كلية المستقبل الجامعة قسم الصيدلة
المرحلة الثانية

PHYSIOLOGY

Hemostasis, Blood Coagulation and Fibrinolysis

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Introduction

Platelets, also known as **thrombocytes**, are small, irregularly shaped cells that play a crucial role in the process of blood clotting.
In addition to their role in hemostasis, platelets have been found to be involved in various other physiological processes such as inflammation, wound healing, and angiogenesis.

Platelets are formed in the bone marrow from megakaryocytes, which are large, multi-lobed cells. Megakaryocytes undergo a process called endomitosis, where they replicate their DNA without undergoing cell division, resulting in the formation of thousands of small cytoplasmic fragments called platelets.

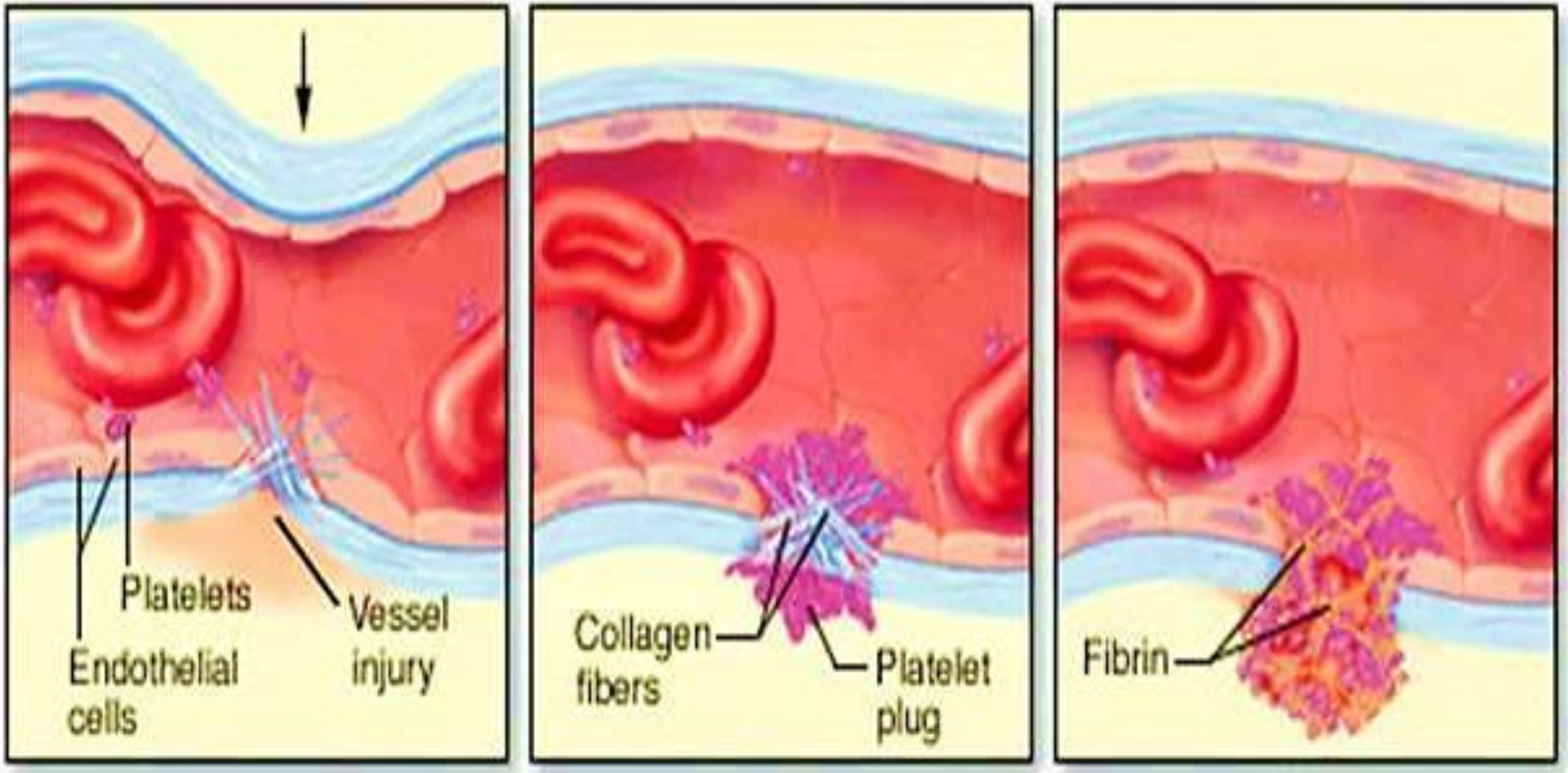
Platelets are disc-shaped cells that lack a nucleus and are only about one-third the size of red blood cells. They contain numerous granules, including alpha granules, dense granules, and lysosomes, which contain various proteins and enzymes involved in blood clotting and other physiological processes.

- In normal condition when a small blood vessel is severed or ruptured, the injury can initiate a series of events that stop the bleeding automatically within a few minutes

- The process to arrest the bleeding is called **Hemostasis.**

Mechanisms of Hemostasis

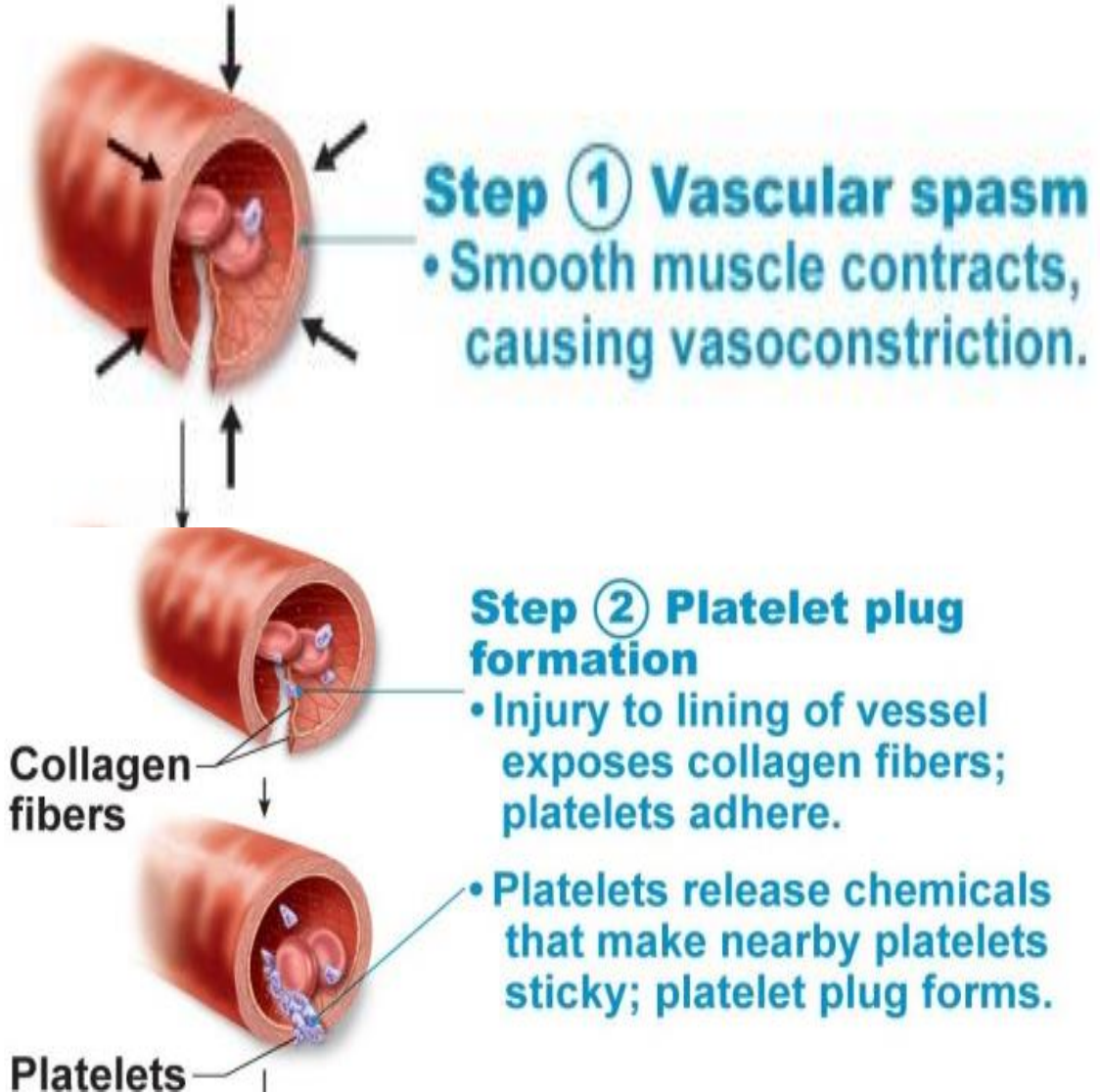
- Vascular constriction:
  (neural, myogenic & humoral)
- Formation of a platelet plug
- Formation of a blood clot
- Anticoagulation and fibrinolysis.



(a) Vasoconstriction (b) Platelet aggregation (c) Clot formation

Stages Of Blood Clotting

- Step 1: Vascular spasms
  - Endothelin
  - Serotonin
- Step 2: Platelet plug formation
  - ADP
  - Serotonin
  - Thromboxane A_2
  - Von Willebrand factor



Stages Of Blood Clotting

Step 3: Coagulation

- **Phase 1:**

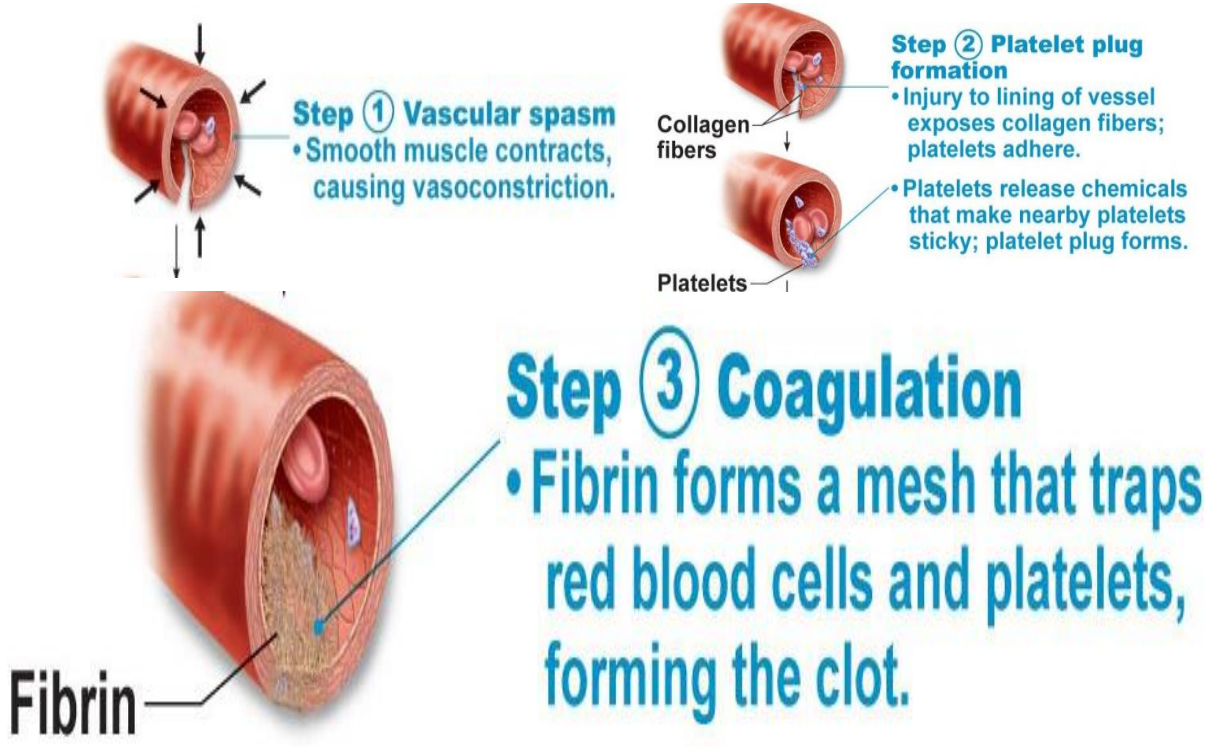
Formation of prothrombinase (also known as prothrombin activator)

- **Phase 2:**

Conversion of prothrombin to thrombin

- **Phase 3:**

Conversion of soluble fibrinogen into insoluble fibrin



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Which activate the platelets? *Answer: Collagen fibers*

What is the source of collagen fibers? *Answer: The damaged vascular wall*

Is this plaque hard or loose?

Answer: Platelets plague alone is a loose plug, but it is usually successful in blocking blood loss if the vascular opening is small.

When it will be hard?

Answer: During the process of blood coagulation

What make platelet plaque be hard?

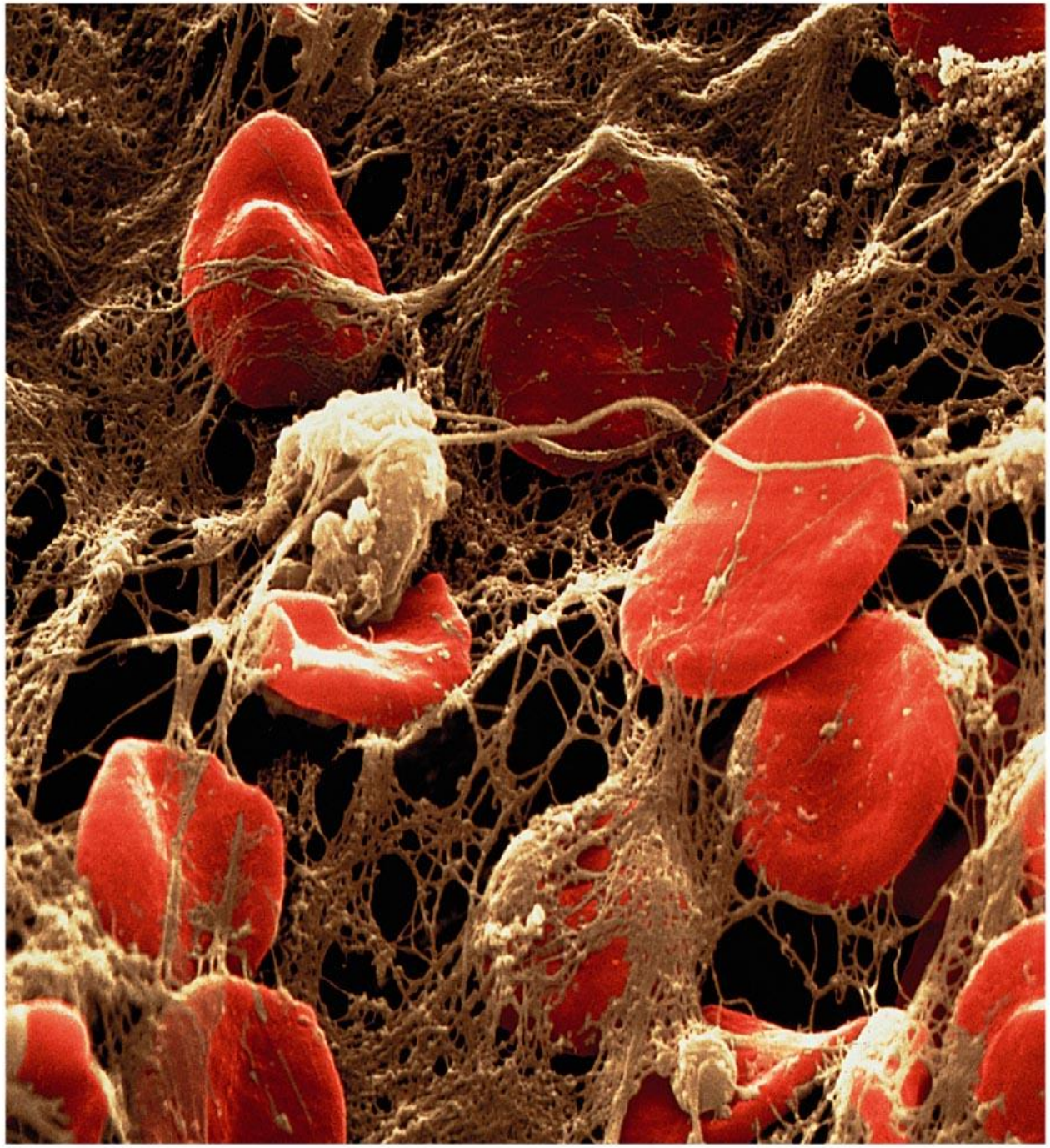
Answer: Fibrin threads attach tightly to the platelets, thus constructing an unyielding plug.

Are these normal or pathological changes?

Answer: normal physiological changes

Factors Effecting Clot Formation

- Normal coagulation:
  - Normal platelet #s
  - All clotting factors
  - Vitamin K
  - Calcium ions
  - TF and PF_3



Preventing Undesirable Clotting

- Smooth lining of BV
- Nitric oxide NO .
- Prostacyclin (PGl(2
- Vitamin E (Quinone(
- Heparin: + Antithrombin III
- Anti-Prothrombin III and Protein C
- Fibrin threads
- Thrombomodulin (endothelium)
- A layer of glycocalyx on the endothelium repels clotting factors & platelets.

Blood Coagulation

General Mechanism of Blood Coagulation

- Formation of prothrombin activator
- Activation of thrombin.
- Blood Coagulation

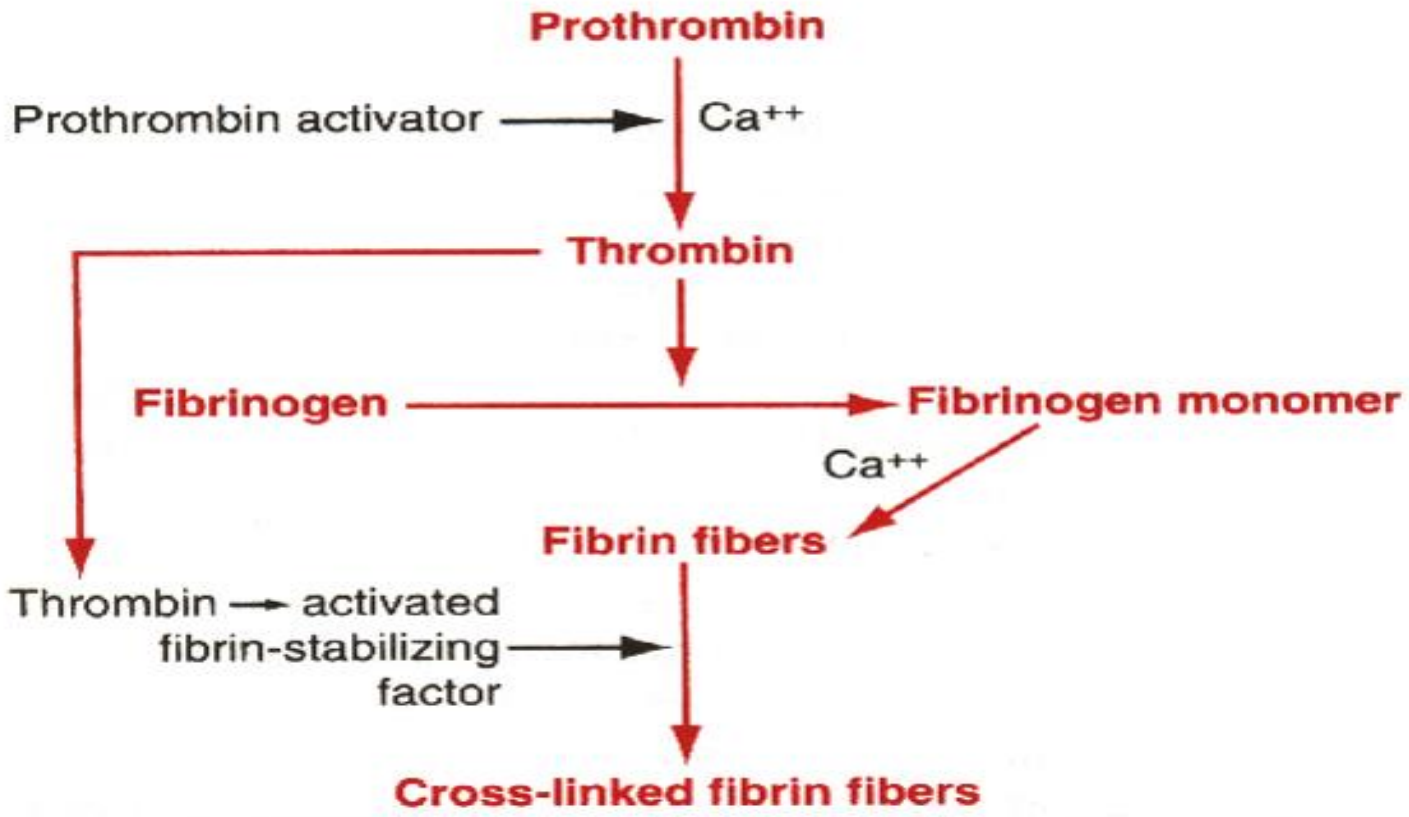
1）Formation of prothrombin activator

In response to rupture of the vessel ,

- a complex cascade of chemical reactions is initiated.
- That forming prothrombin activator

2）Activation of Thrombin

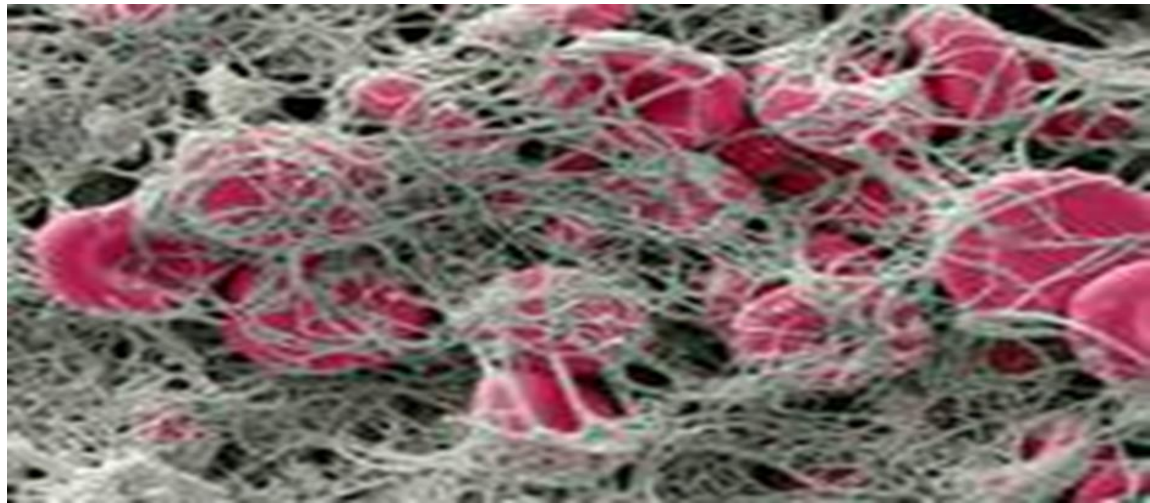
The prothrombin activator catalyzes the conversion of prothrombin into thrombin



3）Blood Coagulation

The thrombin acts as an enzyme to convert fibrinogen into fibrin fibers

- Enmesh platelets, blood cells & plasma to form the clot



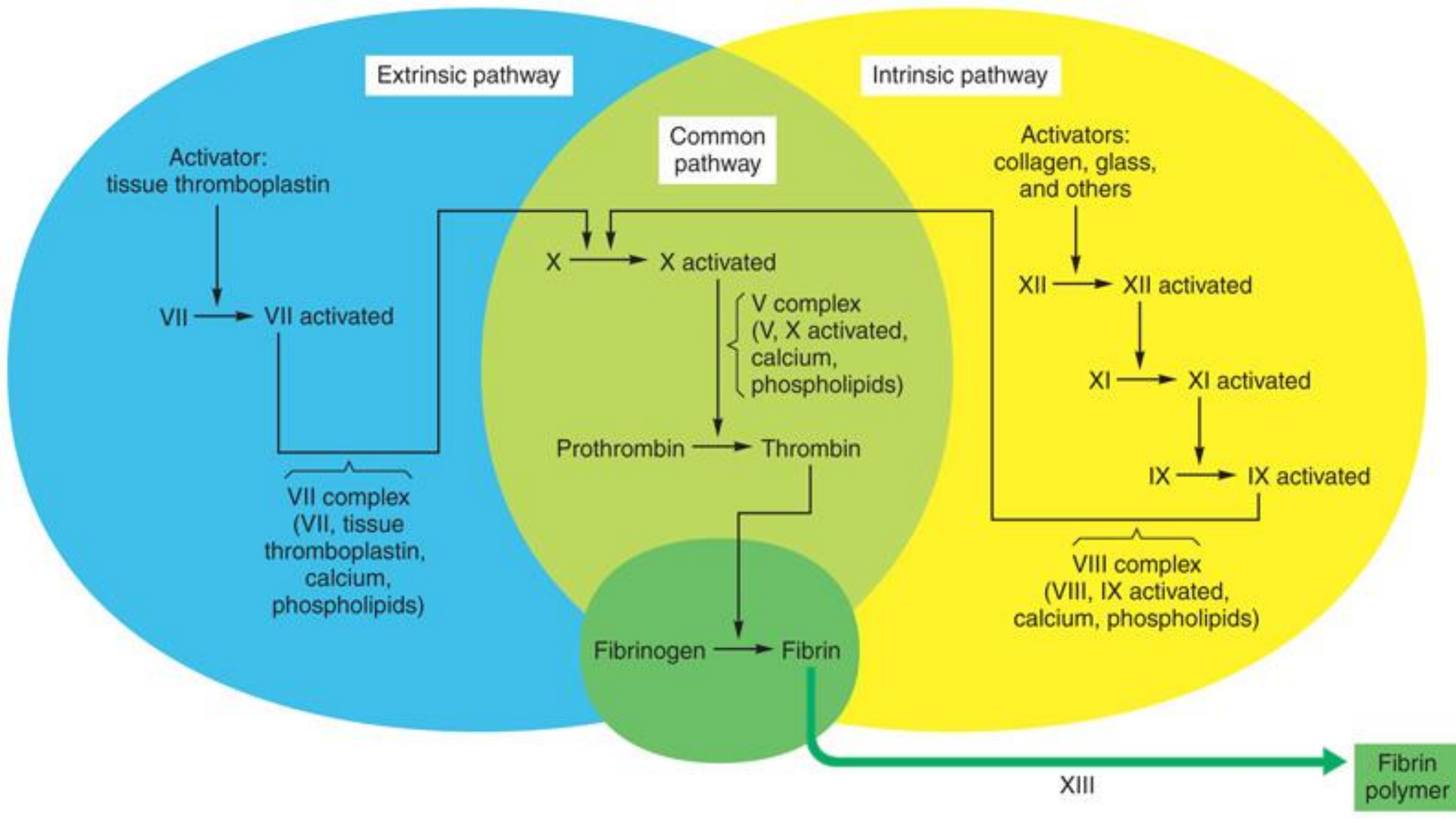
Two pathways of the Formation of prothrombin activator

- Extrinsic pathways :
  - Begins with trauma of the vascular wall & surrounding tissues
- Intrinsic pathways
  - Begin in the blood itself

- In both the extrinsic and intrinsic pathways,
  - A series of plasma proteins called **blood-clotting factors** play major roles.

Most of these are inactive forms of **proteolytic enzymes**.

- When converted to the active forms, Their enzymatic actions cause the successive, cascading reactions of the clotting process.


Extrinsic pathway
Intrinsic pathway
Common pathway
Activator:
tissue thromboplastin
VII
VII activated
VII complex
(VII, tissue
thromboplastin,
calcium,
phospholipids)
X
X activated
V complex
(V, X activated,
calcium,
phospholipids)
Prothrombin
Thrombin
Fibrinogen
Fibrin
Activators:
collagen, glass,
and others
XII
XII activated
XI
XI activated
IX
IX activated
VIII complex
(VIII, IX activated,
calcium, phospholipids)
XIII
Fibrin
polymer

Clotting Factors in Blood and Their Synonyms

Clotting Factor	Synonyms
Fibrinogen	Factor I
Prothrombin	Factor II
Tissue factor	Factor III; tissue thromboplastin
Calcium	Factor IV
Factor V	Proaccelerin; labile factor; Ac-globulin (Ac-G)
Factor VII	Serum prothrombin conversion accelerator (SPCA); proconvertin; stable factor
Factor VIII	Antihemophilic factor (AHF); antihemophilic globulin (AHG); antihemophilic factor A
Factor IX	Plasma thromboplastin component (PTC); Christmas factor; antihemophilic factor B
Factor X	Stuart factor; Stuart-Prower factor
Factor XI	Plasma thromboplastin antecedent (PTA); antihemophilic factor C
Factor XII	Hageman factor
Factor XIII	Fibrin-stabilizing factor
Prekallikrein	Fletcher factor
High-molecular-weight kininogen	Fitzgerald factor; HMWK (high-molecular-weight kininogen)
Platelets	

4) Clot Contraction

- Few minutes after a clot is formed, it begins to **contract** and usually expresses most of the fluid form the clot within 20 – 60 min.
- The fluid expelled is called **serum**, in which all fibrinogen & most of the other clotted factors are removed. In this way, serum differs form **plasma** .
- Serum can not clot because of lack of these factors.

- Abnormalities of hemostasis can result from platelet defects, coagulation defects, and/or excessive production of anticoagulants
- Principal abnormalities include thrombocytopenia and hemophilia

Hemophilia

- Inability to control blood clotting (bleeding not stopped) & the result is spontaneous bleeding .
- Hemophilia A or classic hemophilia (factor VIII deficiency) is the commonest form, X-linked disease .
- Factor VIII is called antihemophilic factor .

- Hemophilia B (factor IX deficiency), X-linked disease.
- Von Willebrand Disease, decreased levels of von Willebrand Factor, an autosomal dominant disease.
- Hemophilia was very common in European royalty

Intravascular Anticoagulants

Antithrombin III

Heparin

Produced by

- mast cells and located in connective tissue
- basophil cells of the blood.

- A large quantities of the heparin is present in the areas of the liver and lungs.

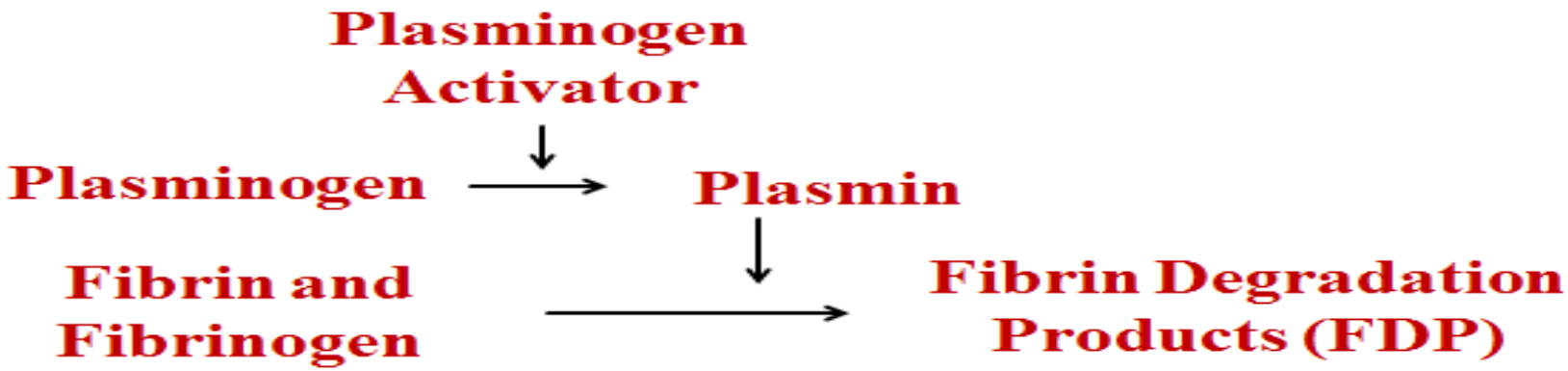
- By itself, it has little or no anticoagulant property, but when it combines with antithrombin III, it increases a hundred-fold the effectiveness of antithrombin III , thus acts as an anticoagulant.

- Heparin is widely used in medical practice to prevent intravascular clotting.

Protein C

Fibrinolysis

- The fibrin formed within BV is gradually dissolved to restore the fluidity of the blood .
- The process of liquefaction or lysis of the fibrin is called **Fibrinolysis**. It's an important component of hemostasis.



Significance of the Fibrinolysis

1- Allows slow clearing (over several days) of excessive clots (allows reopening).

2- Remove minute clots from tiny peripheral vessels (prevent clotting).

3- Maintaining the fluidity of the blood or normal capillary flow (repairing of the damaged tissues).

- **Thrombi and Emboli**
- An abnormal clot that develops in a blood vessel is called a *thrombus*.
- Once a clot has developed, continued flow of blood past the clot is likely to break it away from its attachment and cause the clot to flow with the blood; such freely flowing clots are known as *emboli*.
- **Causes of Thromboembolic Conditions.** The causes are usually twofold:
- (1) a *roughened endothelial surface of a vessel*—as may be caused by arteriosclerosis, infection, or trauma—is likely to initiate the clotting process.

(2) blood often clots *when it flows very slowly* through blood vessels, where small quantities of thrombin and other procoagulants are always being formed.

ANTICOAGULANTS FOR CLINICAL USE

In some thromboembolic conditions, it is desirable to delay the coagulation process. Various anticoagulants have been developed for this purpose. The ones most clinically useful are *heparin* and the *coumarins*.

HEPARIN—INTRAVENOUS ANTICOAGULANT

COUMARINS AS ANTICOAGULANTS : a coumarin, such as oral *warfarin*


Thank you.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