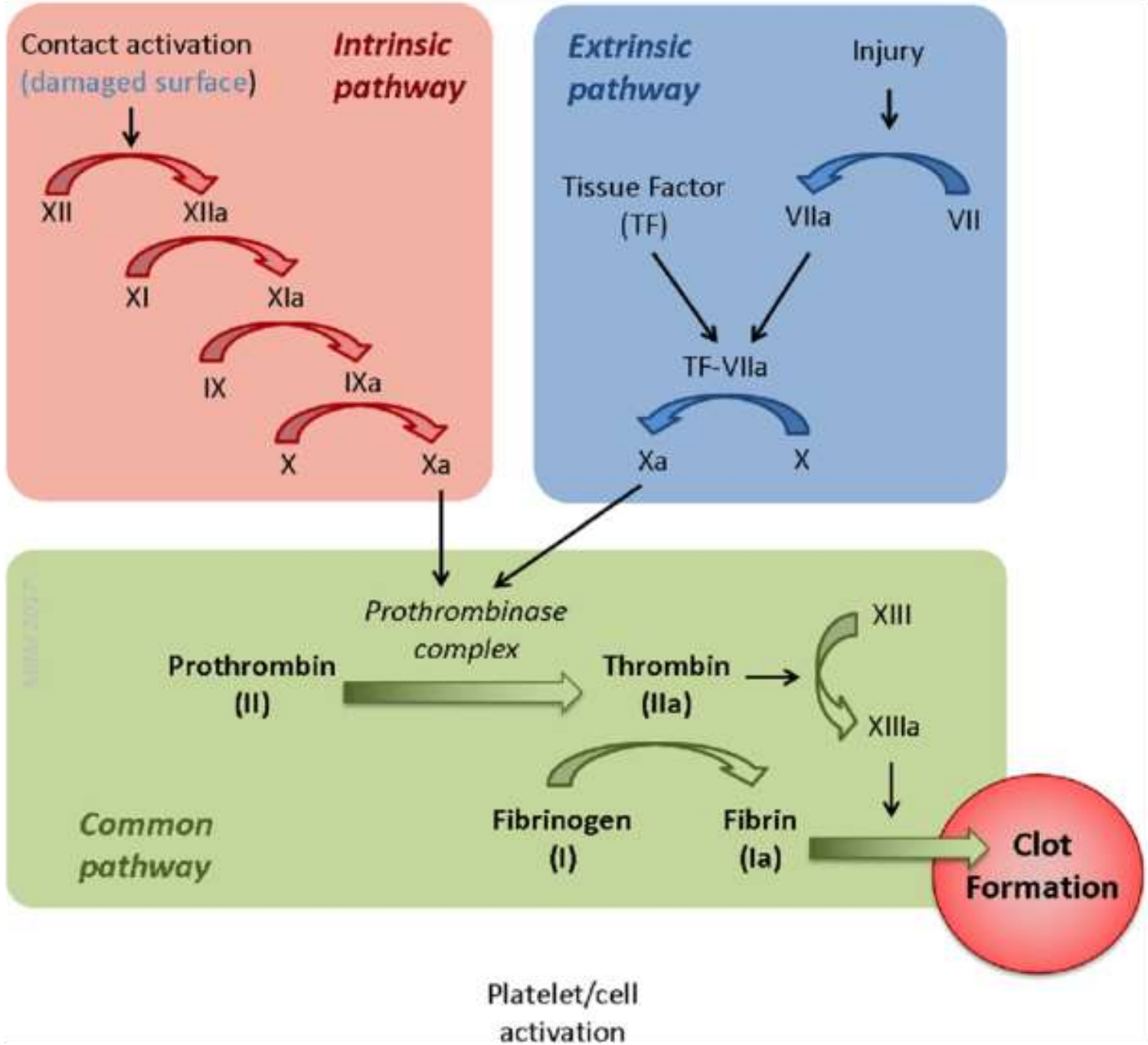
- This occurs when there is trauma to the vascular wall and surrounding tissues.

- The extrinsic system is triggered by the release of tissue factor (thromboplastin from damaged tissue), that activates factor VII.

- The (1) tissue thromboplastin and (2) factor VII activate factor X.

by


EXTRINSIC
SYSTEM
TPL
VIIA
VII
Ca2+
PL
TPL
X
Xa


Contact activation
(damaged surface)
Intrinsic pathway
XII
XIIa
XI
XIa
IX
IXa
X
Xa
Extrinsic pathway
Injury
Tissue Factor
(TF)
VIIa
VII
TF-VIIa
Xa
X
Prothrombinase complex
Prothrombin
(II)
Thrombin
(IIa)
XIII
XIIIa
Fibrinogen
(I)
Fibrin
(Ia)
Common pathway
Clot Formation
Platelet/cell activation

Clot retraction

انكماش

- Clot formation is fully developed in 3-6 min.

→ because contain actin and myosin

- Contraction of platelets trapped within the clot shrinks the fibrin meshwork pulling the edges of the damaged vessel closer together.

انكماش

شبكة سحب حواف

- During clot retraction serum is squeezed from the clot.

عصر

→ plasma without clotting factor

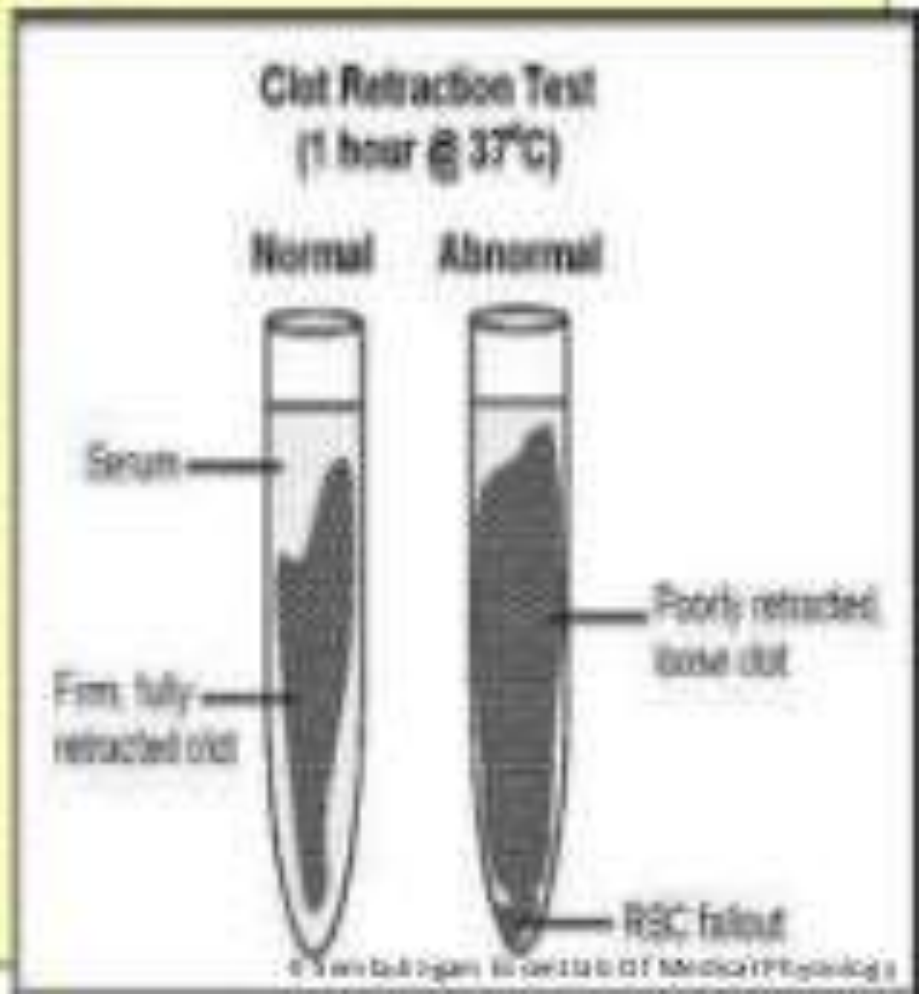
Clot retraction:

- After the formation, the blood clot starts contracting. And after about 30-45 minutes, a straw colored fluid called serum oozes out of the clot.

يخرج بشكل تدريجي

- This process is called Clot retraction.

- The contractile proteins namely, actin, myosin, thrombosthenin are responsible for clot retraction.



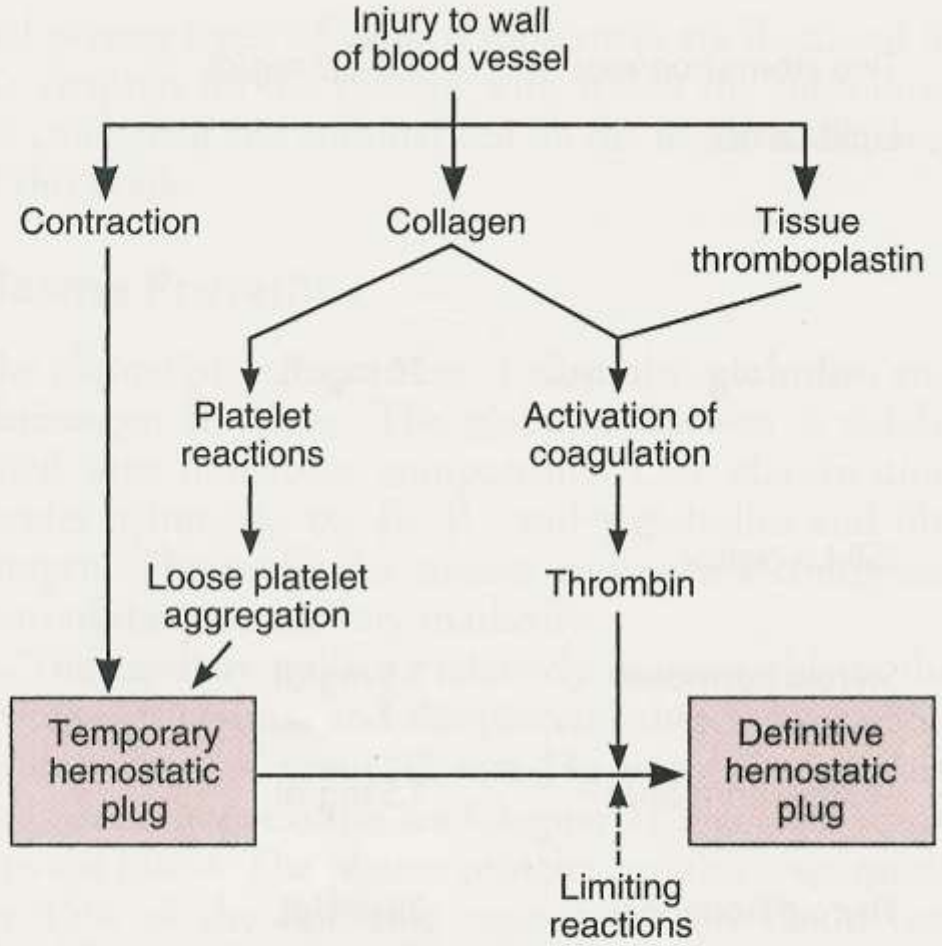


Figure 27–23 Summary of reactions involved in hemostasis. The dashed arrow indicates inhibition. (Modified from Deykin D: Thrombogenesis, N Engl J Med 1967;267:622.)

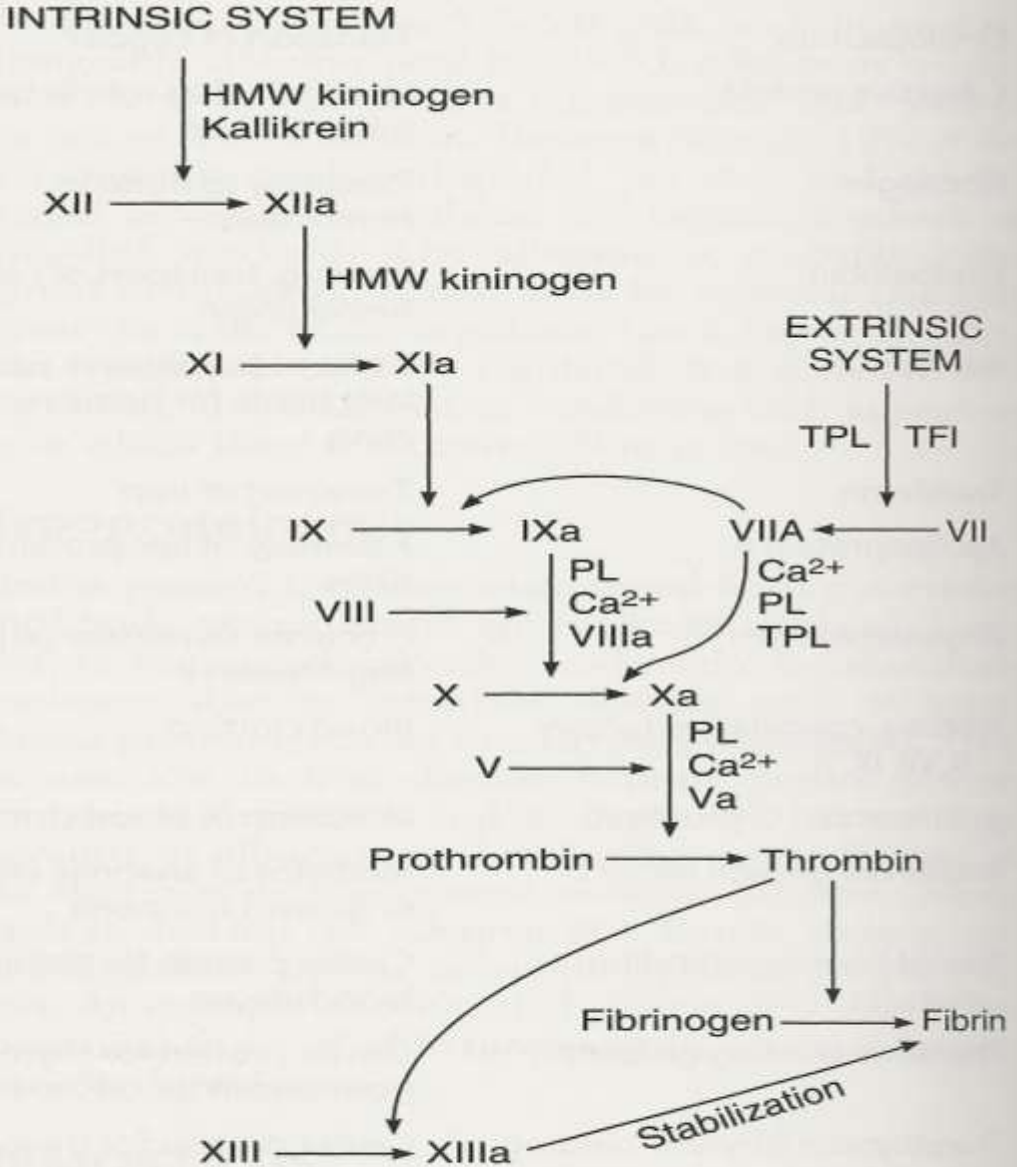


Figure 27–24 The clotting mechanism. a, active form of clotting factor. TPL, tissue thromboplastin; TFI, tissue factor pathway inhibitor. For other abbreviations, see Table 27–8.

Coagulation disorders

- Hypercoagulability states. → increase platlet / clotting factor increase
- Bleeding disorders. → decrease clotting factor and platlet
- Bleeding associated with vascular disorders. → blood vessel weak
- Disseminated intravascular coagulation. → clot every way

Table 1: Thrombogenic and antithrombogenic components in the body

Site	Thrombogenic	Antithrombogenic
Vessel wall	Exposed endothelium	Heparin
	TF	Thrombomodulin
	Collagen	Tissue plasminogen activator
Circulating elements	Platelets	Antithrombin
	Platelet activating factor	Protein C and S
	Clotting factor	Plasminogen
	Prothrombin	
	Fibrinogen	
	vWF	

vWF – Von Willebrand factor; TF – Tissue factor

1. Hypercoagulability state

- Represents an exaggerated form of hemostasis that predisposes to thrombosis and blood vessel occlusion which could be venous (most common), arterial or both
- It can be inherited or acquired
- It can be divided into:
  - Increased platelet function.
  - Increased clotting activity.

Increased platelet function

increased in number
increased in activity

- **Increased platelet count:** → increase in number
  - Reactive disorders (iron-deficiency anemia (children), splenectomy, cancer, chronic inflammatory conditions such as RA and Crohn's).
  - Myeloproliferative disorders (polycythemia vera). → defect in bone marrow → increased in platlet number

- **Endothelial injury** → increase in activity
  - Atherosclerosis. → dysfunctional endothelial
  - Elevated blood lipid and cholesterol level.
  - Smoking.
  - Central venous catheters. → تسبب احتكاك وتهيج داخلي

Accelerated activity of the clotting system

- **Inherited disorders (primary)**
  - Mutation in factor V gene (factor V Leiden)
  - Mutation in the prothrombin gene

- **Acquired (secondary)**
  - Immobility or prolonged bed rest
  - Oral contraceptive agents and pregnancy
  - Myocardial infarction
  - Heart and respiratory failure
  - Malignant diseases → أورام خبيثة → cancer
  - Antiphospholipid antibody syndrome (venous and arterial thrombi)

2. Bleeding disorders

- Could be due to:
  - **Platelet disorders**
    - Thrombocytopenia نقص عدد الصفائح الدموية
    - Impaired platelet function خلل في وظيفة الصفائح
  - **Coagulation disorders**
    - Inherited disorders
    - Acquired disorders

Platelet disorders

- Normal platelet count is 150,000-400,000/µl (250,000).

- Decrease in platelet level below 100,000/µl.
- Spontaneous bleeding occurs if the platelet count falls below 20,000/ µl.
- Platelet deficiency will appear as bleeding in certain areas of the body including:
  - Cutaneous bleeding as purple areas of bruising and pinpoint hemorrhages.
  - Nose and mouth bleeding.
  - Bleeding from GIT and uterine cavity.
  - Intracranial bleeding is very rare even with severe thrombocytopenia.

Causes of thrombocytopenia

- Inadequate platelet production (bone marrow dysfunction).
- Excess pooling of the platelet in the spleen.
- Excess platelet destruction (thrombocytopenia).
- Defect in von Willebrand factor.
- Drug induced thrombocytopenia (sulfonamides, quinine, quinidine, heparin).

Coagulation disorders

- **Inherited:** Defect in one or more of the clotting factors.
- **Hemophilia A:** factor VIII deficiency which is either insufficient or defected.
- Characterized by bleeding in soft tissue, GIT, and joints which produces inflammation of the synovium, with acute pain and swelling.
- Aspirin and NSAIDs should be avoided.
- Treated by facto VIII replacement therapy.

- **Von Willebrand disease:** hereditary deficiency or defect in vWF.
  - It is important in binding the platelets to collagen in blood vessels.
  - Stabilize factor VIII by binding in the circulation and preventing its proteolysis.

Coagulation disorders

- Acquired:

- **Liver disease:** affect the synthesis of the clotting factors and storage of vitamin K.

- **Gallbladder disease:** impair vitamin K absorption (a fat-soluble vitamin).

- **Any disease that impairs vitamin K in body.**

3. Bleeding associated with a vascular disorder

- This occurs due to structurally weak vessel wall or because of damage to the vessel by inflammation or immune system.
- Platelet count and other tests for coagulation factors is normal but easy bruising and spontaneous appearance of pinpoint and purpura of the skin and mucous membrane is common.

❑ Could be caused by:

- Vitamin C deficiency (collagen synthesis).
- Cushing syndrome (protein wasting and loss of vessel tissue support due to excess cortisol).
- Senile purpura (bruising in elderly due impaired collagen synthesis).

4. Disseminated intravascular coagulation

- Characterized by widespread coagulation and bleeding.

↳cancer

- Massive activation of the coagulation sequence leads to fibrin deposition in the microcirculation of the body.

- As a consequence of the thrombotic process, the consumption of platelets and clotting factors and the activation of plasminogen will lead to hemorrhagic diathesis.

- It can be due to the activation of the intrinsic (endothelial injury) or extrinsic (tissue injury) pathway.

CHART 12-2 **Conditions That Have Been Associated with Disseminated Intravascular Coagulation**

Obstetric Conditions

Abruptio placentae
Dead fetus syndrome
Preeclampsia and eclampsia
Amniotic fluid embolism

Cancers

Metastatic cancer
Acute promyelocytic leukemia

Infections

Acute bacterial infections (e.g., meningococcal meningitis)
Histoplasmosis, Aspergillosis
Rickettsial infections (e.g., Rocky Mountain spotted fever)
Parasitic infections (e.g., malaria)
Sepsis/septic shock

Trauma or Surgery

Burns
Massive trauma
Surgery involving extracorporeal circulation
Snake bite
Heatstroke

Hematologic Conditions

Blood transfusion reactions

Thank You