بسم الله الرحمن الرحيم

Physiology

Final | Lecture 9

﴿ وَقُل رَّبِّ أَدْخِلْنِي مُدْخَلَ صِدْقٍ وَأَخْرِجْنِي مُخْرَجَ صِدْقٍ وَاجْعَل لِّي مِن لَّدُنكَ سُلْطَانًا نَّصِيرًا ﴾

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Hemostasis & Blood Coagulation (Pt. I)

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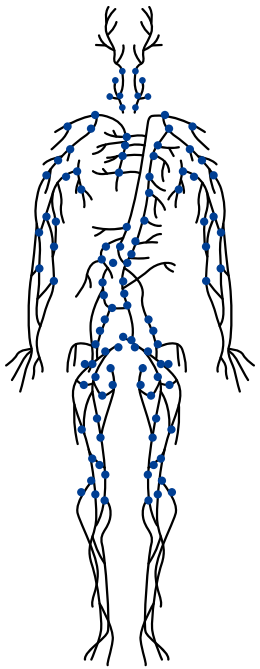

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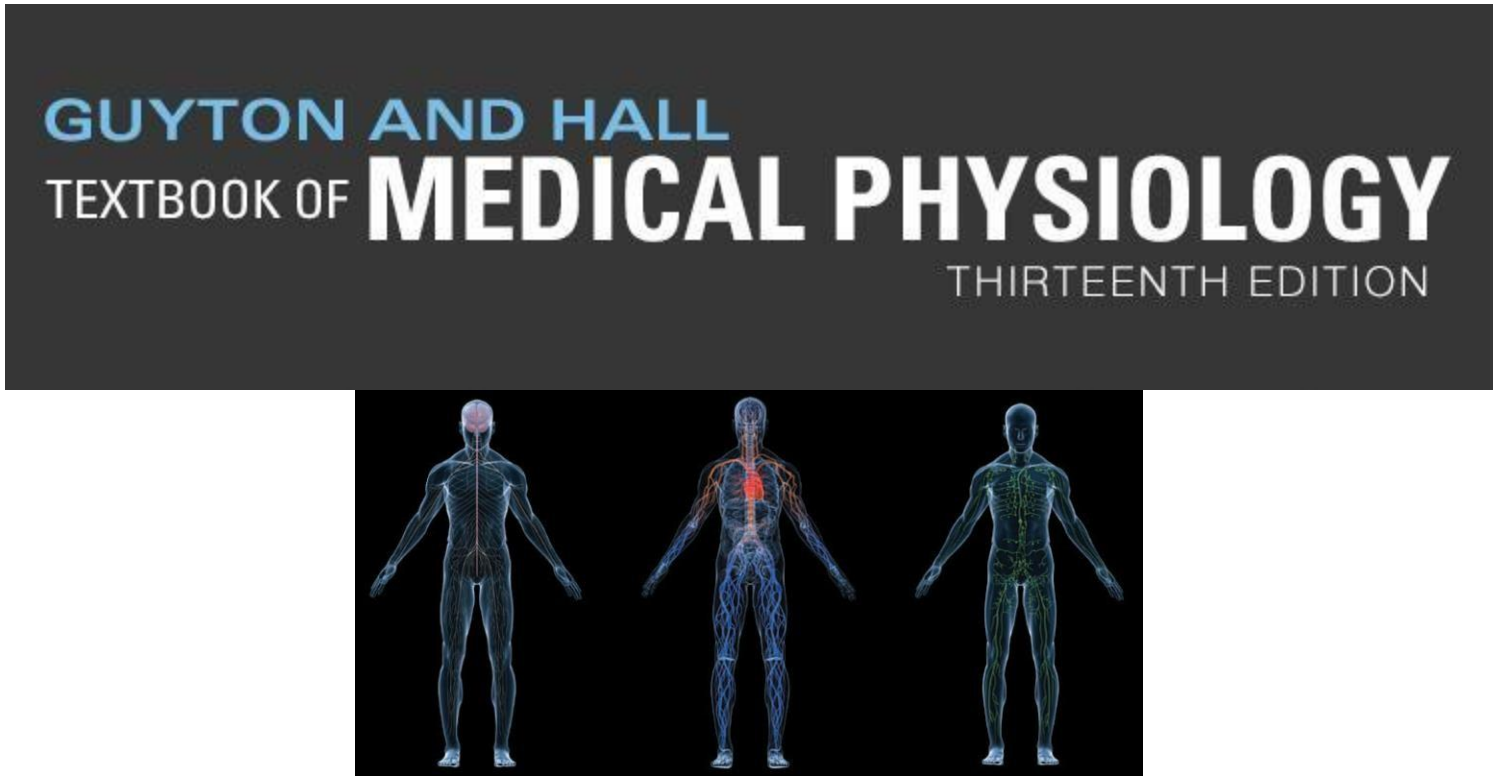

Hemostasis and Blood Coagulation

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اللهم إني أسألك فهم النبيين، وحفظ المرسلين، والملائكة المقربين، اللهم اجعل ألسنتنا عامرًا بذكرك، وقلوبنا بخشيتك، إنك على كل شيء قدير.

Events in Hemostasis

- When we have a cut in our blood vessels, bleeding will take place, so the blood loss is prevented by parts of the blood components that are called 'Platelets'. This is the meaning of **hemostasis**.
- Our bodies respond to these injuries and cuts by 1,2, or 3 of these mechanisms, depending on the size of the cut, the inclusion of other tissues, and the size of the blood vessels that have been injured.

Vascular Constriction

- Local myogenic spasm—most effective.
- Local autacoid factors
- Nervous reflexes-from pain or sensory receptors

Formation of a Platelet Plug

- Small cut in a vessel; have a plug instead of the complete clotting mechanism

Events in Hemostasis

1) Vascular Constriction

- **Local myogenic spasms: the strongest automatic mechanism** of contraction which is a result of injury to the smooth muscle walls of blood vessels which causes vasoconstriction and thus helps reduce bleeding and it can last for minutes to hours.
- **Local autocoid factors:** like TXA2 (vasoconstricting prostaglandin), that are released from either the re-activated platelets, or damaged (activated) cells at the injury site.
- **Nervous reflexes from pain or sensory receptors** which signal a vasoconstriction reflex.

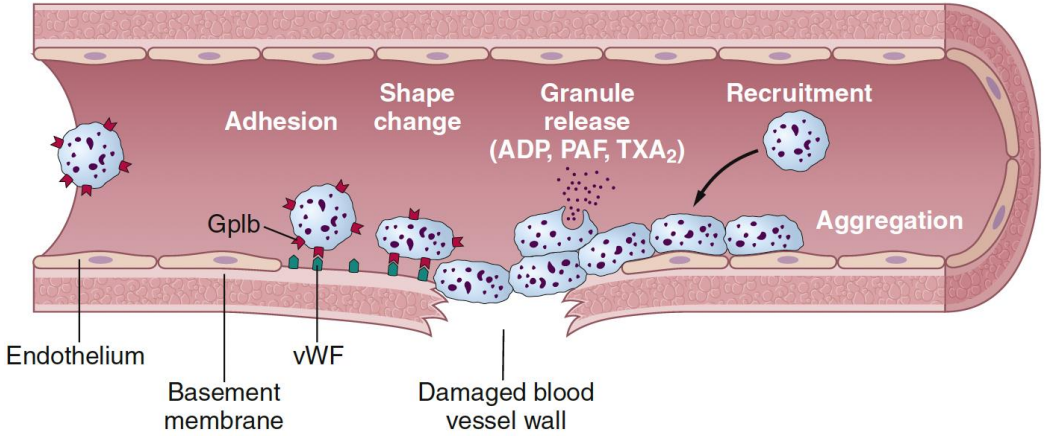
2) Formation of a Platelet Plug

- **Small cut in a vessel; form a plug instead of the complete clotting mechanism:** Under normal circumstances, platelets exhibit **repulsion** from the endothelial wall due to surface glycoproteins. However, when the endothelial layer undergoes damage (cut, injury, etc) the underlying collagen and vWF is exposed to the endothelial cells. Platelets are then triggered to **adhere** to the endothelial wall and become activated. Platelet activation leads to release of factors, such as ADP, TXA2, and other platelet-activating factors, that **recruit** and **stimulate** other platelets to adhere on top of the injury site, rapidly creating a **platelet plug** (positive feedback mechanism). Platelet plugs are very effective for small blood vessel injuries, and in many cases full clot formation is unnecessary because the plug alone can stop the bleeding.

Diagram on the next slide

Platelet Plug Formation

This diagram depicts what was discussed earlier. To add on, platelets adhere to the collagen underneath the endothelium through **glycoprotein receptors** on their membranes. These receptors bind to **vWF**, which circulates in the blood and helps accumulate platelets at the site of injury.
In **von Willebrand disease**, there is a deficiency or a dysfunction of vWF. As a result, platelets become loose and unable to adhere effectively to the site of injury, leading to **impaired platelet plug formation and excessive bleeding.**
Note how in the top image, you can see several platelets adhering to each other with the help of vWF. Once the platelets are **activated**, **granules that are found in the platelets will be released**, thus stimulate and recruit more platelets.
Platelet activation involves **swelling, a change to an irregular shape, formation of pseudopods, and contraction of cytoskeletal fibers to drive granule release.**
These granules include TXA2 (a vasoconstricting prostaglandin), ADP, platelet-activating factor (PAF), and other substances that enhance platelet adhesion and aggregation.

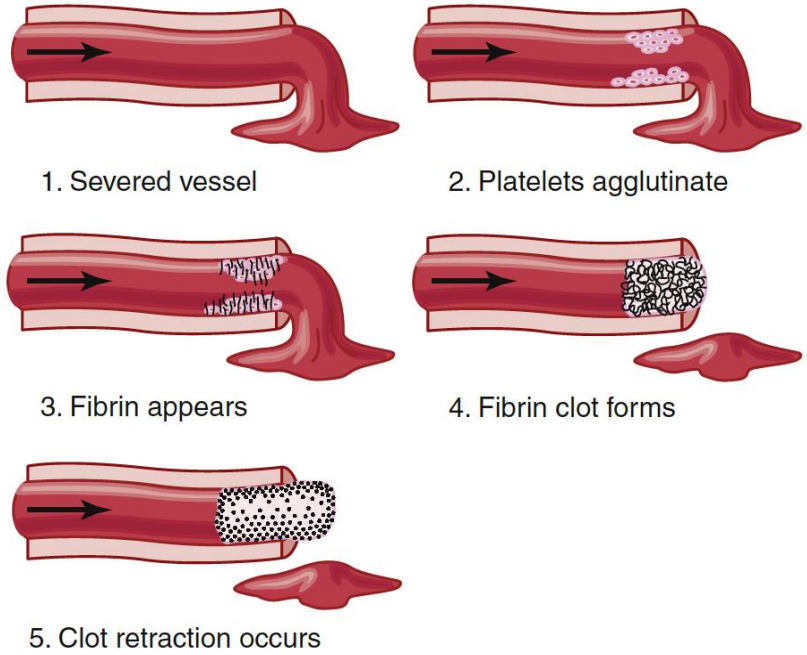


Von Willebrand factor (vWF) serves as an adhesion **bridge** between subendothelial collagen and the glycoprotein Ib (GpIb) platelet receptor.

Blood Clotting

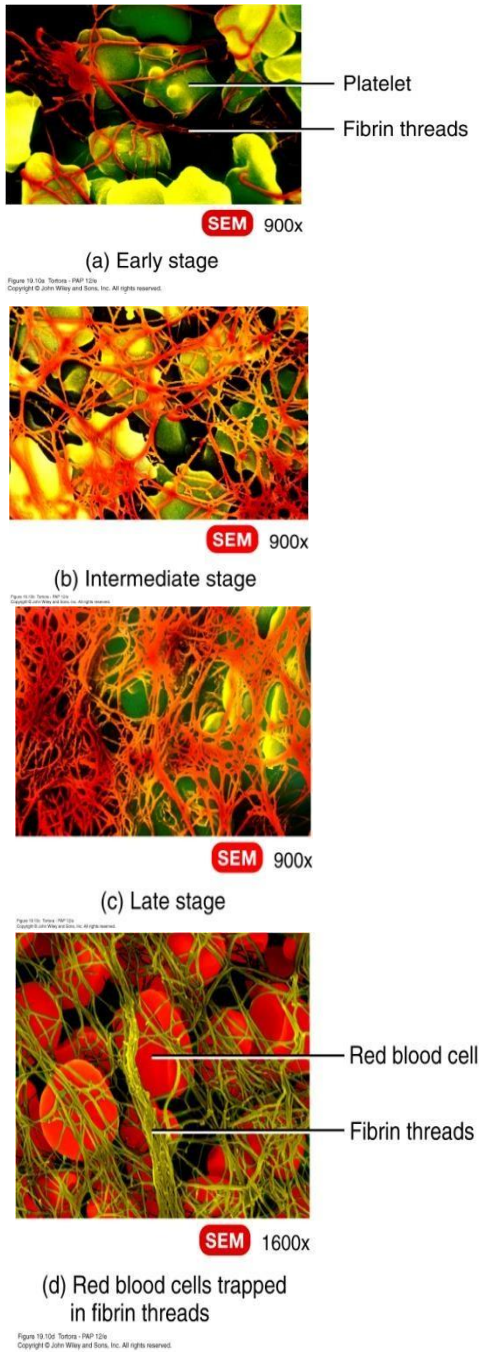
- Earlier, we mentioned that in most cases, a platelet plug is sufficient to prevent excessive bleeding. However, in some cases, platelet plugs alone aren't enough, and the body resorts to a **third** mechanism—**blood clotting.**
- Simply, when tougher meshwork is needed to stop the bleeding, which will be formed by **fibrin threads.** Platelets and RBCs as well as other substances will be trapped in this clot. The fluid, viscous nature of the blood becomes gel-like as the clot forms.

- This will be explained in detail later, so don't fret if you don't understand it completely. :)



Blood Clotting

- Blood clotting **requirements:**
  - Serum is blood plasma minus clotting proteins
  - **Clotting** – series of chemical reactions culminating in formation of fibrin threads
  - **Clotting (coagulation) factors** (mostly are proenzymes) – Ca^{2+}, several inactive enzymes, various molecules associated with platelets like phospholipids or released by damaged tissues which help initiate the chemical cascade.

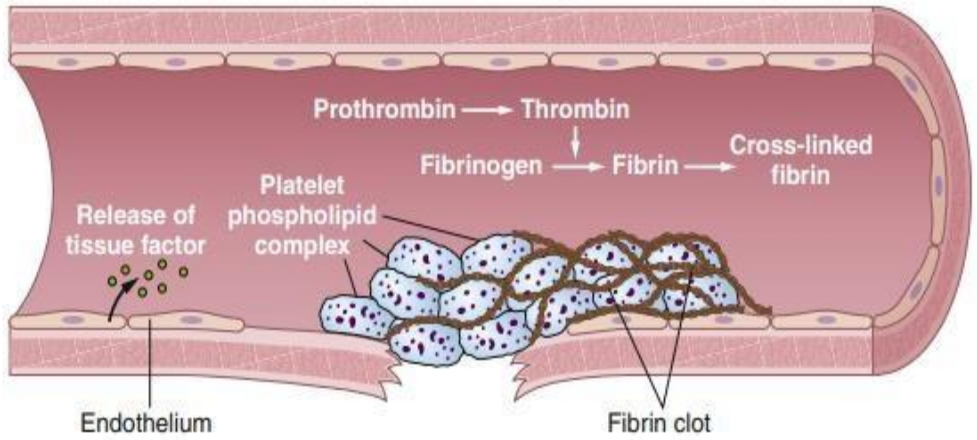


✓ EM imagery for different stages of fibrin clot formation.

Blood Clotting

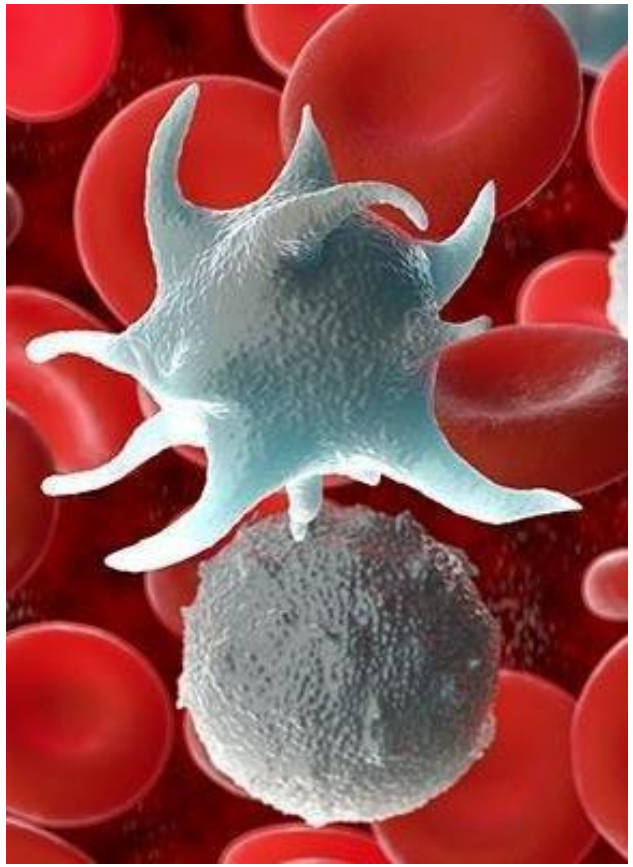
Exposure of blood to vasc wall- release of TF (III or thromboplastin) from endo cells , phospholipids, thrombin activation- ----------Fibrin

- As you can see, in this diagram, the damage involves both the tissue and blood vessels. In a case like this one, **tissue factor (AKA factor III or thromboplastin)** is released and initiates the **extrinsic pathway,** which leads to the conversion of prothrombin to **thrombin**. **Thrombin,** a protease, will convert fibrinogen (soluble) to fibrin. **Fibrin** is a highly-reactive monomer that polymerizes into insoluble fibers. These fibers form a meshwork that traps platelets, RBCs, released platelet factors, and activated thrombin. The resulting clot extends until it seals the rupture in the vessel.



Events in Hemostasis

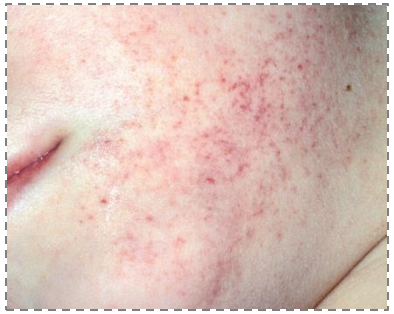
- **Platelets**
  - Fragmented megakaryocytes; after released via capillaries
  - 150,000-300,000
  - Do not have nuclei and cannot reproduce
  - Contain actin and myosin (thrombosthenin) Crucial for granule release and clot retraction stage
  - Mito-Produce ATP
  - Release prostaglandins
  - Release endothelial cell growth factor; they contain fragments of ER & GA. Equipping them for synthesis & storage of certain enzymes, prostaglandins, endothelial growth factor (important for healing).
  - Surface glycoproteins for adherence to damaged vessels: their surface glycoproteins, which normally **repel** platelets from the intact endothelium, mediate **adhesion** to the damaged vessel wall during injury.
  - Half-live of 8-12 days, they just get replaced, not much repair going on. Site of destruction is mainly **spleen and liver,** in trabeculae and sinusoids.



Events in Hemostasis

- **Mechanism of the Platelet Plug**

  a. Platelets swell; irregular shape with pseudopods
  b. Become sticky and adhere to collagen
  c. Thromboxane A_2 and ADP enhance adherence and PAF.
  d. Damaged wall activates increasing numbers of platelets
  e. Important in closing small tears or ruptures in very small vessels (petechiae). In circumstances of low platelet count, like in **thrombocytopenia**, small tears and ruptures in blood vessels all over the body will result in bleeding and formation of **petechiae**.



Blood Coagulation

- Blood coagulation is a physiological process regulated by a balance between two systems: pro-coagulant and anti-coagulant.
- The **procoagulant system** promotes **clotting during injury**, such as cuts or bleeding, overriding the anti-coagulant mechanisms. In contrast, the **anticoagulant system prevents unnecessary clot formation under normal conditions.**
- **Coagulation is beneficial when needed**, but if it occurs without necessity, it can be harmful.
- Uncontrolled clotting may lead to **thrombosis**, and if a thrombus dislodges, it can block vital blood vessels, causing serious complications. Therefore, proper regulation ensures that clotting occurs only when required.

Blood Coagulation

- **Basic Theory**

  a. Depends on the state of balance of 50 or more possible blood procoagulants and anticoagulants
  b. Procoaglants overrides, formation of prothrombin activator
  c. Conversion of prothrombin to thrombin
  d. Conversion of fibrinogen to fibrin

3 Stages of Clotting

1.Extrinsic or intrinsic pathways lead to formation of prothrombinase/ Prothrombin activator factor

2. Prothrombinase converts prothrombin into thrombin

3. Thrombin converts fibrinogen (soluble) into fibrin (insoluble) forming the threads of the clot

*Initially, Fibrin fibers exist in a **loose, unbound state,** Upon activation by **thrombin, Factor XIII (Fibrin Stabilizing Facto** becomes **active.** This factor catalyzes the formation of **covalent cross-links** between fibrin monomers, strengthen the fibrin network. As a result, the clot becomes **more stable** and **mechanically resilient.**

Thus, the rate-limiting factor in causing blood coagulation is usually the formation of prothrombin activator

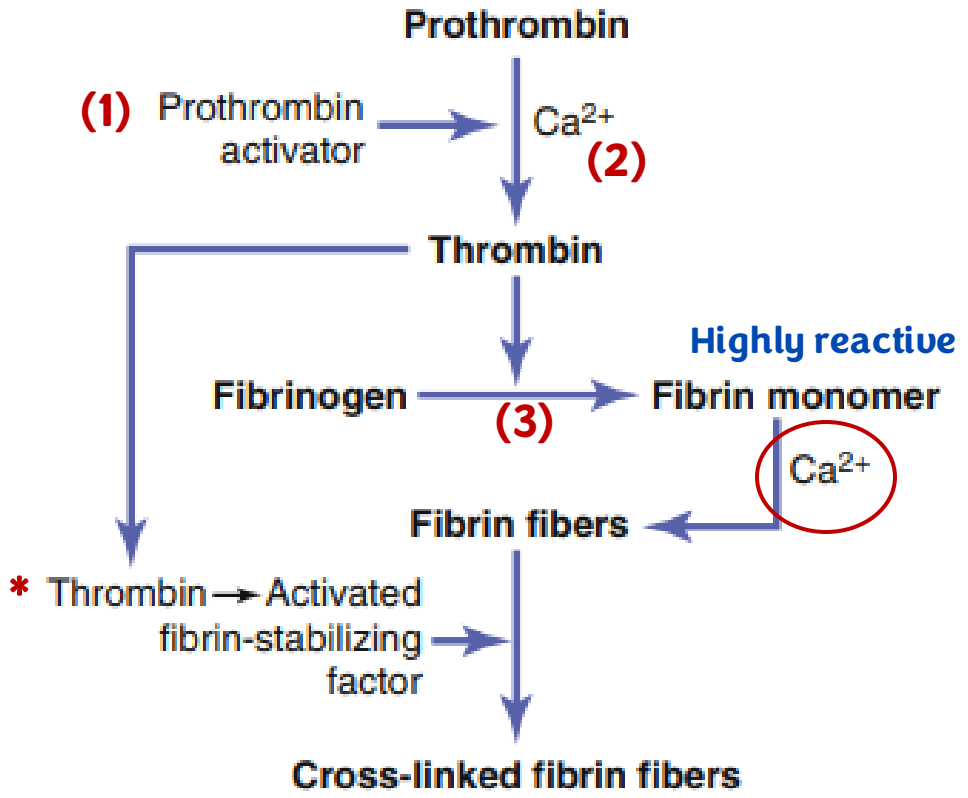


Figure 37-3 Schema for conversion of prothrombin to thrombin

Clotting Factors

Table 37-1 Clotting Factors in Blood and Their Synonyms[a]

Clotting Factor	Synonym(s)
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; high-molecular-weight kininogen (HMWK)
Platelets	

[a]These are listed here mainly for historical interest.

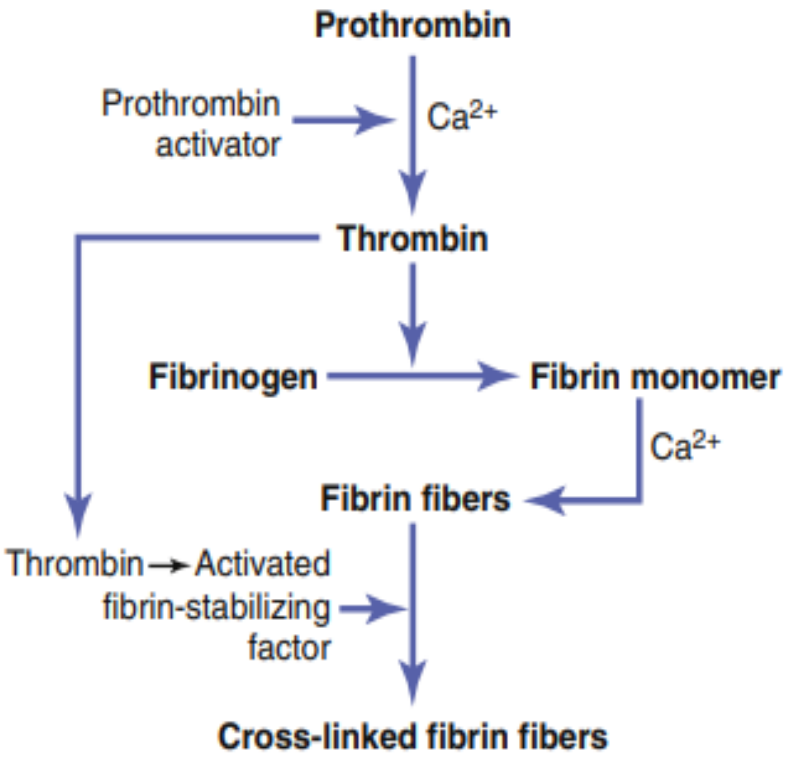


Figure 37-3 Schema for conversion of prothrombin to thrombin

Hemostasis: Prevention of Blood Loss

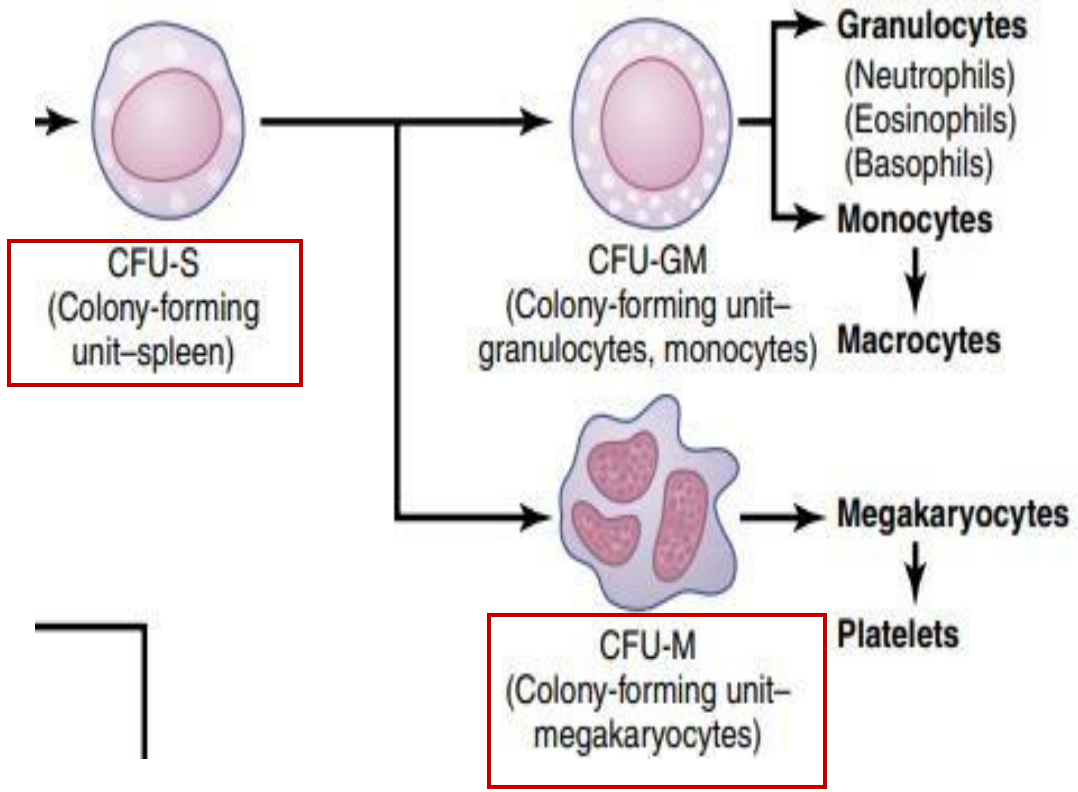
- **Vascular constriction**
- **Formation of a platelet plug**
- **Formation of a blood clot**
- **Healing of vascular damage ± re-canalization**

Vascular Constriction

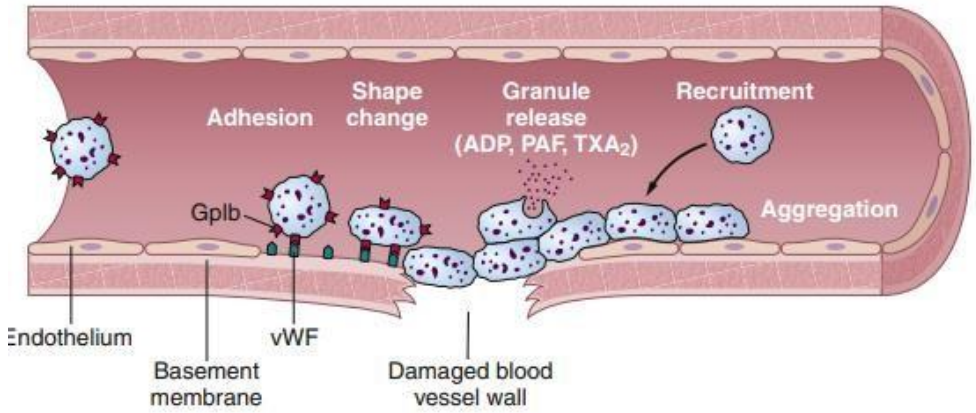
- **Myogenic spasm**
- **Local autocoid factors from damaged tissues and platelets**
- **Nervous reflexes**
- **Smaller vessels: thromboxane A_2 released by platelets**

Platelets (Thrombocytes)

- **1- 4 µm discs**
- **Released by fragmentation of megakaryocytes**
- **150-300,000 per µL**
- **Half-life in blood of 8-12 days**



Platelet Functions



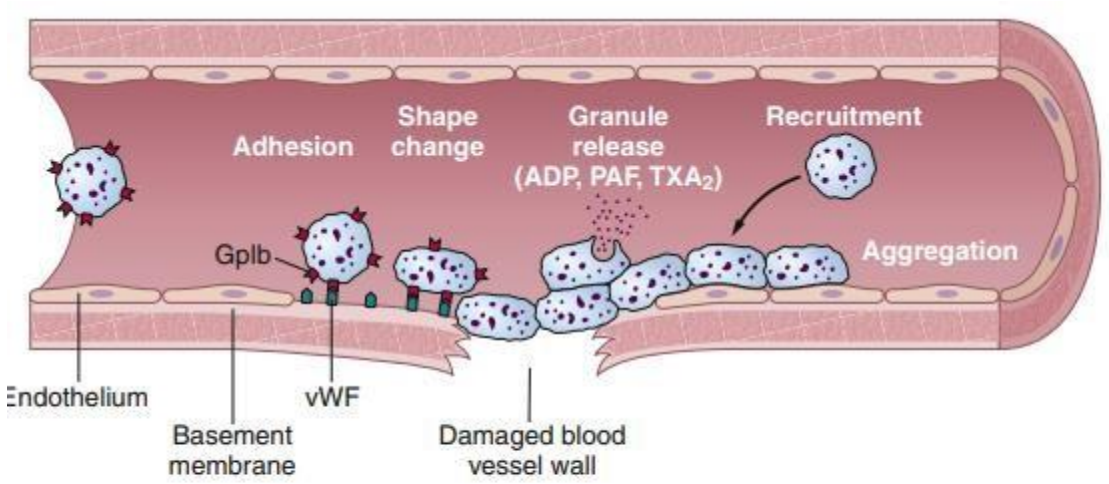
- **Contractile capabilities**
  - **actin, myosin, thrombosthenin**
- **Residual ER and Golgi**
  - **synthesize enzymes, prostaglandins,**

  fibrin-stabilizing factor, PDGF, store Ca^{++} Which is important for coagulation cascade
- **Mitochondria / enzymes**
  - **produce ATP, ADP**

PDGF: Platelet-Derived Growth Factor

Platelet Plug Formation

Von Willebrand factor (vWF) serves as an adhesion bridge between subendothelial collagen and the glycoprotein Ib (GpIb) platelet receptor.



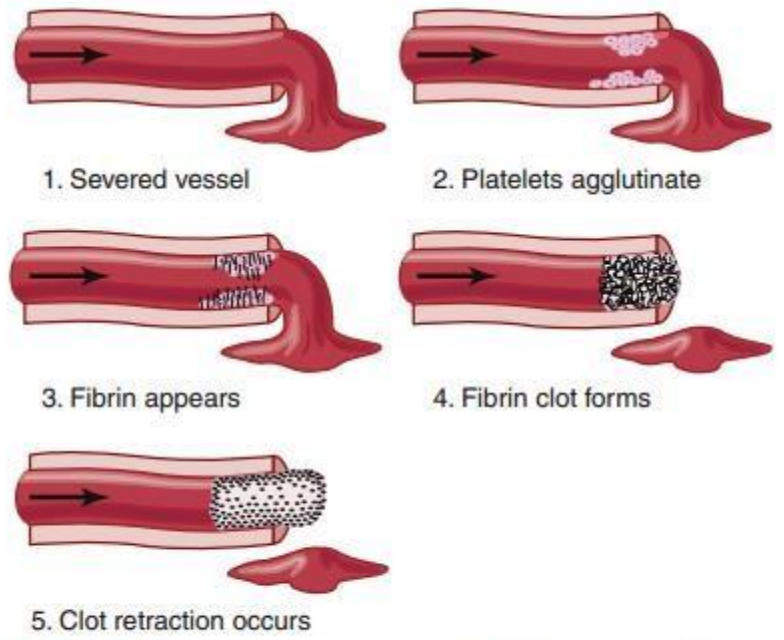


Figure 37-2. Clotting process in a traumatized blood vessel. *(Modified from Seegers WH: Hemostatic Agents. Springfield, IL: Charles C Thomas, 1948.)*

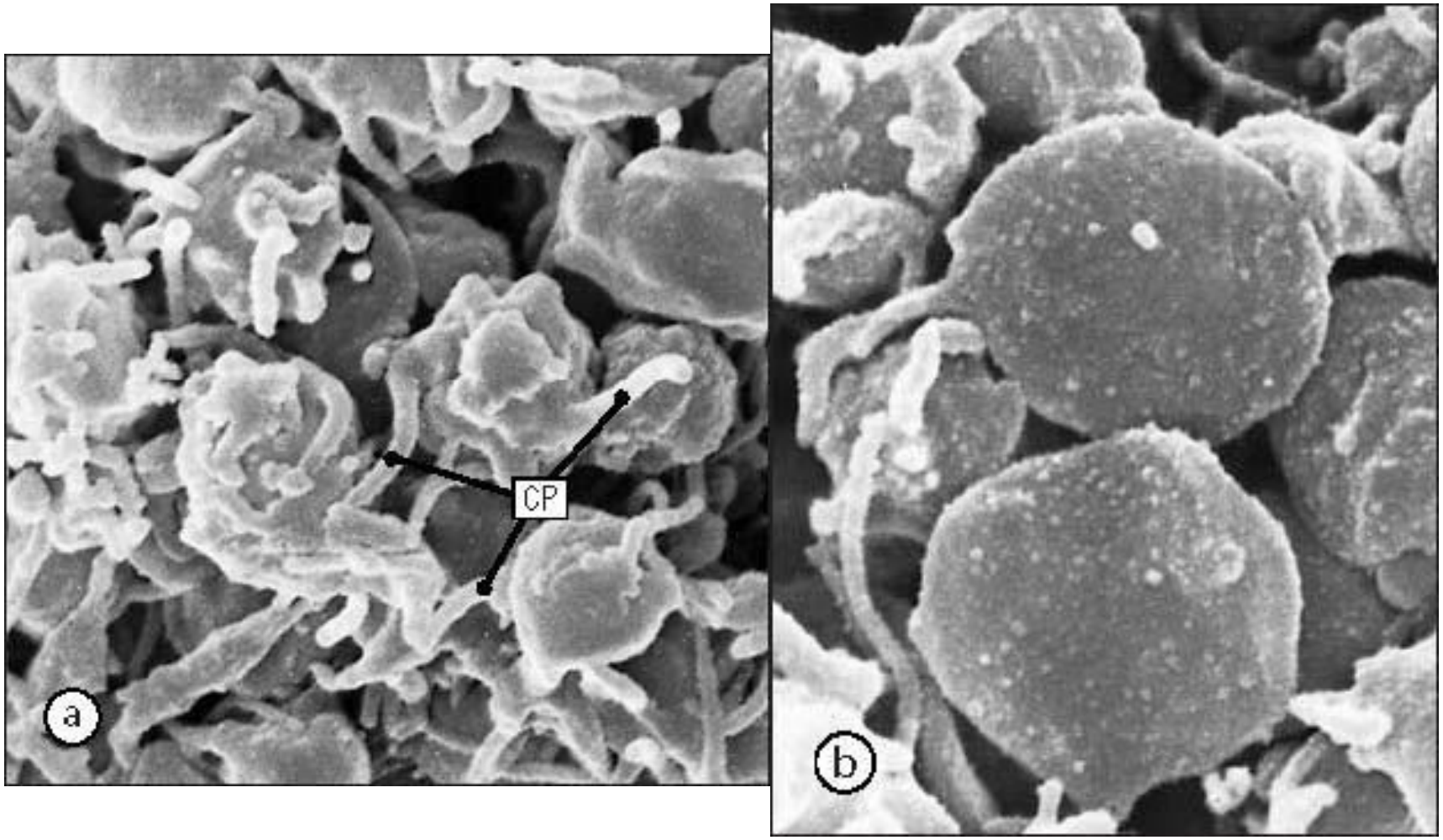
Platelet Membranes

- **Surface glycoprotein**
  - **Repels intact endothelium**
  - **Adheres to injured endothelium and exposed collagen**
- **Membrane phospholipids**
  - **Activate blood clotting**

Formation of the Platelet Plug

- **Contact with damaged endothelium**
  - **Assume irregular forms**
  - **Contract and release granules (ADP, thromboxane A_2)**
- **Adhere to collagen and vWF**
- **Other platelets accumulate, adhere, and contract, form plug, initiate clotting**
- **Very low platelets → petechaiae, bleeding gums**

Platelet Plug



- ✓ Platelets have an irregular shape with pseudopodia (“foot-like extensions”)
- ✓ They become entrapped within the fibrin network, which stabilizes the plug.
- ✓ In addition to platelets, some red blood cells (RBCs) can also be trapped within this fibrin mesh, contributing to the bulk and strength of the clot.

Clot Formation and Progression

Begins in 15- 20 seconds in severe vascular trauma

Occlusive clot within 3-6 minutes unless very large vascular defect
requiring medical intervention

20-60 minutes: Clot retraction

1- 2 weeks : Invasion by fibroblasts

Organization into fibrous tissue

the exact timing can vary depending on the pathway activated. There are two main pathways:

1.Fast pathway : Activated by severe vascular injury involving surrounding tissues. Clot formation is rapid, occurring within seconds to a few minutes.

2.Slower pathway: Activated without extensive tissue damage, taking 1-6 minutes to form a stable clot.

Clot Formation and Progression

Begins in 15- 20 seconds in severe vascular trauma

Occlusive clot within 3-6 minutes unless very large vascular defect

20-60 minutes: Clot retraction

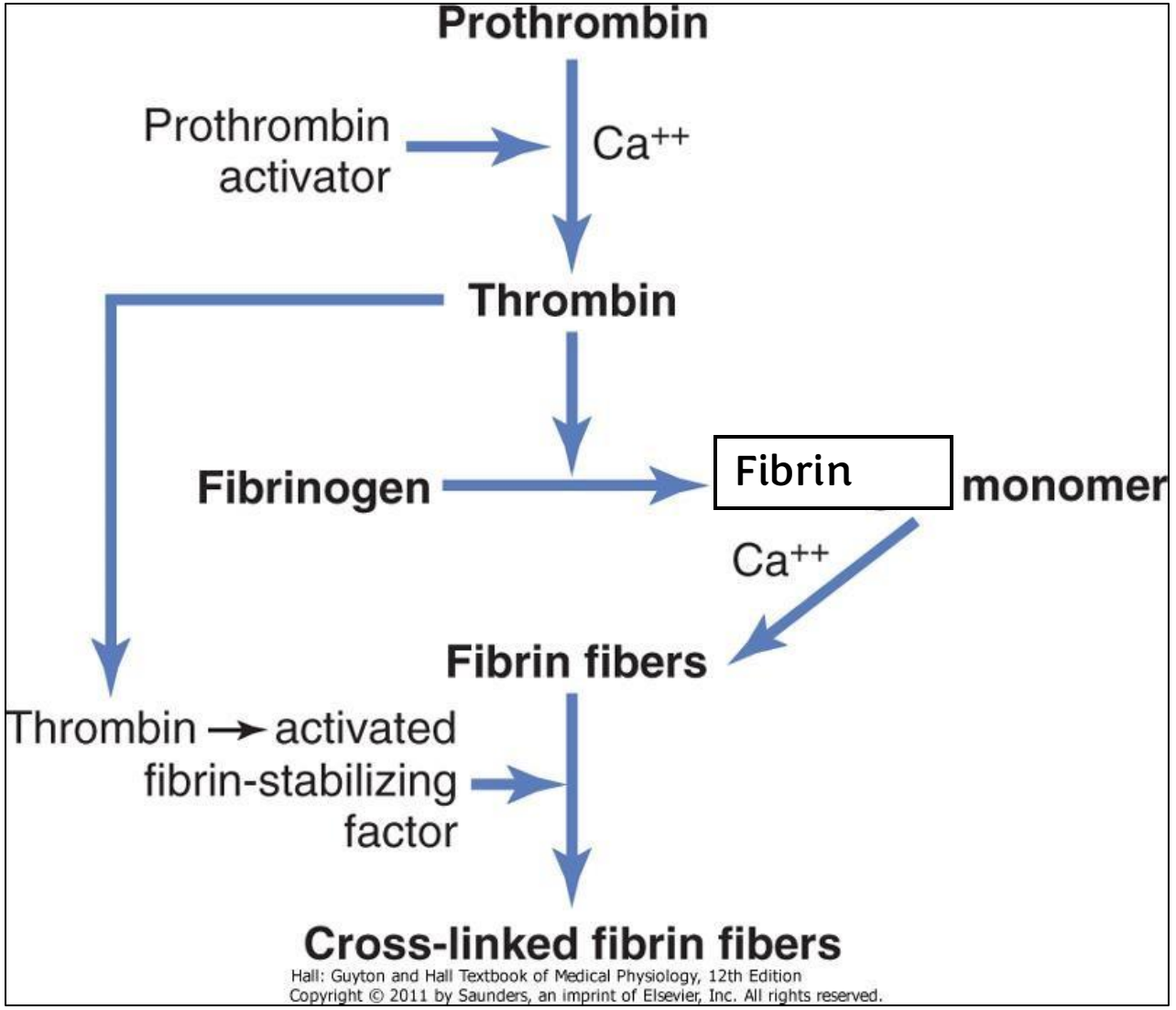
1- 2 weeks : Invasion by fibroblasts

Organization into fibrous tissue

Healing stage

- **Clot retraction** represents the contractile function of platelets, After a clot is formed, fibrin threads extend throughout the clot and attach to the edges of the damaged vessel. **As the platelets contract, they pull on these fibrin threads, bringing the edges of the wound closer together.** Consequently, the clot becomes smaller and tighter, and **serum is extruded from the clot.**

Key Steps in Blood Clotting



Effector Proteins for Clotting

- **Prothrombin**
  - **α 2 globulin, MW 68,700; 15 mg/dl in plasma**
  - **Vitamin K-dependent synthesis in liver**
  - **Cleaved by PT activator to thrombin, MW 33,700**
    - ✓ **This cleavage effectively reduces the molecular weight of prothrombin by approximately half.**
- **Fibrinogen**
  - **MW 340,000; 100-700 mg/dl in plasma**
  - **Synthesized in the liver (acute phase reactant)**
  - **Usually intravascular (because of it's size) ; can extravasate with increased vascular permeability (during cut or injury it can leave the vessel into the tissues)**

➢ If **coagulation** occurs **outside** the blood vessels (as the presence of infection or an inflammatory respons, In such cases, the body forms a localized barrier (walling off) within the tissue fluid to isolate and contain the site of infection) fibrinogen must also escape into the extravascular space, since other clotting factors are small enough to pass through the vessel wall. However, **if fibrinogen remains within the circulation, coagulation cannot occur outside.**

Fibrin Production

- **Thrombin (weak protease) cleaves four small peptides from fibrinogen**

  → fibrin monomer → spontaneous polymerization

  Highly reactive

- **Long fibers form clot reticulum**

- **Fibrin stabilizing factor XIII**
  - **In plasma and released from platelets**
  - **Activated by thrombin**
  - **Covalent bonds, and cross-linking of fibrin monomers and adjacent fibrin fibers**

Clot Extension

- **Thrombin remains localized / is bound to platelets and trapped in the clot**
- **Can act on prothrombin to generate more thrombin (positive feedback)**
- **Thrombin also produces more prothrombin activator by acting on other clotting factors**
- **Additional fibrin monomers and polymers are generated at the periphery of the clot**

Clot Retraction

- **Begins within 20-60 minutes**
- **Fibrin binds to damaged vessel wall**
- **Platelets bind to multiple fibrin fibers**
  - **contract via actin, myosin, thrombosthenin, and FSF (FactorVIII), Ca++ from organells**
- **Clot tightens, expressing serum, and closing the vascular defect**

✓ **If Fibrin-Stabilizing Factor is deficient, the fibrin clot is unstable, and clot retraction is impaired.**

Generating Prothrombin Activator

- **Coagulation can be initiated by vascular injury or trauma, but the source of the trigger differs between the two pathways:**

1. **Extrinsic Pathway**
- ✓ Triggered by **damage to tissues surrounding blood vessels.**
- ✓ Damaged tissue releases **tissue factor** (TF, Factor III, thromboplastin), a lipoprotein with phospholipid, which acts as a cofactor/enzyme to initiate the pathway.
- ✓ Involves **fewer steps** and is **faster**, rapidly generating thrombin to start clot formation.

2.**Intrinsic Pathway**
- ✓ Triggered by **damage or trauma to the blood itself**, such as exposure of blood components to subendothelial collagen.
- ✓ The pathway is **entirely blood-borne**, activating a cascade of clotting factors within the circulation.

- **Both pathways share the same principle:**
- ✓ Activation of proenzymes (inactive clotting factors).
- ✓ Cascade of enzymatic reactions.
- ✓ Requirement for calcium ions as cofactors.

- The **extrinsic** pathway is generally **faster** due to fewer steps, whereas the **intrinsic** pathway is **slower but amplifies clotting more extensively.**

Generating Prothrombin Activator

- **Two pathways**
  - **Extrinsic pathway – Trauma to vessel wall and adjacent tissues**
  - **Intrinsic pathway – Trauma to the blood or exposure of the blood to collagen**
- **Both pathways involve “clotting factors”—mostly inactive proteases that are activated in cascades**

Physiology Quiz 9

QUIZ

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1	22	A regular shape	An irregular shape
V1 → V2			