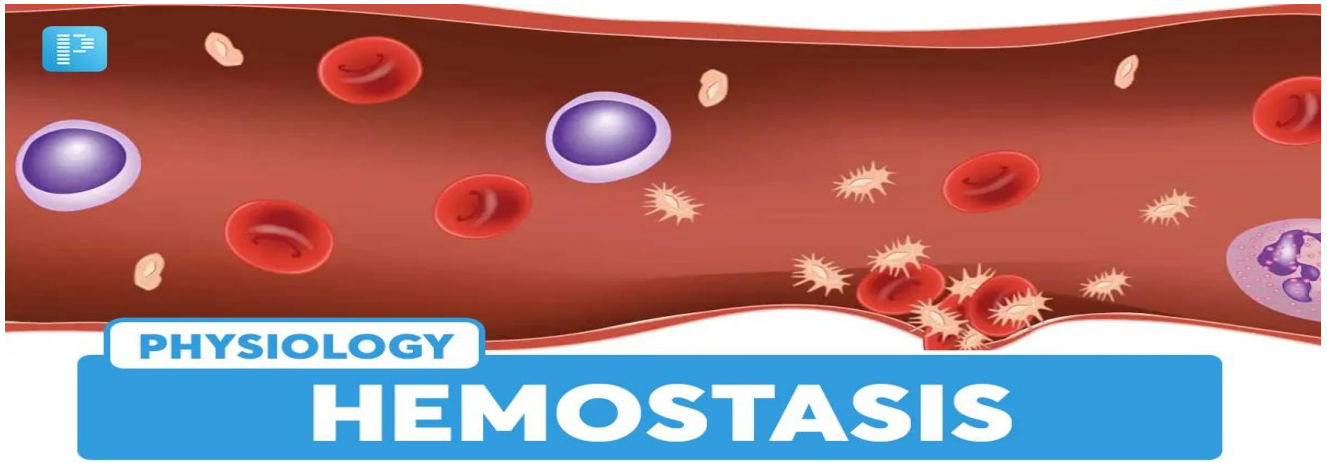
HLS MODULE
PHYSIOLOGY (LECTURE 8)
HEMOSTASIS



BY

Dr. Fatma Farrag Ali

Associate Professor of Medical Physiology

Faculty of Medicine - Mutah University

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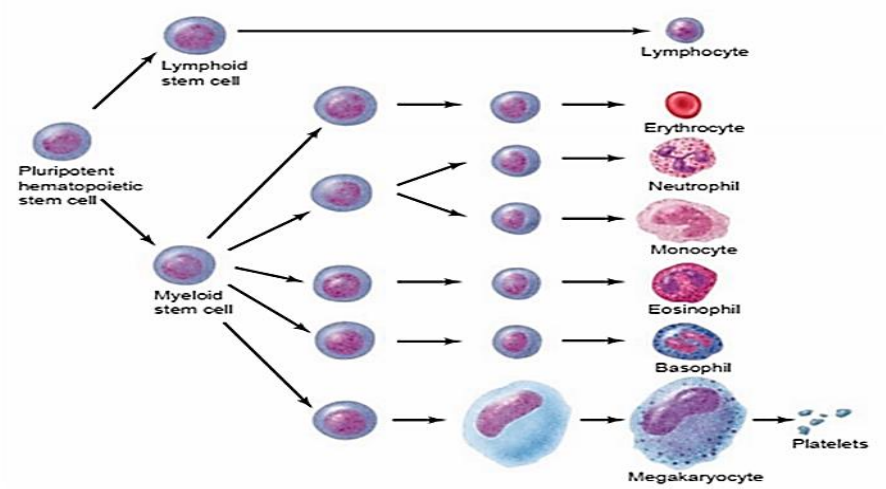
PLATELETS (THROMBOCYTES)

- Platelets are small, granulated bodies that aggregate at sites of vascular injury.
- They lack nuclei and are 2–4 µm in diameter (much smaller than erythrocytes).
- They are produced in **red bone marrow from megakaryocytes**.
- Small fragments of megakaryocytes break off and enter blood as platelets which play an important role in preventing blood loss.
- **Their normal count ranges between 250,000-400,000 (average: 300,000/µL)**.
- They normally have a half-life of about 4 days.
- Between 60% and 75% of the platelets are in the circulating blood, and the remainder are mostly in the spleen. Splenectomy causes an **increase in the platelet count (thrombocytosis)**.



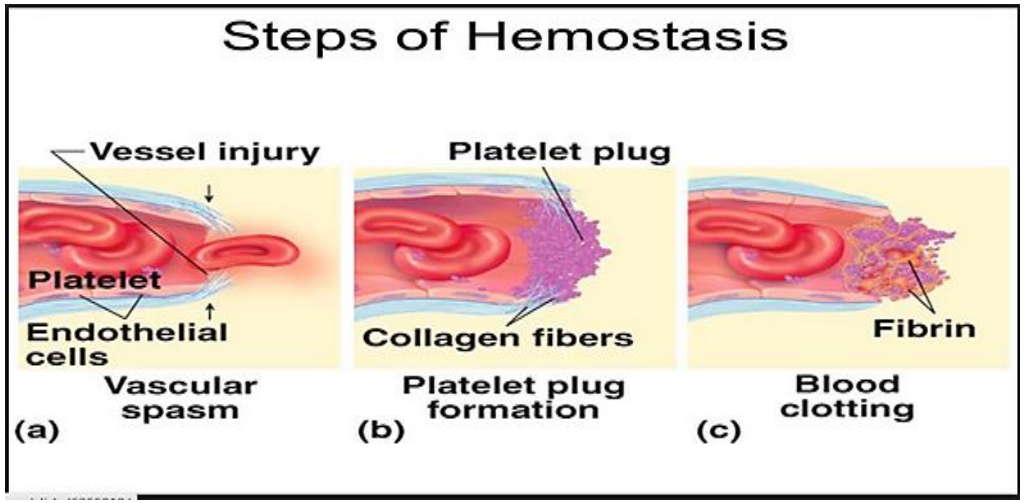
Hemostasis: Preventing Blood Loss

HEMOSTASIS is the process of stoppage of bleeding by forming clots in the walls of damaged blood vessels thus preventing blood loss while maintaining blood in a fluid state within the vascular system.

- ✓ When a blood vessel is damaged, blood can leak into other tissues (hematoma) or blood can be lost from the body.
- ✓ The body can tolerate a small amount of blood loss and can produce new blood to replace it. But, a large amount of blood loss can lead to death.
- ✓ Physiological hemostatic mechanisms are most effective in dealing with injuries in small vessels (arterioles, capillaries, and venules) which are the most common sources of bleeding in everyday life.
- ✓ In contrast, the body usually can't control bleeding from a medium or large artery.
- ✓ Venous bleeding leads to less rapid blood loss because veins have low blood pressure.

When a small blood vessel is damaged or injured, loss of blood is minimized by three processes:

1) **Vascular spasm.**
2) **Platelet plug formation (temporary hemostatic plug).**
3) **Blood clotting or coagulation (Definitive clot).**



(1) Vascular Spasm

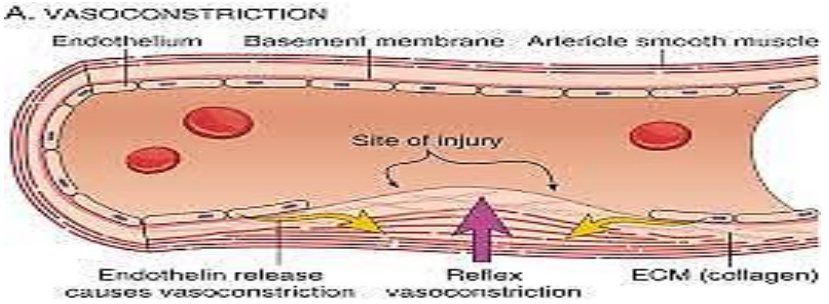
Vascular spasm is an immediate but temporary constriction of a blood vessel that results when smooth muscle within the wall of the vessel constricts.

It slows the flow of blood in the affected area.

It can close small vessels completely and stop the flow of blood through them.

Mechanism of vascular spasm:

- **Damage to blood vessels can activate nervous system reflexes that cause vascular spasm.**
- **Chemicals also produce vascular spasm.** For example**, platelets release serotonin and thromboxane A_2 ; TXA_2 (**which is derived from certain prostaglandins) **and endothelial cells lining blood vessels release** the peptide **endothelin.**



(2) Platelet Plug Formation

- **Platelet plug is an accumulation of platelets that can seal up a small break in a blood vessel**.
- Platelet plug formation is very important in maintaining the integrity of blood vessels because small tears occur in the small vessels many times each a day.
- **People who lack normal number of platelets (or defective function of platelets) tend to develop numerous small hemorrhages in their skin and internal organs.**
- **The formation of platelet plug occurs through a series of steps (but in actuality many of these steps occur at the same time):**

Platelet Adhesion

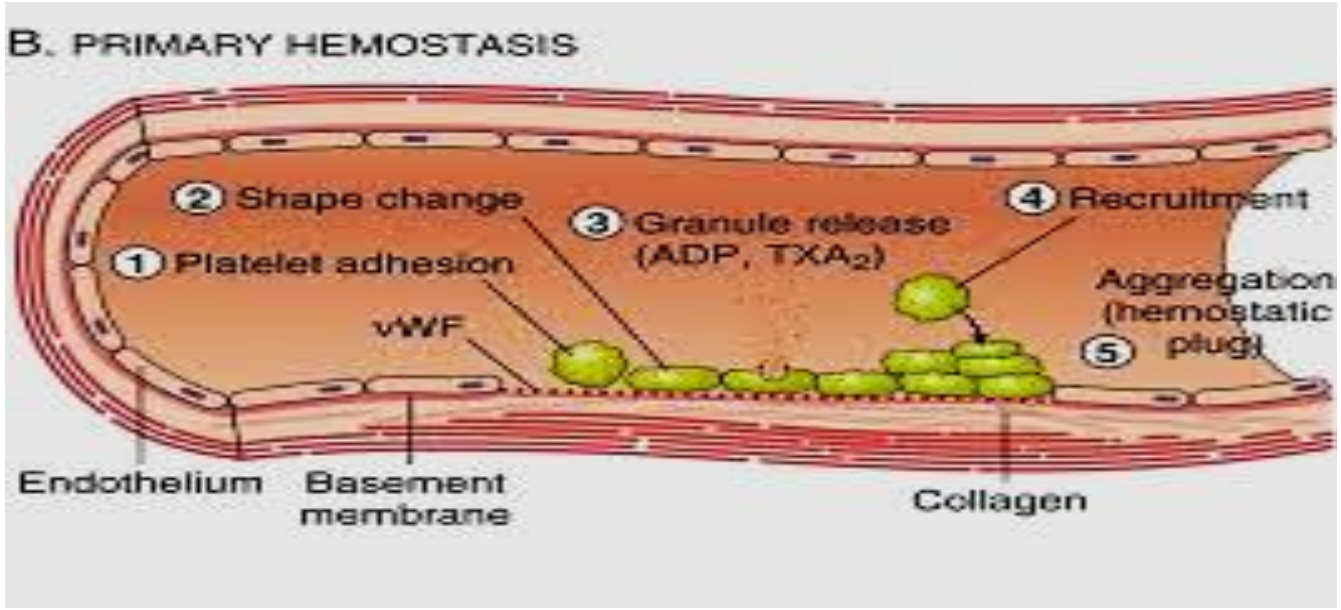
- First, **platelets stick to the collagen** exposed by blood vessel damage.
- Most **platelet adhesion is mediated through von Willebrand factor (vWF)** (a protein produced and secreted by blood vessel endothelial cells and platelets).
- **vWF forms a bridge between collagen and platelets** by binding to platelet surface receptors and collagen.
- **After platelets adhere to collagen, they become activated, change shape, and release chemicals.**

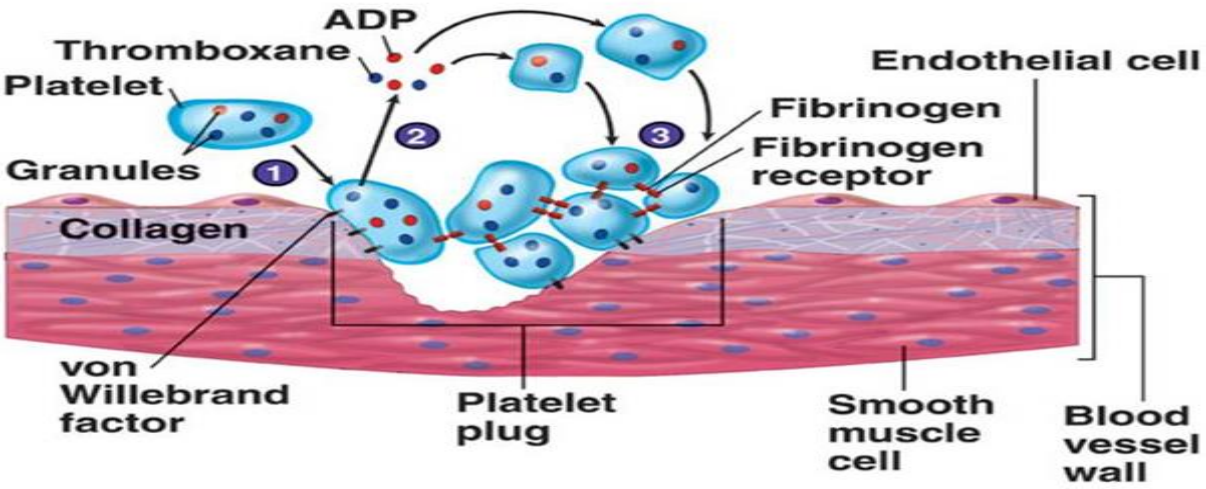
Platelets Release Reaction

Platelets release chemicals as ADP and thromboxane A_2 which bind to their respective receptors on the surfaces of **other platelets activating the platelets**.

Platelets Aggregation

- ✓ **The activated platelets also release ADP and thromboxane A_2 (TXA_2)which activates more platelets**.
- ✓ Thus, a cascade of chemical release activates many platelets. **This is an example of positive feedback.**
- ✓ As **platelets become activated**, they express **surface receptors called fibrinogen receptors which can bind to fibrinogen**.
- ✓ **Fibrinogen forms bridges between the fibrinogen receptors of numerous platelets resulting in a platelet plug**.


B. PRIMARY HEMOSTASIS
2 Shape change
3 Granule release (ADP, TXA_2)
4 Recruitment
1 Platelet adhesion
vWF
Aggregation (hemostatic 5 plug)
Endothelium
Basement membrane
Collagen


ADP
Thromboxane
Platelet
Granules
Collagen
Endothelial cell
Fibrinogen
Fibrinogen receptor
von Willebrand factor
Platelet plug
Smooth muscle cell
Blood vessel wall

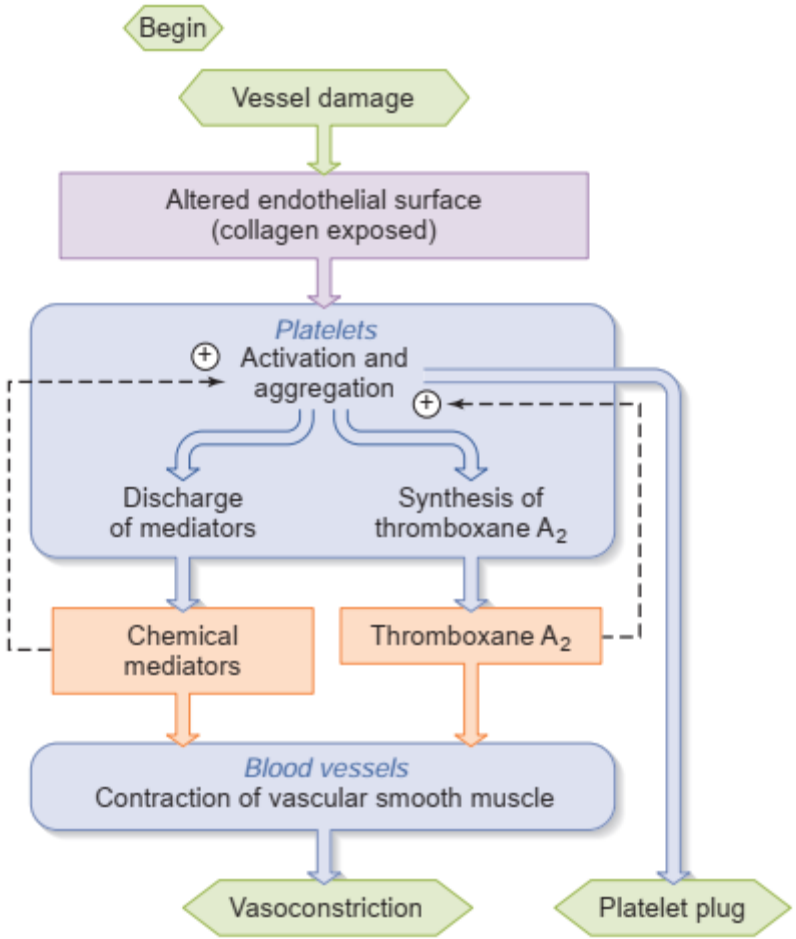


Figure 12.72 Sequence of events leading to formation of a platelet plug and vasoconstriction following damage to a blood vessel wall. Note the two positive feedbacks in the pathways.

Clinical Importance of Platelet Activation

Platelet activation results in platelet plug formation and production of chemicals such as phospholipids (PL or PF) that are important for blood clotting.

Thus inhibition of platelet activation reduces the formation of blood clots.

Aspirin inhibits thromboxane synthesis……..reduced platelet activation.

Platelet plugs and blood clots can block blood vessels producing heart attack and strokes.

Low dose aspirin is recommended for patients at high risk of cardiovascular disease.

Drugs that reduces platelet activation by blocking ADP receptors on platelet surface are also administered to prevent clotting and to treat heart attacks along with other anticoagulants.

Once started, why does the platelet plug not continuously expand, spreading away from the damaged endothelium along intact endothelium in both directions?

- The **adjacent undamaged endothelial cells** synthesize and release the eicosanoid known as **prostacyclin** (also termed **prostaglandin I_2 [PGI_2]**), which is **a profound inhibitor of platelet aggregation**.
- **In addition, the adjacent endothelial cells also release nitric oxide (NO)**, which is not only **a vasodilator** but also **an inhibitor of platelet adhesion, activation, and aggregation**.

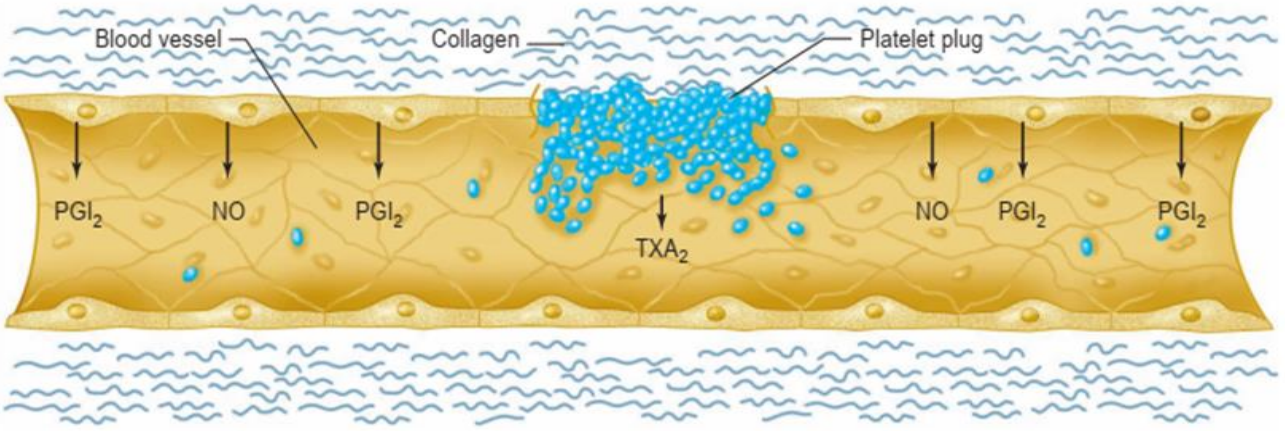


Figure 12.73 Prostacyclin (prostaglandin I_2 [PGI_2]) and nitric oxide (NO), both produced by endothelial cells, inhibit platelet aggregation and therefore prevent the spread of platelet aggregation from a damaged site. TXA_2 5 Thromboxane A_2.

(3) Blood Clotting: Clot Formation

- Blood vessel constriction and platelet plugs alone are not sufficient to close large tears or cuts in blood vessels.
- When a blood vessel is severely damaged, blood clotting or coagulation results in the formation of a clot.
- **Blood coagulation** is the **transformation of blood** into a solid gel called **a clot or thrombus**, which **consists mainly of a protein polymer known as fibrin**.
- **A clot is a network of threadlike protein fibers**, called **fibrin**, that traps blood cells, platelets and fluid.
- Clotting occurs locally around the original platelet plug and is the dominant hemostatic defense.
- **The formation of blood clot depends on a number of proteins found within plasma called clotting factors**.
- **Normally, clotting factors are inactive** and don't cause clotting. **Following injury**, the **clotting factors are activated**.

Clot formation is a complex process involving many chemical reactions, but it is summarized in THREE STAGES:

Stage 1:

The chemical reactions can be started in TWO ways:

1) **Inactive clotting factors come in contact with exposed connective tissue (collagen) resulting in their activation (intrinsic pathway).** **OR**
2) **Chemicals such as thromboplastin (tissue factor) are released from injured tissues causing activation of clotting factors (extrinsic pathway).**

After the initial clotting factors are activated, they in turn activate other clotting factors. A series of reactions results in which each clotting factor activates the next until the clotting factor **prothrombin activator** is formed.

Stage 2:

Prothrombin activator converts an inactive clotting factor called prothrombin to its active form, thrombin.

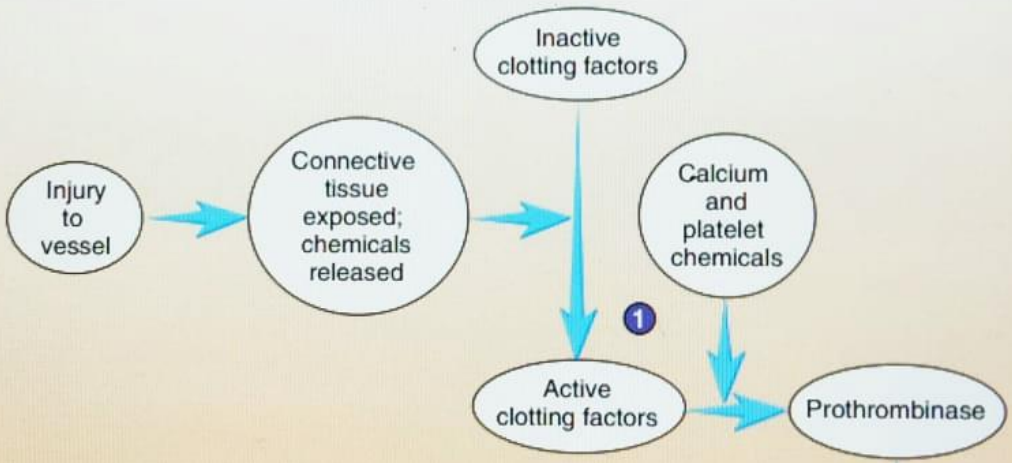
Stage 3:

Thrombin converts the plasma protein fibrinogen to fibrin and stabilizes it (stabilization).

- ✓ The fibrin, initially a loose and soft mesh of interlacing strands.
- ✓ it is **rapidly stabilized and strengthened** by the enzymatically mediated formation of covalent cross-linkages. This chemical linking is catalyzed by an **enzyme known as factor XIIIa (in addition to Ca^{2+})**, which is **formed from plasma protein factor XIII in a reaction also catalyzed by thrombin**.
- ✓ At each step of the clotting process, each clotting factor activates many additional clotting factors, resulting in the formation of a clot.

Stage 1

1. Inactive clotting factors in the plasma are activated by exposure to connective tissue or by chemicals released from tissues. Through a series of reactions, the activated clotting factors form prothrombinase.

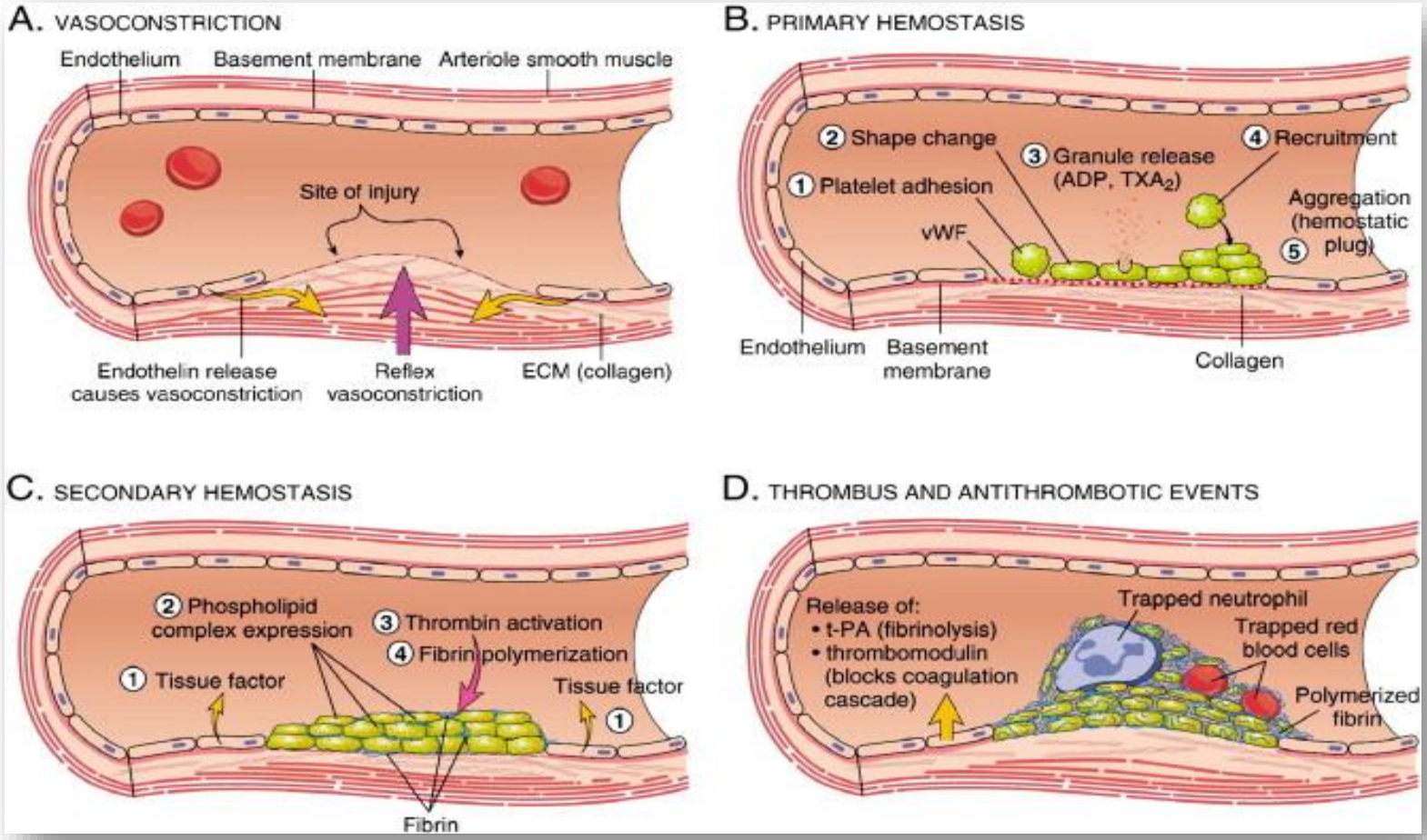


Stage 2

2. Prothrombinase converts prothrombin to thrombin.

Stage 3

3. Thrombin converts fibrinogen to fibrin (the clot).


A. VASOCONSTRICTION
Endothelium
Basement membrane
Arteriole smooth muscle
Site of injury
Endothelin release causes vasoconstriction
Reflex vasoconstriction
ECM (collagen)
B. PRIMARY HEMOSTASIS
2 Shape change
3 Granule release (ADP, TXA2)
4 Recruitment
1 Platelet adhesion
vWF
Aggregation (hemostatic plug)
5
Endothelium
Basement membrane
Collagen
C. SECONDARY HEMOSTASIS
2 Phospholipid complex expression
3 Thrombin activation
4 Fibrin polymerization
1 Tissue factor
Tissue factor
1
Fibrin
D. THROMBUS AND ANTITHROMBOTIC EVENTS
Release of:
• t-PA (fibrinolysis)
• thrombomodulin (blocks coagulation cascade)
Trapped neutrophil
Trapped red blood cells
Polymerized fibrin

Role of Thrombin in Blood Clotting

- Thrombin **catalyzes the formation of loose fibrin**.
- It also **activates factor XIII (XIIIa)**, which **stabilizes the fibrin network**.
- It exerts a profound **positive feedback effect on its own formation.** It does so by **activating several proteins in the cascade and also by activating platelets** (helping more platelet aggregation and release of PF OR PL). Therefore, once thrombin formation has begun, reactions leading to much more thrombin generation are activated by this initial thrombin.

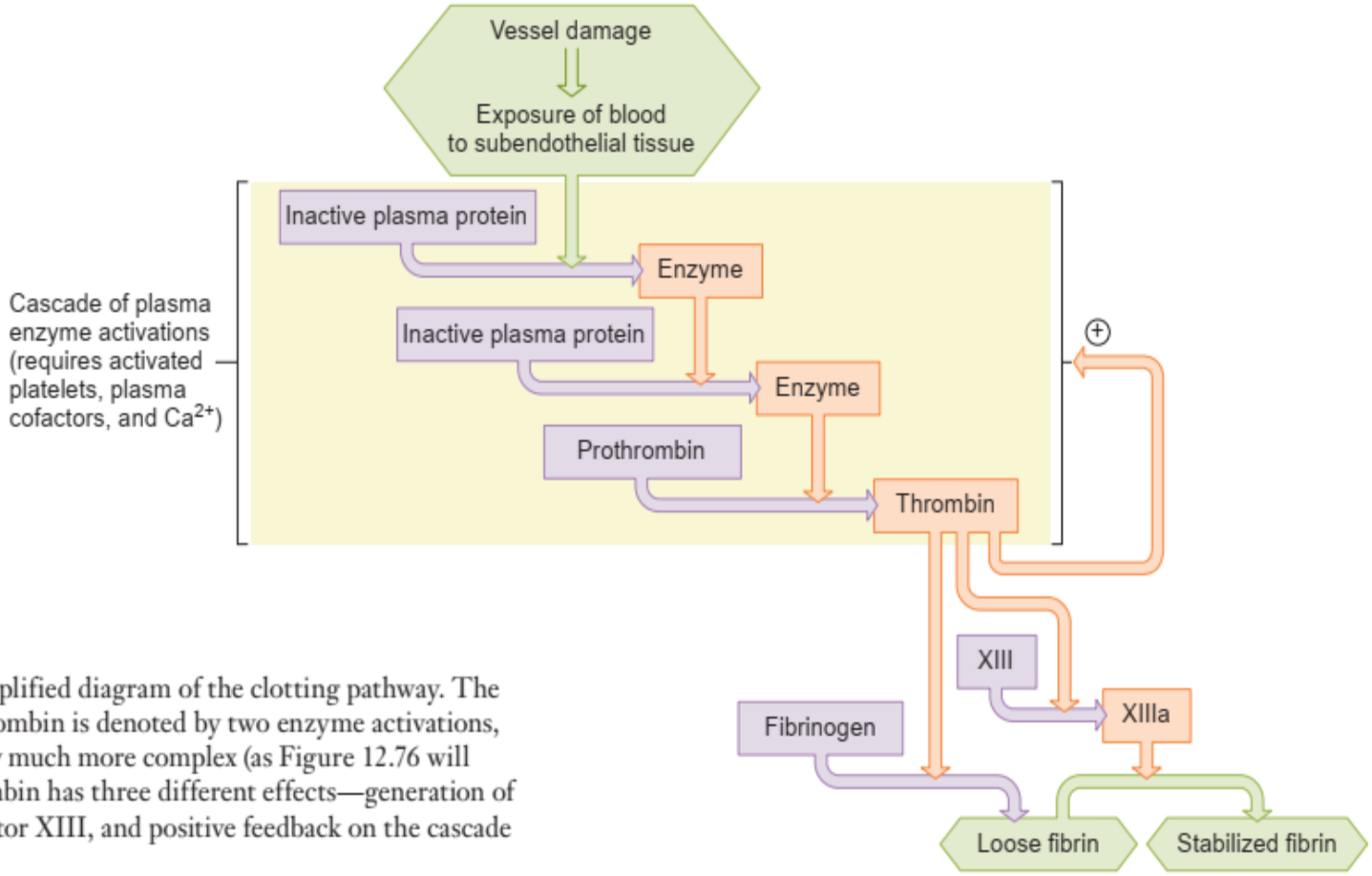


Figure 12.74 Simplified diagram of the clotting pathway. The pathway leading to thrombin is denoted by two enzyme activations, but the story is actually much more complex (as Figure 12.76 will show). Note that thrombin has three different effects—generation of fibrin, activation of factor XIII, and positive feedback on the cascade leading to itself.

Stage 1 of Clotting Cascade

Those leading from vessel damage to the prothrombin activator formation.

These early reactions consist of **TWO pathways that merge at the step just before the prothrombin–thrombin reaction**.

There are also several points at which the two pathways interact.

The pathways are called:

(1) **The intrinsic pathway**, so named because **everything necessary for it is in the blood**.

(2) **The extrinsic pathway**, so named because **a cellular element outside the blood is needed**.

The intrinsic pathway

- **The first plasma protein in the intrinsic pathway is called factor XII**.
- It is **activated to factor XIIa** when it **contacts** certain types of surfaces, including the **collagen fibers underlying damaged endothelium**.
- **Contact activation of factor XII also explains why blood coagulates when it is taken from the body and put in a glass (test) tube**.
- This happens because the glass surface acts like collagen and induces the same activation of factor XII and aggregation of platelets as a damaged vessel surface.
- A silicone coating delays clotting by reducing the activating effects of the glass surface.
- **Factor XIIa then catalyzes the activation of factor XI to factor XIa.**
- **XIa activates factor IX to factor IXa.**
- **IXa (in presence of VIIIa) then activates factor X to factor Xa.**
- **Xa is the enzyme that converts prothrombin to thrombin.**

The extrinsic pathway for initiating the clotting cascade.

- This pathway **begins with a protein called tissue factor**, which is not a plasma protein.
- **Tissue factor binds a plasma protein, factor VII, which becomes activated to factor VIIa**.
- **The complex of tissue factor and factor VIIa catalyzes the activation of factor X**.
- In addition, **it catalyzes the activation of factor IX, which can then help activate even more factor X by way of the intrinsic pathway.**

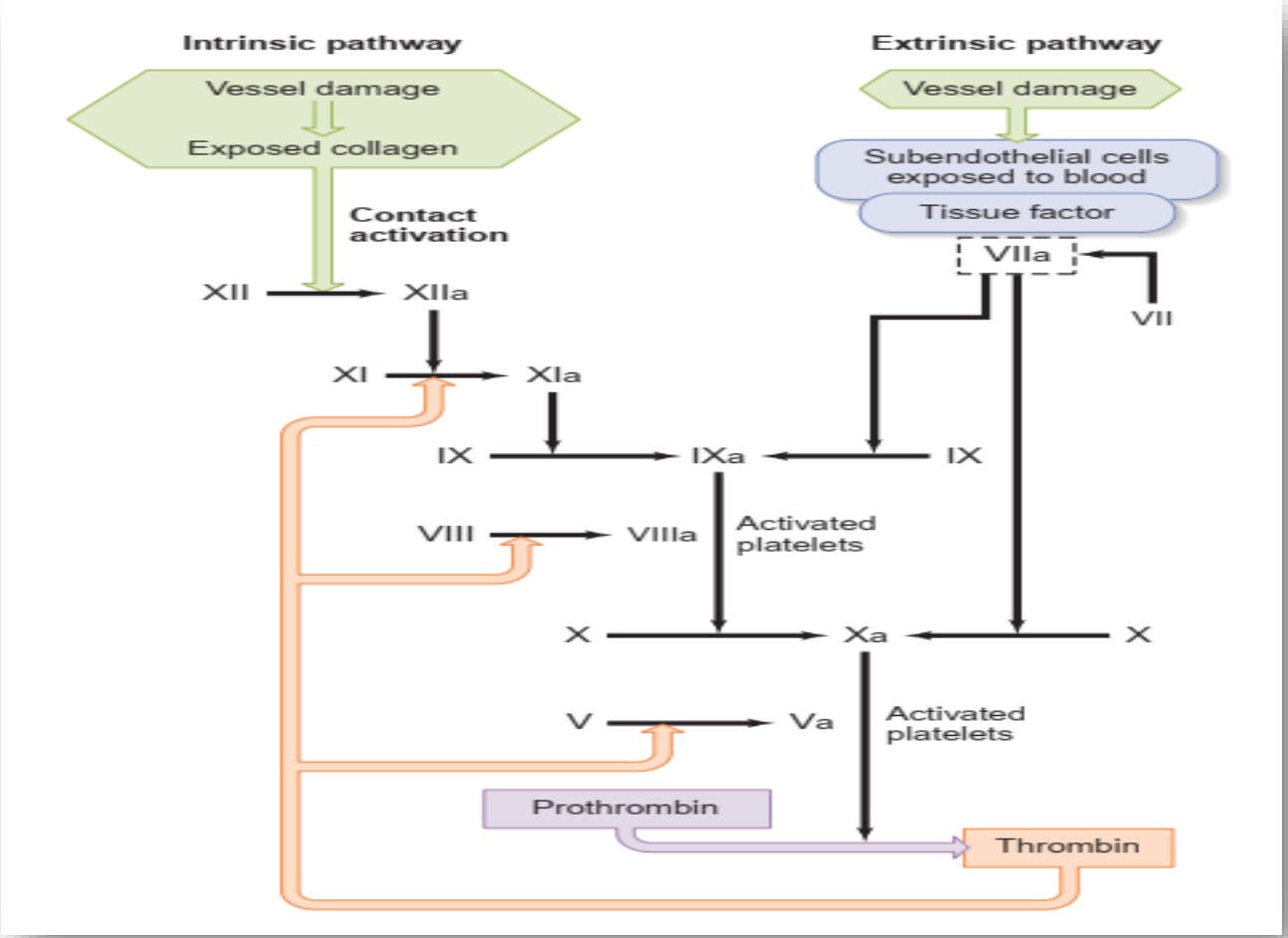
TABLE 12.13 Official Designations for Clotting Factors, Along with Synonyms More Commonly Used

Factor I (fibrinogen)
Factor Ia (fibrin)
Factor II (prothrombin)
Factor IIa (thrombin)
Factor III (tissue factor, tissue thromboplastin)
Factor IV (Ca^{21})
Factors V, VII, VIII, IX, X, XI, XII, and XIII are the inactive forms of these factors; the active forms add an "a" (e.g., factor XIIa). There is no factor VI.
Platelet factor (PF)

Thrombin contributes to the activation of:

(1) Factors XI and VIII in the intrinsic pathway.

(2) Factor V, with factor Va then serving as a cofactor for factor Xa.



- ✓ **Most clotting factors are manufactured in the liver and many of them require vitamin K for their synthesis**.
- ✓ In addition, **many of the chemical reactions of clot formation require Ca^{2+} and the chemicals released from platelets**.
- ✓ **The clotting process can be severely impaired by low levels of vitamin K, low levels of Ca^{2+}, low number of platelets or reduced synthesis of clotting factors because of liver dysfunction**.
- ✓ **Humans relay on TWO sources of vitamin K**. About half comes from the diet and the other half comes from bacteria within the large intestine.
- ✓ Antibiotics taken to fight bacterial infection sometimes kill these intestinal bacteria reducing vitamin K levels and causing bleeding problems.
- ✓ Vitamin K supplements may be necessary for patients on prolonged antibiotic therapy.
- ✓ Newborns lack these intestinal bacteria and thus routinely receive a vitamin K injection at birth.

Effect of Ca^{2+} on Blood Coagulation

- ✓ Plasma Ca^{2+} is required at various steps in the clotting cascade.
- ✓ However, Ca^{2+} concentration in the plasma can never decrease enough to cause clotting defects because death would occur before such low concentrations were reached.

The liver also plays several important indirect roles in clotting; as a result, persons with liver disease often have serious bleeding problems.

- **First, the liver is the site of production for many of the plasma clotting factors.**
- **Second, the liver produces bile salts, and these are important for normal intestinal absorption of the lipid-soluble vitamin K. The liver requires this vitamin to produce prothrombin and several other clotting factors.**

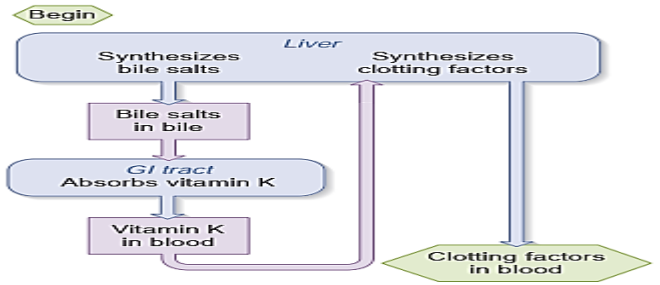


Figure 12.77 Roles of the liver in blood clotting.

Clot Retraction

- **After a clot has formed, it begins to condense into a more compact structure through a process known as clot retraction**.
- **Platelets contain the contractile proteins, actin and myosin** which operate in a fashion similar to that in muscle.
- **Platelets form small extensions that attach to fibrin through surface receptors. Contraction of the extension pulls on the fibrin and leads to clot retraction**.
- **During clot retraction, serum is squeezed out of the clot**.
- **Retraction of the clot pulls the edges of the damaged blood vessel together helping stop the flow of blood and enhancing healing**.
- **The vessel is repaired** as fibroblasts move into the damaged area and new connective tissue forms.

Control of Clot Formation

- Without control, clotting would spread from the point of its initiation throughout the blood vessel.
- Fortunately, the **blood contains several anticoagulants** which prevent clotting factors from forming clots under normal conditions.
- **At an injury site, however, the activation of clotting factors is very rapid. Enough clotting factors are activated that the anticoagulants can no longer prevent a clot from forming.**
- **Away from the injury site, there are enough anticoagulants to prevent clot formation from spreading.**


Thank
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