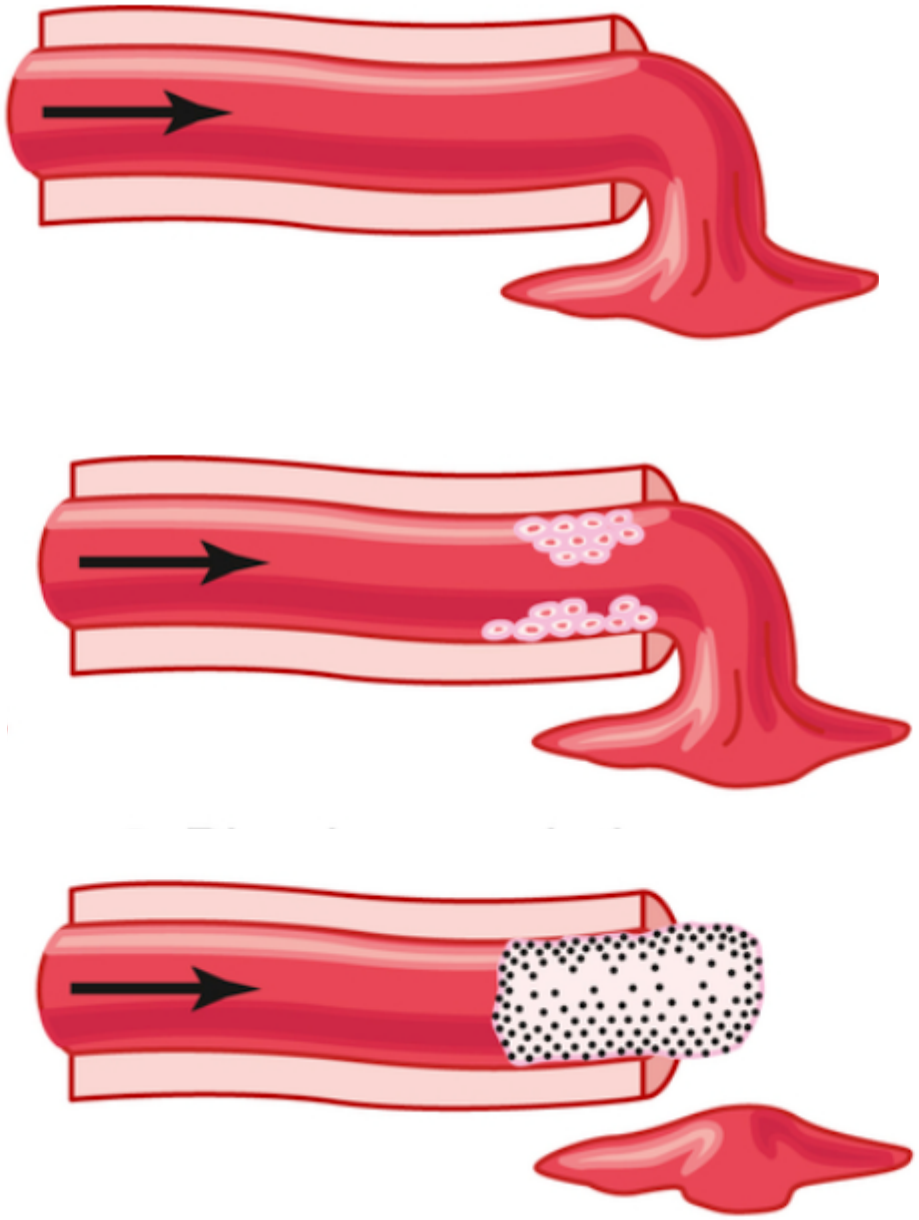
Hemostasis > Events of hemostasis

Hemostasis means prevention of blood loss and includes the following events:

(1) Vascular constriction.
(2) Formation of a platelet plug.
(3) Formation of a blood clot as a result of blood coagulation.
(4) Fibrous organization or dissolution of the blood clot



Doctors Notes are either in blue color or have a blue Background

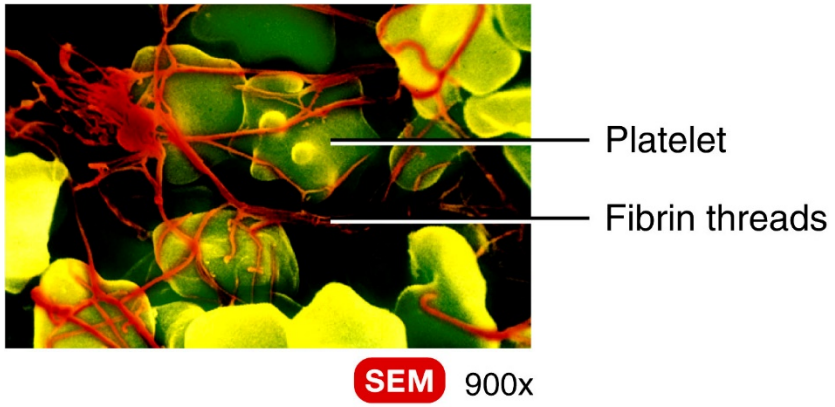
Hemostasis

3. Blood clot

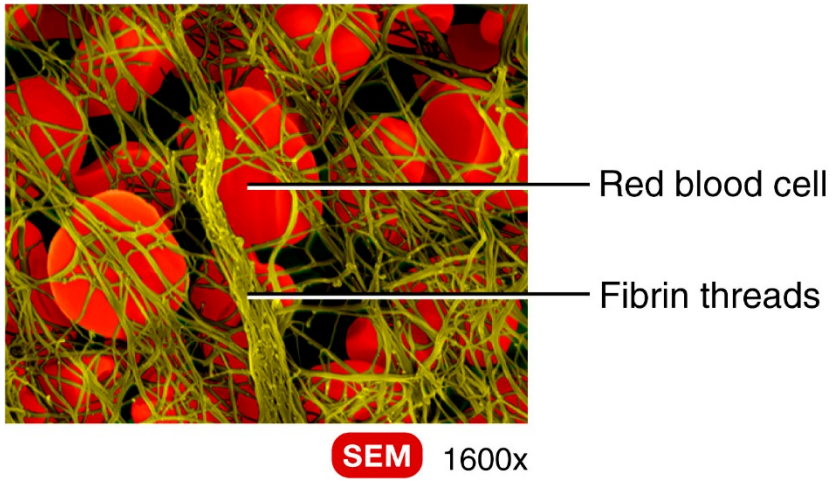
- Series of chemical reactions culminating in formation of fibrin threads.

- Clotting (coagulation) factors – Ca^{2+}, several inactive enzymes, various molecules associated with platelets or released by damaged tissues.

** The clot begins to develop in 15 to 20 seconds if the trauma to the vascular wall is severe and in 1 to 2 minutes if the trauma is minor.
** Within 3 to 6 minutes after rupture of a vessel, the entire opening or broken end of the vessel is filled with clot if the vessel opening is not too large.
** After 20 to 60 minutes, the clot retracts, which closes the vessel still further.



(a) Early stage



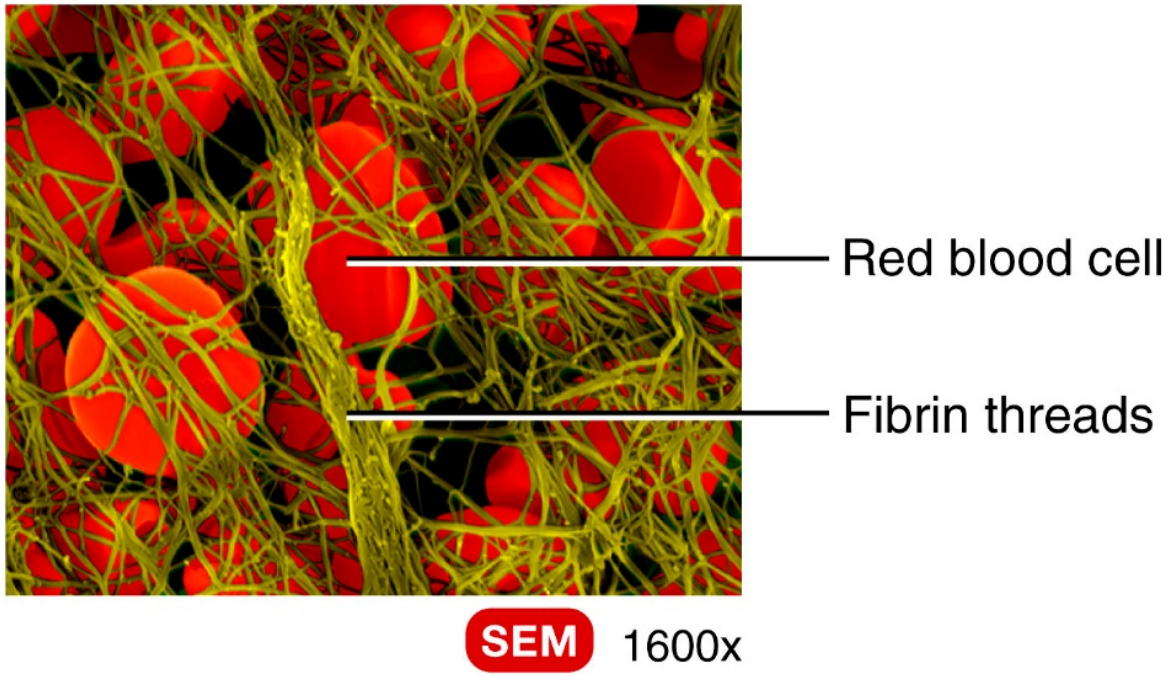
(d) Red blood cells trapped in fibrin threads

Hemostasis

3. Blood clot

- A **meshwork of fibrin** fibers running in all directions and entrapping **blood cells**, **platelets**, and **plasma**.

- The fibrin fibers also adhere to damaged surfaces of blood vessels, thereby prevents further blood loss.



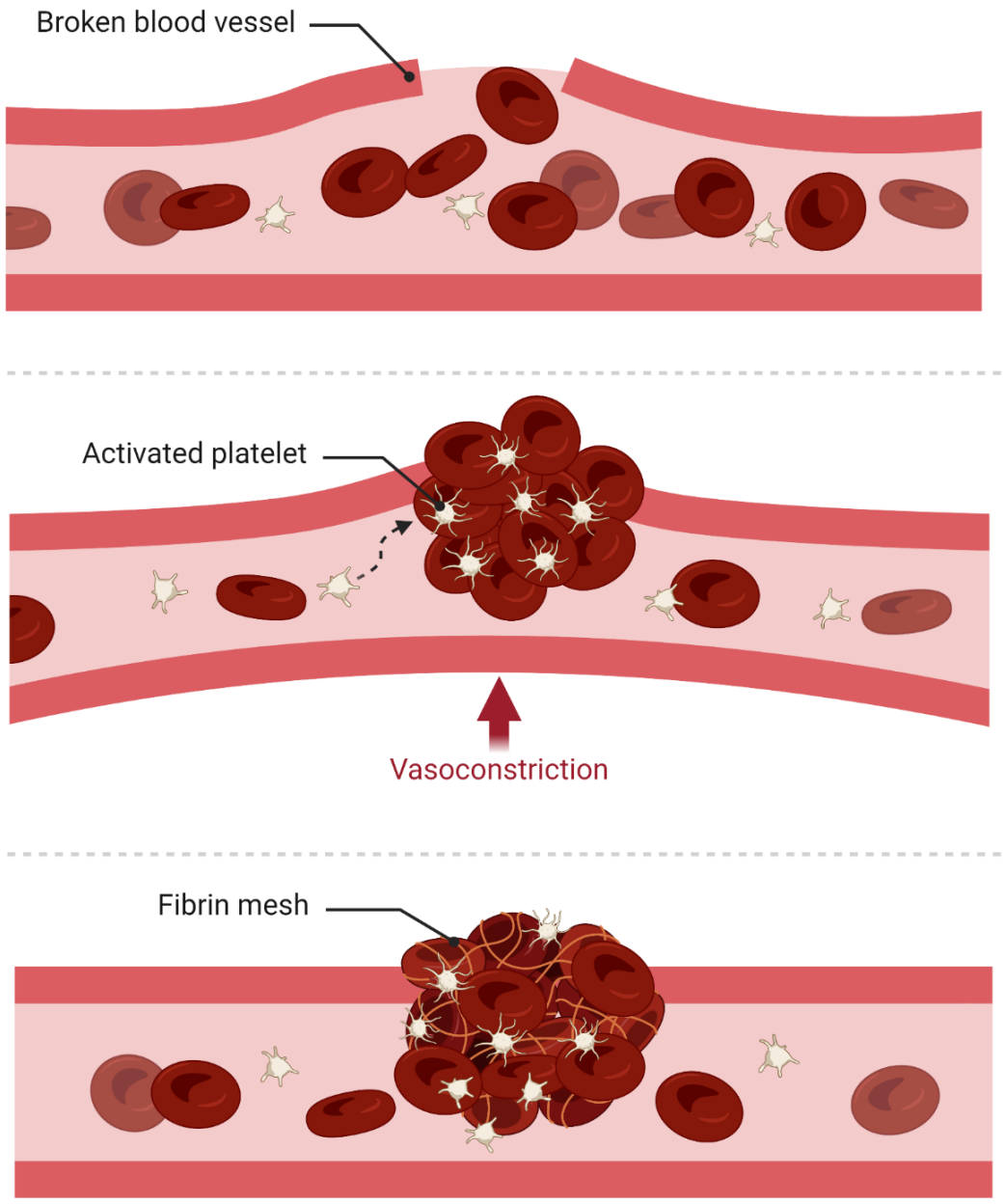
(d) Red blood cells trapped in fibrin threads

Figure 19.10d Tortora - PAP 12/e

Hemostasis 3. Clot retraction

- Within a few minutes after a clot is formed, platelets begin to contract and usually express most of the fluid from the clot within 20 to 60 minutes.

- As the clot retracts, the edges of the broken blood vessel are pulled together, thus contributing still further to hemostasis.
- **Serum:** is blood plasma minus its fibrinogen and most of the other clotting factors.

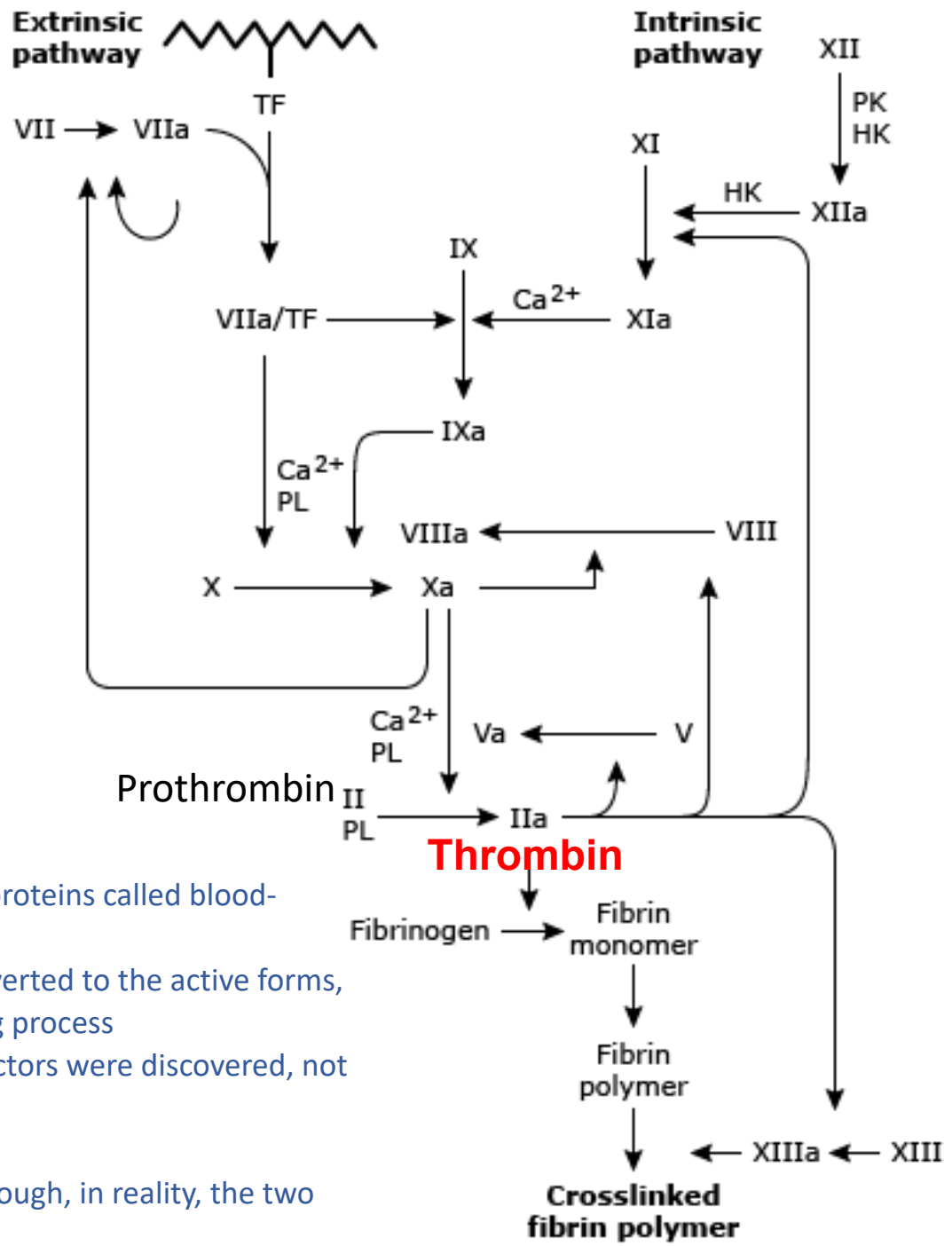


** The platelets contribute directly to clot **contraction** by activating platelet thrombosthenin, actin, and myosin molecules.

Hemostasis

3. Blood coagulation

1. Extrinsic or intrinsic pathways lead to formation of prothrombinase.
2. Prothrombinase converts prothrombin into thrombin
3. Thrombin converts fibrinogen (soluble) into fibrin (insoluble) forming the threads of the clot

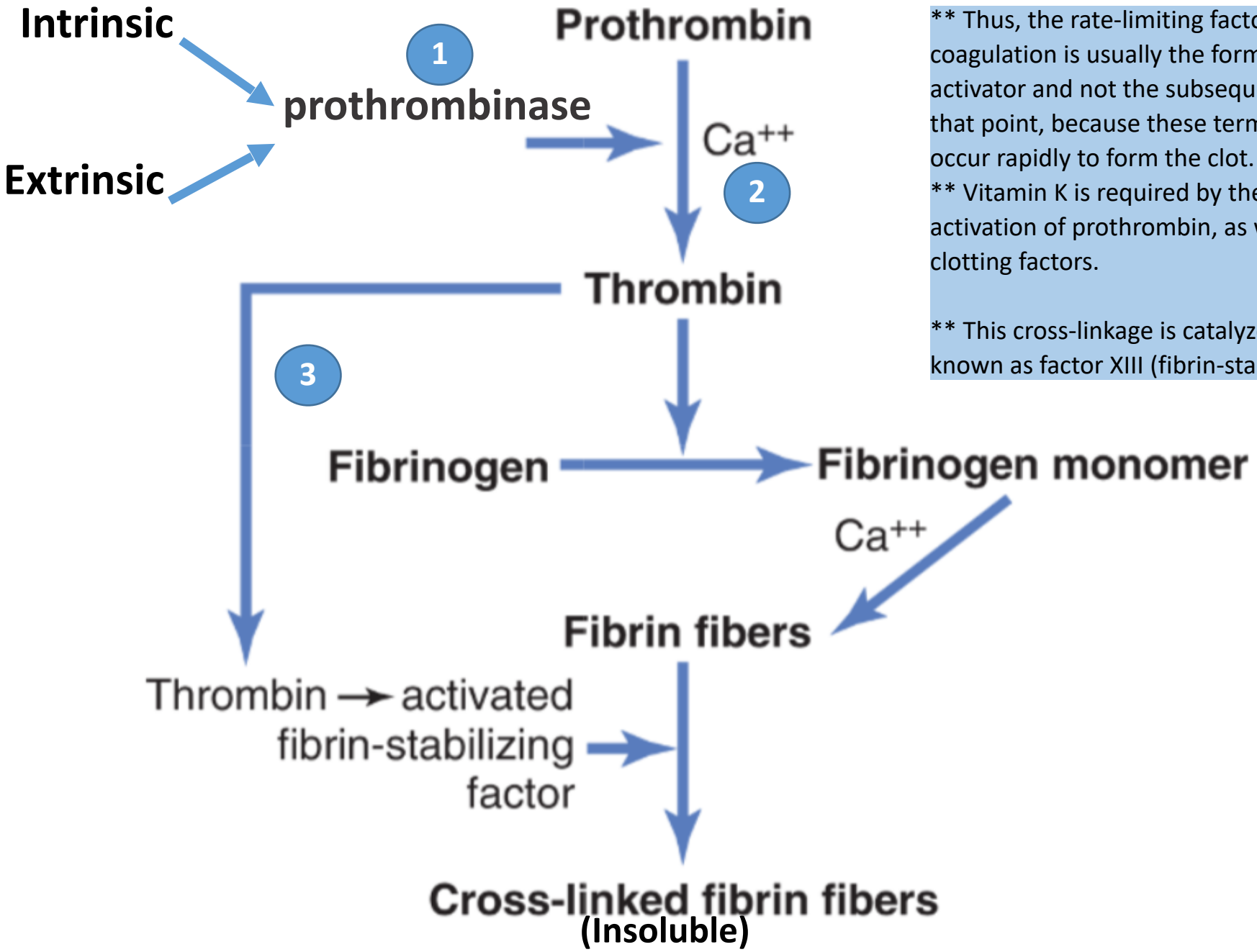


**In both the extrinsic and the intrinsic pathways, a series of different plasma proteins called blood-clotting factors plays a major role.

**Most of these proteins are inactive forms of proteolytic enzymes. When converted to the active forms, their enzymatic actions cause the successive, cascading reactions of the clotting process

**These factors are designated by roman numerals in the order in which the factors were discovered, not the order in which they participate in the clotting
Process.

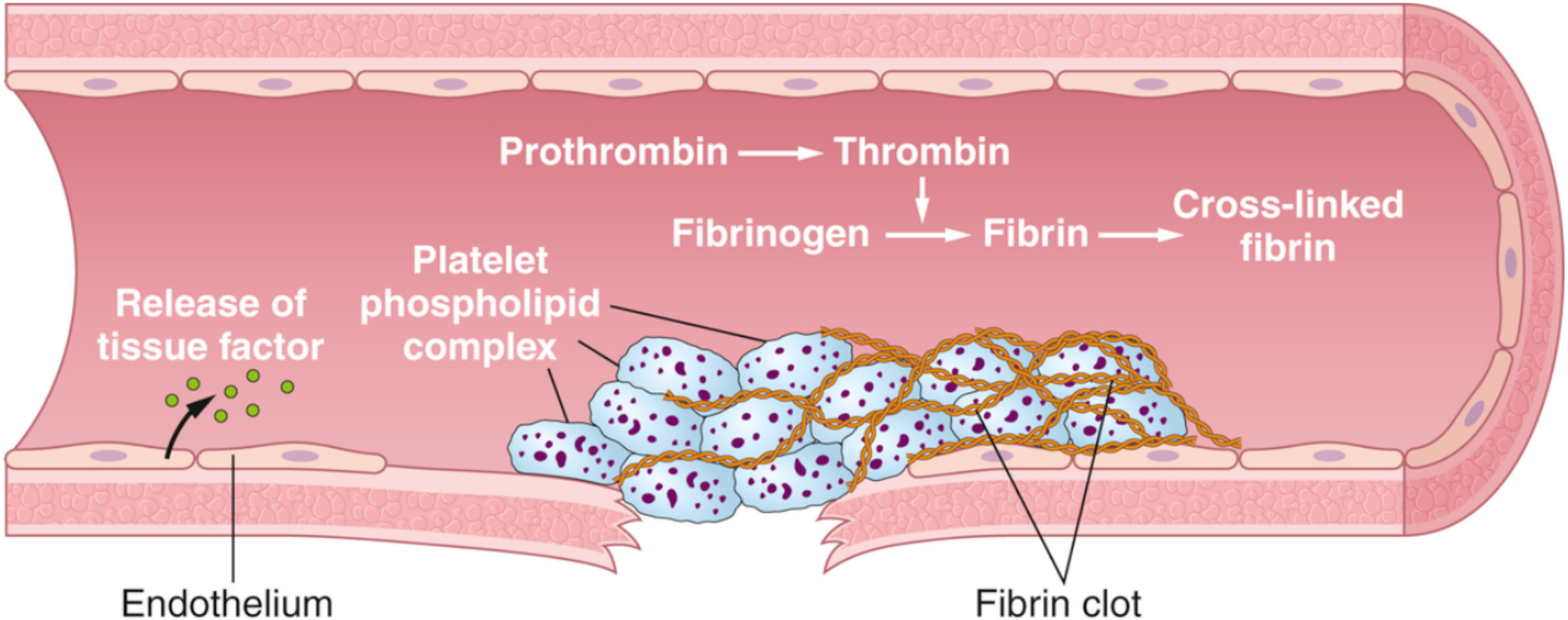
**Prothrombin activator is generally considered to be formed in two ways, although, in reality, the two ways interact constantly with each other.



** Thus, the rate-limiting factor in causing blood coagulation is usually the formation of prothrombin activator and not the subsequent reactions beyond that point, because these terminal steps normally occur rapidly to form the clot.

** Vitamin K is required by the liver for normal activation of prothrombin, as well as a few other clotting factors.

** This cross-linkage is catalyzed by a clotting factor known as factor XIII (fibrin-stabilizing factor)


Prothrombin
Thrombin
Fibrinogen
Fibrin
Cross-linked fibrin
Platelet phospholipid complex
Release of tissue factor
Endothelium
Fibrin clot

Hemostasis 3. Prothrombin and Thrombin

- Prothrombin is a plasma protein (α2-globulin).
- It is an unstable protein that can split easily into smaller compounds, one of which is thrombin (half MW).
- Prothrombin is formed continually by the liver, and it is continually being used throughout the body for blood clotting.
- Vitamin K is required by the liver for normal activation of prothrombin, as well as a few other clotting factors.
- Much of the prothrombin first attaches to prothrombin receptors on the platelets already bound to the damaged tissue.

3. Action of Thrombin on Fibrinogen to Form Fibrin

- Thrombin is an enzyme with weak proteolytic capabilities.
- It acts on fibrinogen to remove four low-molecular-weight peptides from each molecule of fibrinogen, forming one molecule of fibrin monomer.
- Fibrin monomer has the automatic capability to polymerize with other fibrin monomer molecules to form fibrin fibers.

3. Action of Thrombin on Fibrinogen to Form Fibrin

- In the early stages of polymerization, the fibrin monomer molecules are held together by **weak noncovalent** hydrogen bonding (weak clot).
- **Fibrin-stabilizing factor** that is present in small amounts in normal plasma **globulins** but is also released from **platelets** entrapped in the clot (**inactive**).
- **Thrombin** activates the fibrin-stabilizing factor which cause **covalent bonds** between more and more of the fibrin monomer molecules, as well as **multiple cross-linkages** between adjacent fibrin fibers, thus adding **strength** of the fibrin meshwork.

Hemostasis Fibrinogen

- Fibrinogen is a high-molecular-weight protein that occurs in the plasma.
- Fibrinogen is formed in the liver.
- Because of its large molecular size, little fibrinogen normally leaks from the blood vessels into the interstitial fluids, and because fibrinogen is one of the essential factors in the coagulation process, interstitial fluids ordinarily do not coagulate.

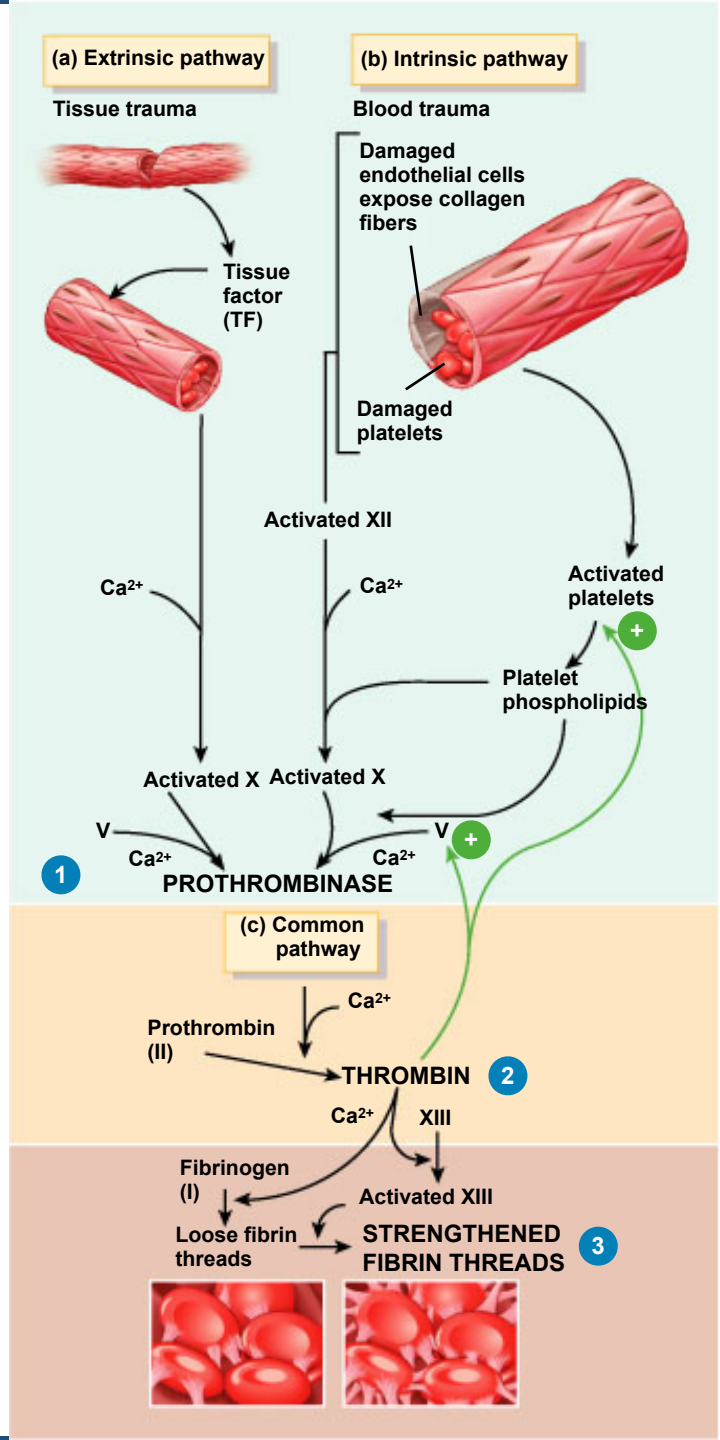
**Yet, when the permeability of the capillaries becomes pathologically increased, fibrinogen does then leak into the tissue fluids in sufficient quantities to allow clotting of these fluids in much the same way that plasma and whole blood can clot.

Hemostasis 3. Blood coagulation

- Prothrombin activator is generally considered to be formed in two ways:

(1) by the **extrinsic pathway** that begins with trauma to the vascular wall and surrounding tissues

(2) by the **intrinsic pathway** that begins in the blood itself.



Hemostasis 3. Blood coagulation

*Extrinsic pathway

Fewer steps then intrinsic and occurs rapidly

Tissue factor (TF) leaks into the blood from cells *outside (extrinsic to)* blood vessels and initiates formation of prothrombinase

*Intrinsic pathway

More complex and slower than extrinsic

Activators are either in direct contact with blood or contained *within (intrinsic to)* the blood

Outside tissue damage not needed

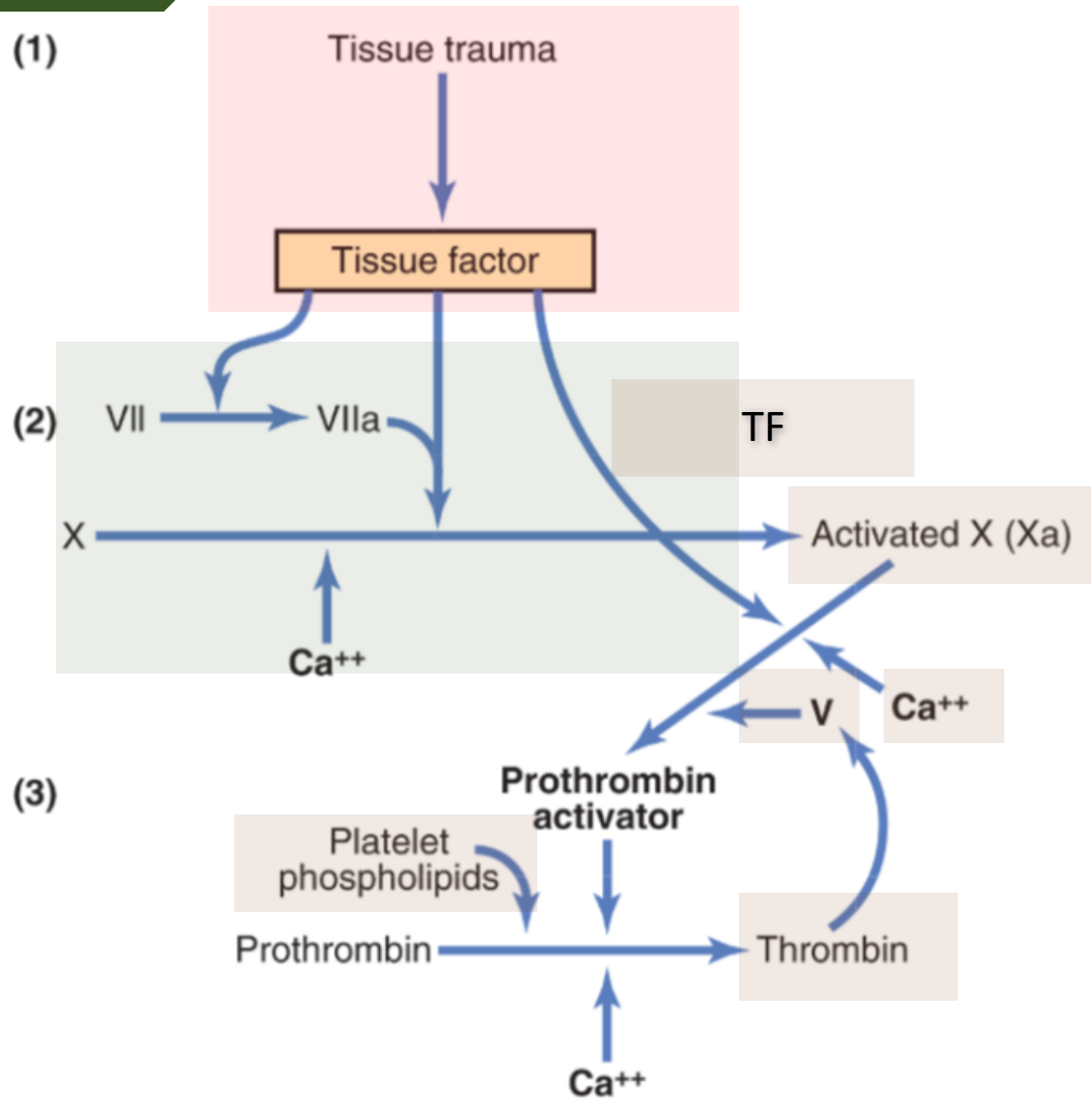
Also forms prothrombinase

**The intrinsic and extrinsic mechanisms usually operate simultaneously. When a blood vessel ruptures during tissue injury, the intrinsic mechanism stops blood in the injured vessel, and the extrinsic mechanism clots blood that escaped into the tissue before the vessel was sealed off. Typically, clots are fully formed in 3 to 6 minutes.

** the extrinsic pathway can be explosive, limited only by the amount of **tissue factor** released from the traumatized tissues and by the **quantities of Factors X, VII, and V in the blood.** With severe tissue trauma, clotting can occur in as little as **15 seconds**. The intrinsic pathway is much slower to proceed, usually requiring 1 to 6 minutes to cause clotting.

Hemostasis 3. Extrinsic pathway

1. Release of tissue factor
2. Activation of factor X—role of factor VII and tissue factor.
3. Effect of Xa to form prothrombin activator—role of factor V



** Tissue factor: Traumatized tissue releases a complex of several factors called tissue factor. This factor is composed especially of **phospholipids** from the membranes of the tissue plus **a lipoprotein** complex that functions mainly as a **proteolytic enzyme**.

** 2. The **activated Factor X** combines immediately with tissue phospholipids that are part of **tissue factors** or with additional **phospholipids** released from **platelets**, as well as with **Factor V** to form the complex called **prothrombin activator.**

** 4. Thus, in the final prothrombin activator complex, **activated factor X** is the **actual protease** that causes splitting of prothrombin to form thrombin. **Activated factor V** greatly **accelerates** this protease activity, and **platelet phospholipids** act as a **vehicle** that further accelerates the process. Note especially the **positive feedback effect of thrombin**, acting through factor V, to accelerate the entire process once it begins.

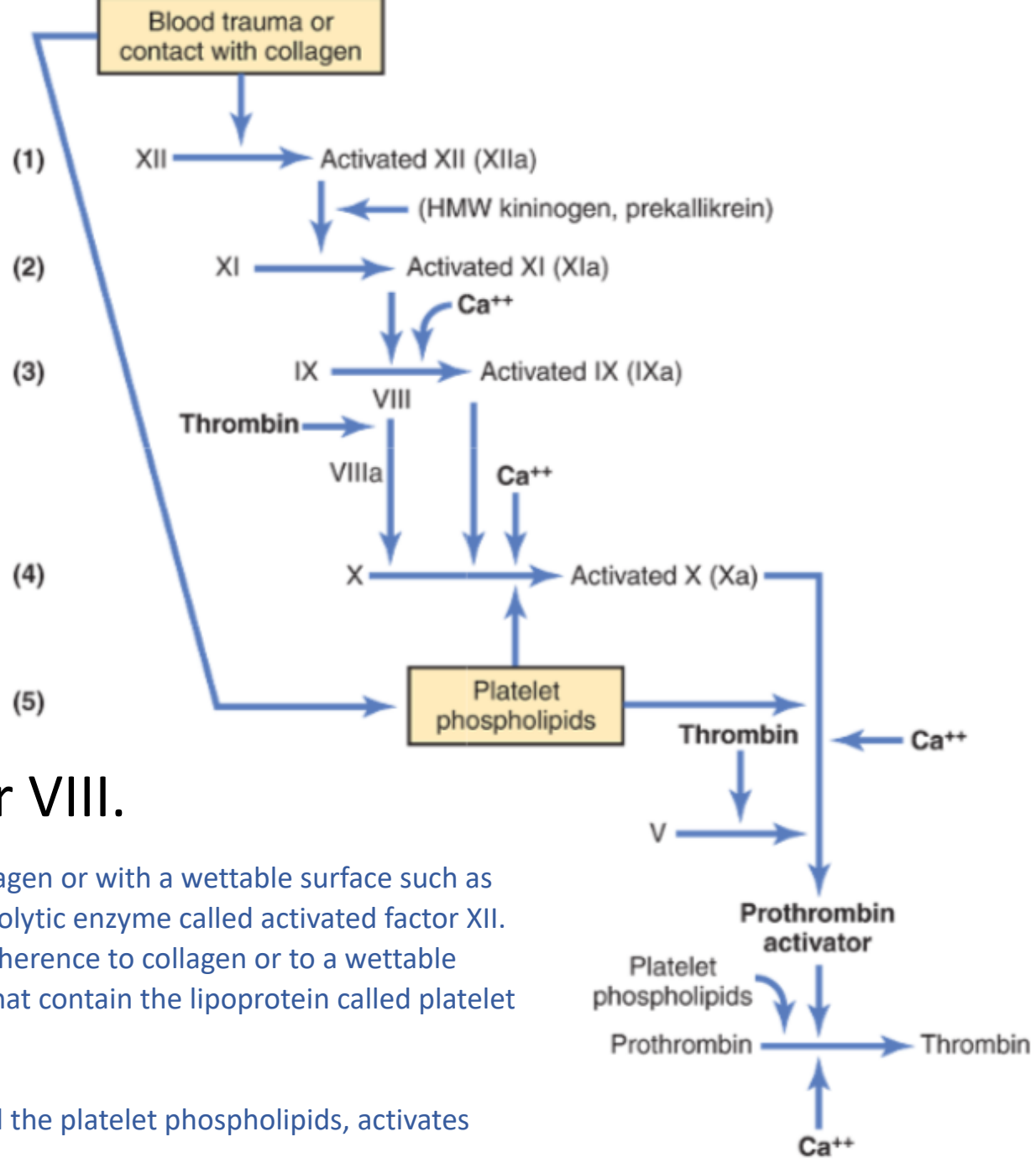
3. Intrinsic pathway

1. Blood trauma causes activation of factor XII and release of platelet phospholipids

2. Activation of factor XI

3. Activation of factor IX

4. Activation of factor X—role of factor VIII.



** (1) When factor XII is disturbed, such as by coming into contact with collagen or with a wettable surface such as glass, it takes on a new molecular configuration that converts it into a proteolytic enzyme called activated factor XII. Simultaneously, the blood trauma also damages the platelets because of adherence to collagen or to a wettable surface (or by damage in other ways); this releases platelet phospholipids that contain the lipoprotein called platelet factor 3, which also plays a role in subsequent clotting reactions.

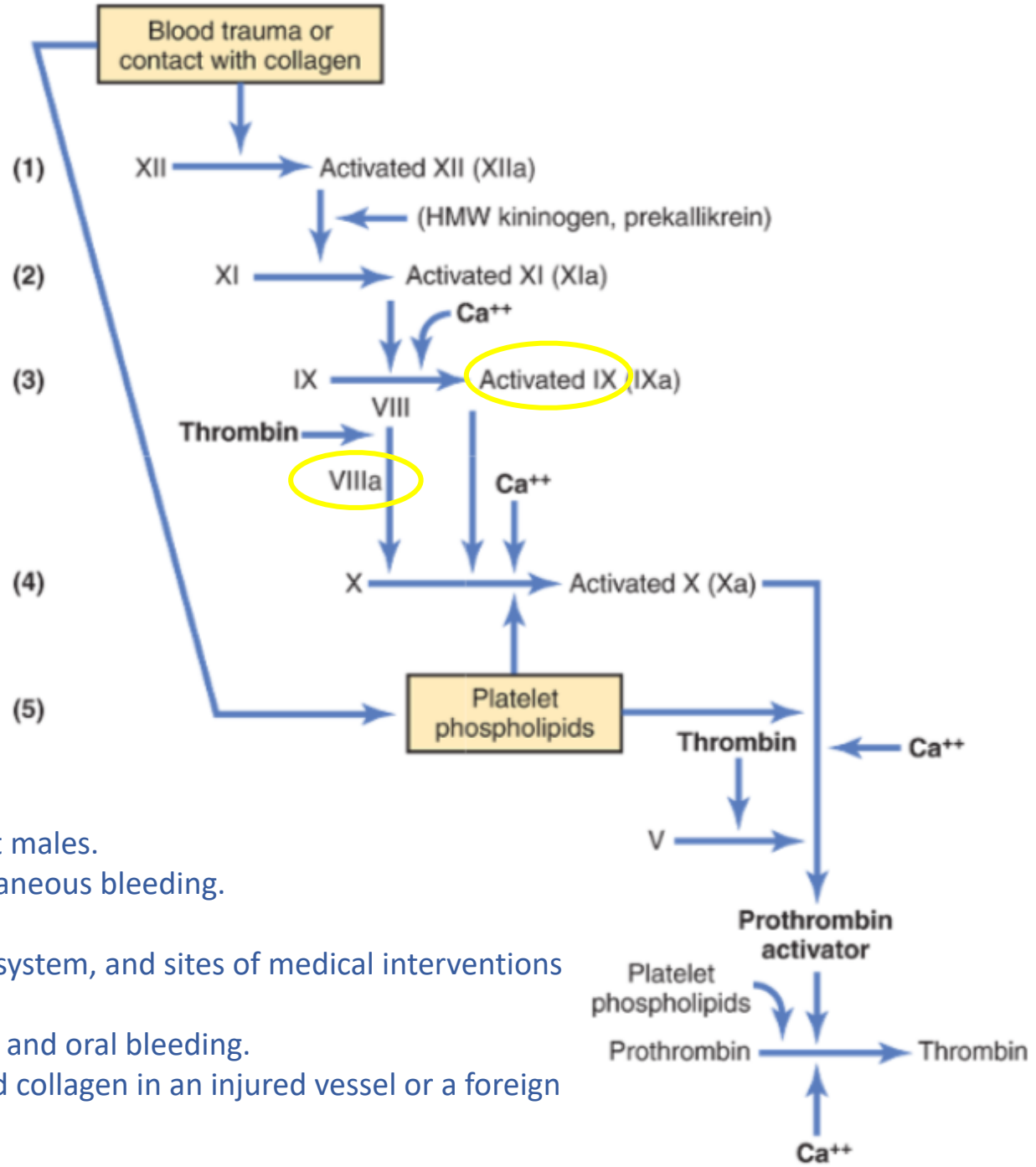
** (4) The activated factor IX, acting in concert with activated factor VIII and the platelet phospholipids, activates factor X.

Hemostasis

3. Intrinsic pathway

hemophilia A or classic hemophilia (85%) : deficiency of Factor VIII

hemophilia B (15%): deficiency of Factor IX.



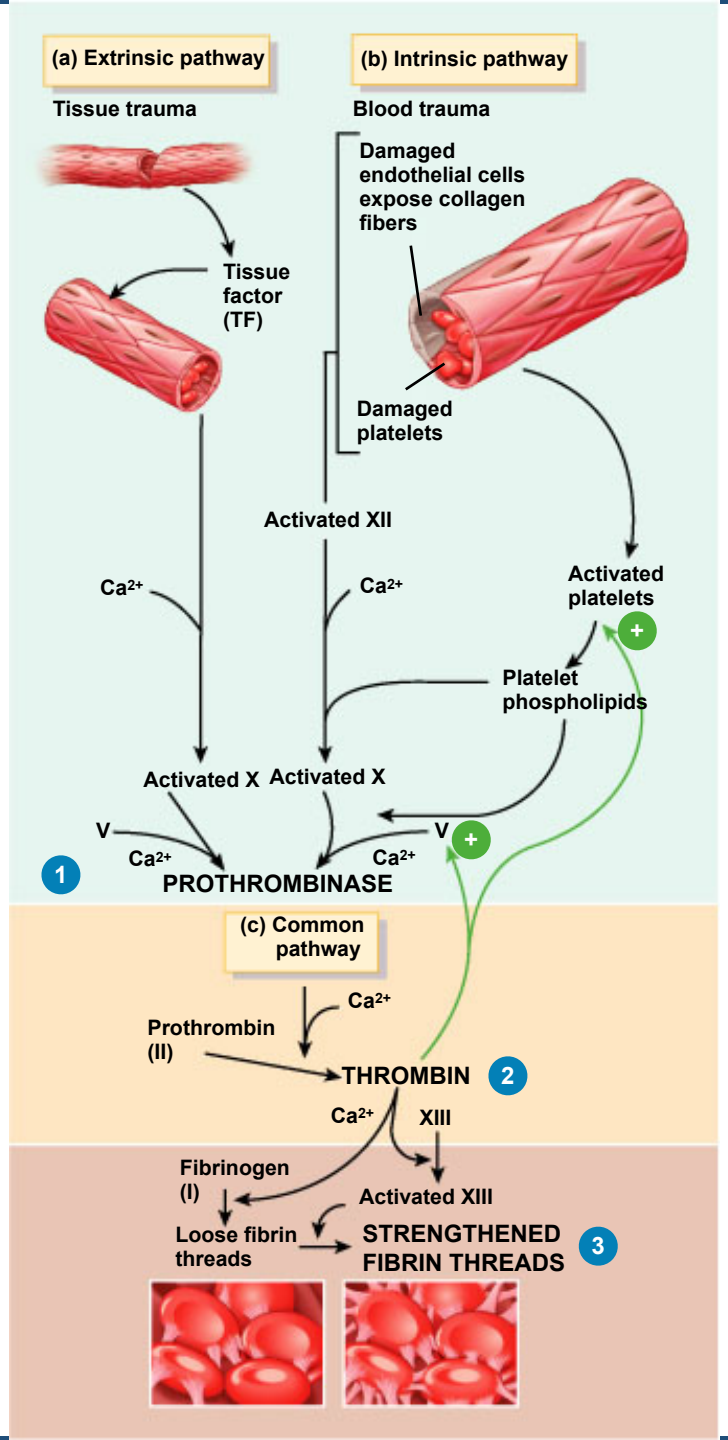
** Hemophilia A and B are X-linked disorders that predominantly affect males.
** Patients with more severe hemophilia are more likely to have spontaneous bleeding.
** Immediate and delayed bleeding after trauma is common
** Common sites of bleeding in newborns include the central nervous system, and sites of medical interventions including circumcision, heel sticks, and venipunctures.
** **Children** – Bruising, joint bleeds, and other sites of musculoskeletal, and oral bleeding.
** ** **factor XII** is activated by coming into contact with either exposed collagen in an injured vessel or a foreign surface such as a glass test tube

Hemostasis 3. Blood coagulation

Thrombin has 2 positive feedback effects:

- Accelerates formation of prothrombinase (V)
- Thrombin activates platelets

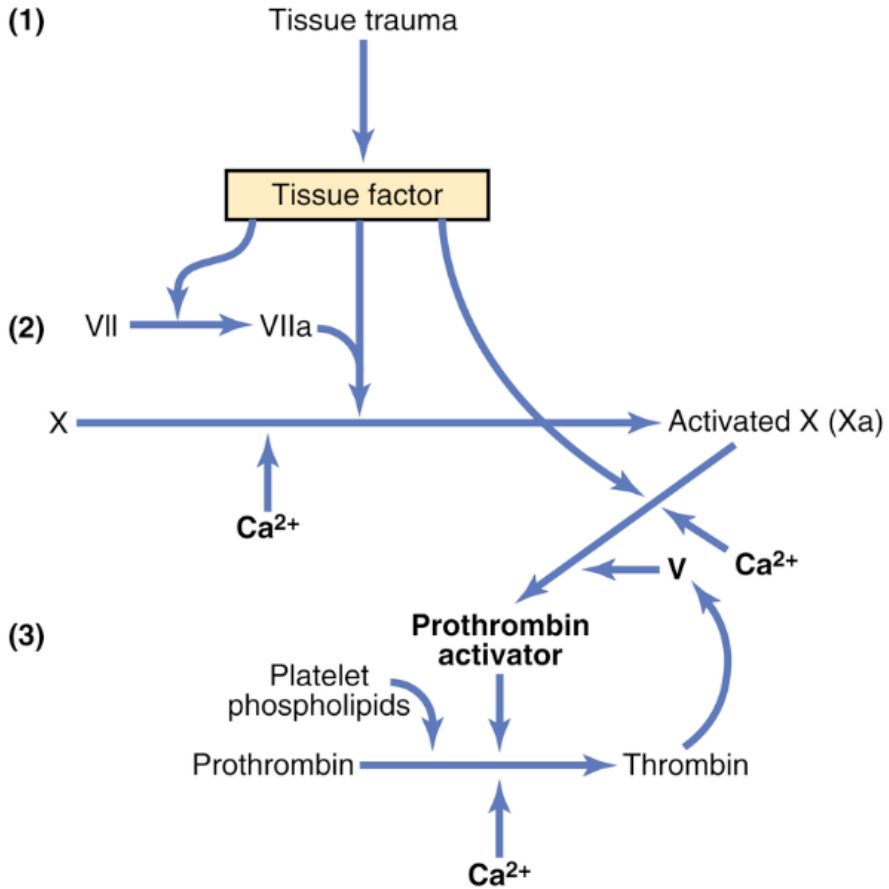
*****Roles of Thrombin Multitasking thrombin, in addition to (1) converting fibrinogen into fibrin, also (2) activates factor XIII to stabilize the resultant fibrin mesh, (3) acts in a positive-feedback fashion to facilitate its own formation, and (4) enhances platelet aggregation, which in turn is essential to the clotting process

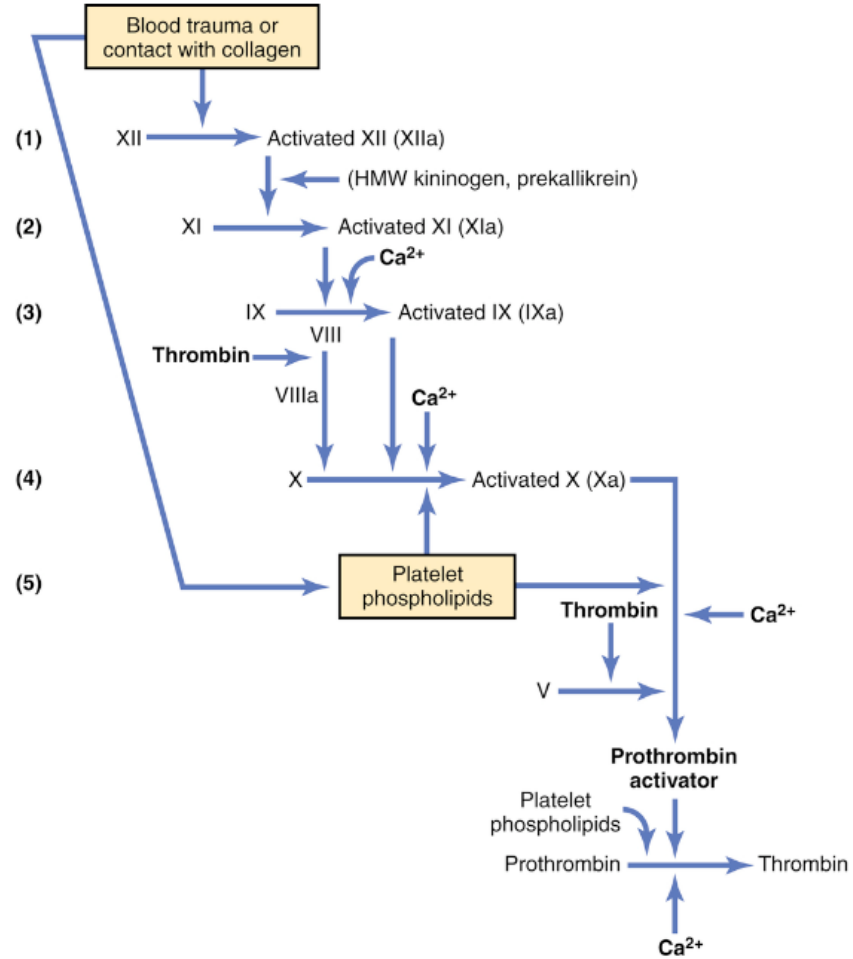


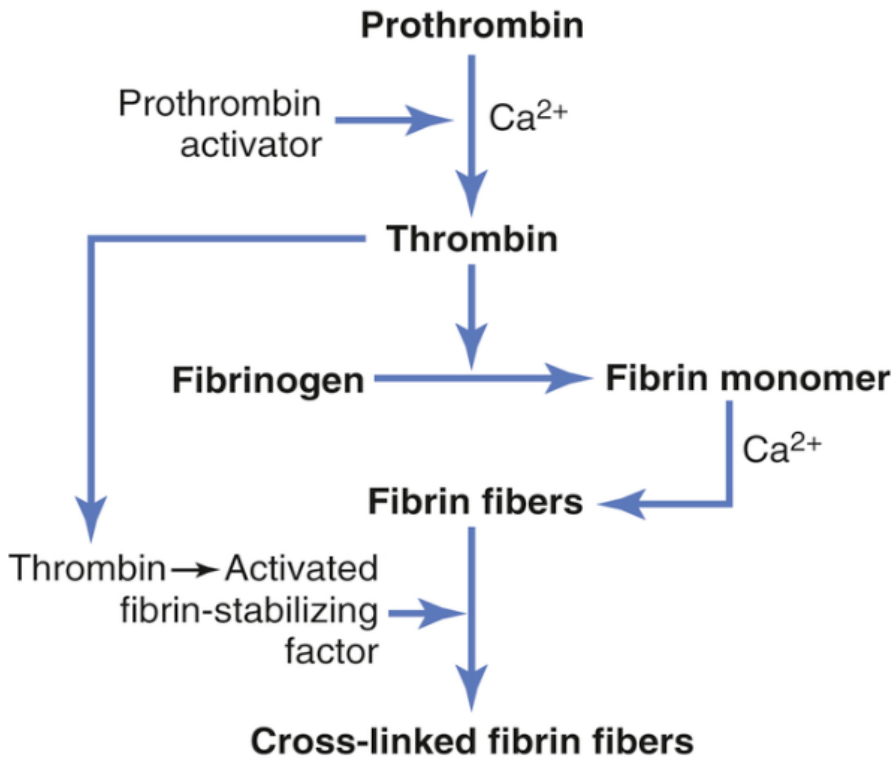
Think!

Why do we use Ethylenediaminetetraacetic acid (EDTA) tube to collect blood for CBC?

Except for the first two steps in the intrinsic pathway, calcium ions are required for promotion or acceleration of all the blood-clotting reactions.
→ Therefore, in the absence of calcium ions, blood clotting by either pathway does not occur.


(1)
Tissue trauma
Tissue factor
(2)
VII
VIIa
X
Activated X (Xa)
Ca2+
V
Ca2+
(3)
Prothrombin activator
Platelet phospholipids
Prothrombin
Thrombin
Ca2+

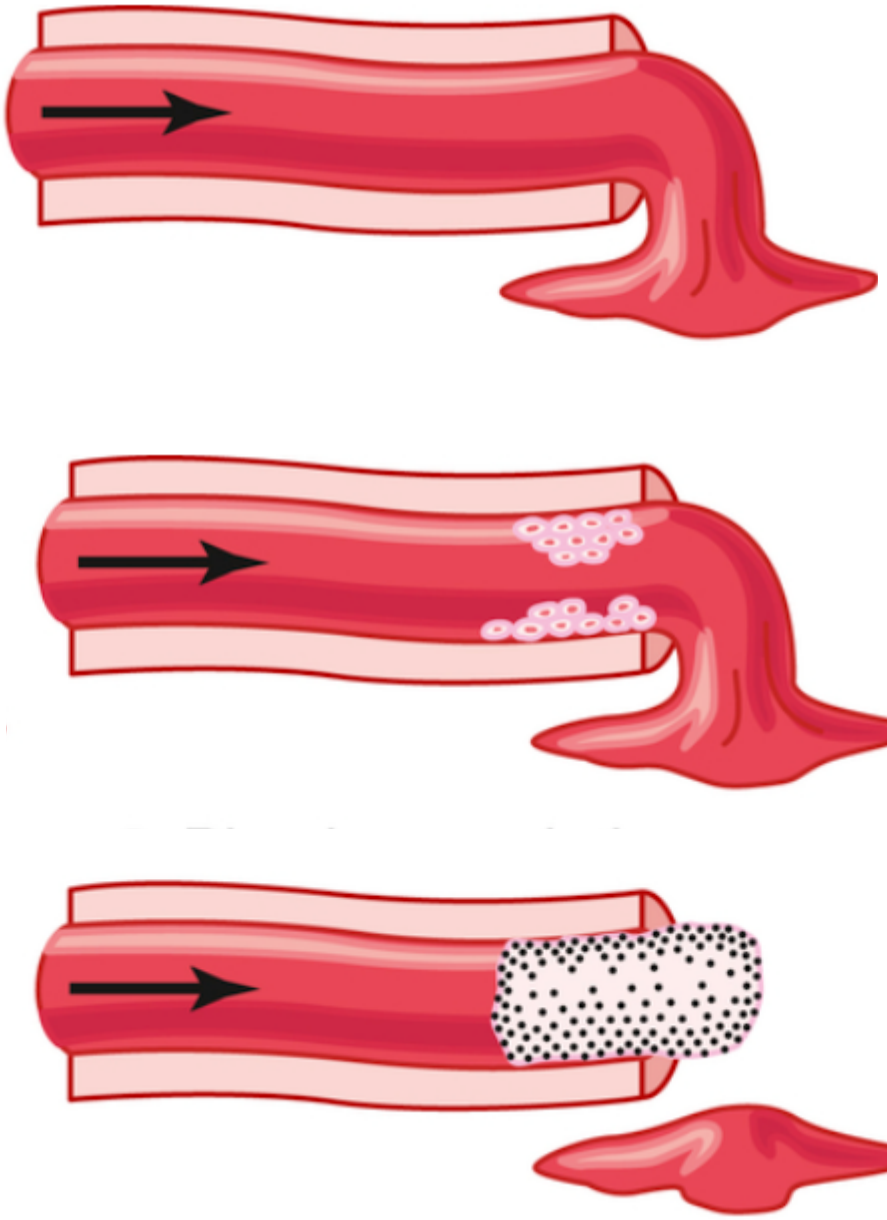

Blood trauma or contact with collagen
(1)
XII
Activated XII (XIIa)
(HMW kininogen, prekallikrein)
(2)
XI
Activated XI (XIa)
Ca2+
(3)
IX
Activated IX (IXa)
VIII
Thrombin
VIIIa
Ca2+
(4)
X
Activated X (Xa)
(5)
Platelet phospholipids
Thrombin
Ca2+
V
Prothrombin activator
Platelet phospholipids
Prothrombin
Thrombin
Ca2+


Prothrombin
Prothrombin activator
Ca2+
Thrombin
Fibrinogen
Fibrin monomer
Ca2+
Fibrin fibers
Thrombin
Activated fibrin-stabilizing factor
Cross-linked fibrin fibers

Hemostasis > Events of hemostasis

Hemostasis means prevention of blood loss and includes the following events:

(1) Vascular constriction.
(2) Formation of a platelet plug.
(3) Formation of a blood clot as a result of blood coagulation.
(4) Fibrous Organization or Dissolution of the Blood Clot



Hemostasis 4. Growth of fibrous tissue

Once a blood clot has formed, it can follow one of two courses:

(1) It can become invaded by *fibroblasts,* which subsequently form connective tissue all through the clot (promoted at least partially by **growth factor** secreted by **platelets**)

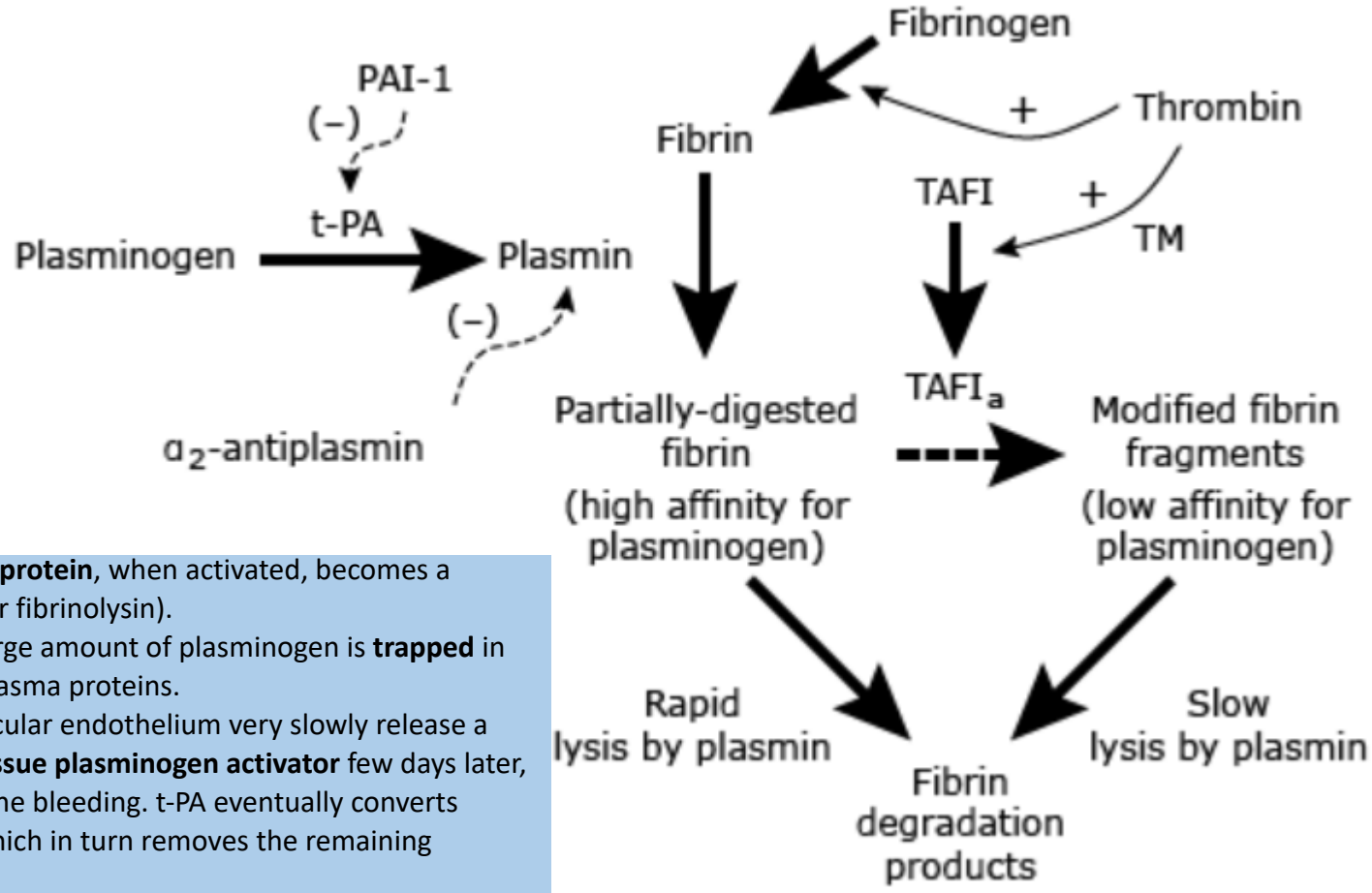
(2) it can dissolve.

** A clot is not meant to be a permanent solution to vessel injury. It is a transient device to stop bleeding until the vessel can be repaired.

** The aggregated platelets secrete a chemical that helps promote the invasion of fibroblasts from the surrounding connective tissue into the wounded area of the vessel. Fibroblasts form a scar at the vessel defect..

Hemostasis

4. Lysis of clot



Plasminogen is a **plasma protein, when activated, becomes a substance called plasmin (or fibrinolysin).
When **a clot is formed**, a large amount of plasminogen is **trapped** in the clot along with other plasma proteins.
The injured tissues and vascular endothelium very slowly release a powerful activator called **tissue plasminogen activator** few days later, after the clot has stopped the bleeding. t-PA eventually converts plasminogen to plasmin. which in turn removes the remaining unnecessary blood clot.

**If clots were not removed after they performed their hemostatic function, their accumulation would eventually obstruct the vessels

Prevention

Normal Intravascular Anticoagulants

- **Endothelial surface factors**
- **Antithrombin action of fibrin and antithrombin III.**
- **Heparin.**

More than 50 important substances that cause or affect blood coagulation have been found in the blood and in the tissues—some that promote coagulation, called procoagulants, and others that inhibit coagulation, called anticoagulants. Whether blood will coagulate depends on the balance between these two groups of substances. In the blood stream, the anticoagulants normally predominate, so the blood does not coagulate while it is circulating in the blood vessels. However, when a vessel is ruptured, procoagulants from the area of tissue damage become activated and override the anticoagulants, and then a clot does develop.

Prevention — Normal Intravascular Anticoagulants

➢**Endothelial Surface Factors**

- 1) the *smoothness* of the endothelial cell surface
- 2) a layer of **glycocalyx** on the endothelium
- 3) a protein bound with the endothelial membrane, **thrombomodulin,** which binds **thrombin**.
- the **thrombomodulin-thrombin** complex also activates a plasma **protein C**, that acts as an anticoagulant by **inactivating** activated **Factors V and VIII.**
- 4) Intact endothelial cells also produce other substances such **a prostacyclin and nitric oxide (NO)** that inhibit **platelet aggregation** and initiation of blood clotting

When the endothelial wall is damaged, **its smoothness and its glycocalyx-thrombomodulin layer are lost, which activates both **Factor XII** and the **platelets**, thus setting off the intrinsic pathway of clotting. If Factor XII and platelets come in contact with the **subendothelial collagen**, the activation is even **more powerful.**

➢**Antithrombin Action of Fibrin and Antithrombin III.**

- Among the most important anticoagulants in the blood are those that remove thrombin from the blood.

(1) the **fibrin fibers** that are formed during the process of clotting (85 to 90%)

(2) The thrombin that does not adsorb to the fibrin fibers soon combines with **antithrombin III.** (an alpha-globulin)

Prevention — Normal Intravascular Anticoagulants

➢**Heparin**

- Highly negatively charged conjugated polysaccharide
- Powerful anticoagulant, but its concentration in the blood is normally low.
- Widely used as a pharmacological agent.
- Increases effectiveness of antithrombin III.
- Inhibits thrombin, activated factors xII, xI, x, and Ix.
- Produced in basophil and mast cells.

Prevention Outside body Anticoagulants

- When blood is collected in a glass test tube normally clots in about 6 minutes.
- **Siliconized containers** often does not clot for 1 hour or more. silicone prevents contact **activation of platelets and Factor XII.**
- **Heparin** → when blood must be passed through a heart-lung machine or artificial kidney machine and then back into the person.
- **Soluble oxalate, citrate ion**→ decreases the ionic calcium level → blood coagulation is blocked

Thromboembolic Conditions → Causes

- A thrombus → an abnormal clot that develops in a blood vessel.
- An embolus → freely flowing clots.
- Emboli that originate in large arteries or in the left side of the heart → brain, kidneys, or elsewhere.
- Emboli that originate in the venous system or in the right side of the → lungs (pulmonary embolism).

Several factors, acting independently or simultaneously, can cause *thromboembolism*: (1) Roughened vessel surfaces associated with atherosclerosis can lead to thrombus formation (see p. 327). (2) Imbalances in the clotting–anticlotting systems can trigger clot formation. (3) Slow-moving blood is more apt to clot, probably because small quantities of fibrin accumulate in the stagnant blood, for example, in blood pooled in varicosed leg veins (see p. 364) or pooled in ineffectively pumping atria during atrial fibrillation (see p. 313). (4) Widespread clotting is occasionally triggered by release of tissue thromboplastin into the blood from large amounts of traumatized tissue. widespread clotting can occur in **septicemic shock**, in which bacteria or their toxins initiate the clotting cascade.

- **Cause of Thromboembolic Conditions**

(1) Any 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.

Thromboembolic Conditions DIC

- **Disseminated Intravascular Coagulation**
- This often results from the presence of **large amounts** of **traumatized tissue** in the body that releases **great quantities of tissue factor** into the blood.
- **Septicemia**, in which either circulating bacteria or bacterial toxin
- Plugging of small peripheral vessels greatly diminishes delivery of oxygen and other nutrients to the tissues.
- Bleeding → The reason for this is that so many of the clotting factors are removed by the widespread clotting

Think!

There is genetically engineered tissue plasminogen activator (t-PA) available.

When can you use tPA ?

Self Reading!

Prothrombin time [**PT**]

Activated thromboplastin time [**aptt**]