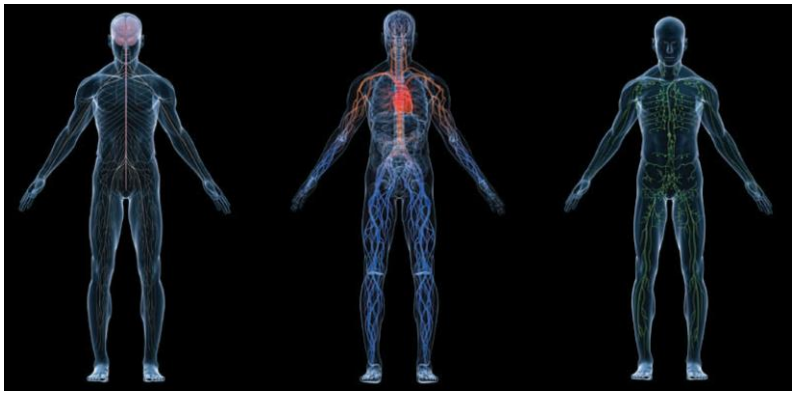
UNIT VI

GUYTON AND HALL
TEXTBOOK OF MEDICAL PHYSIOLOGY
THIRTEENTH EDITION



Hemostasis and Blood Coagulation

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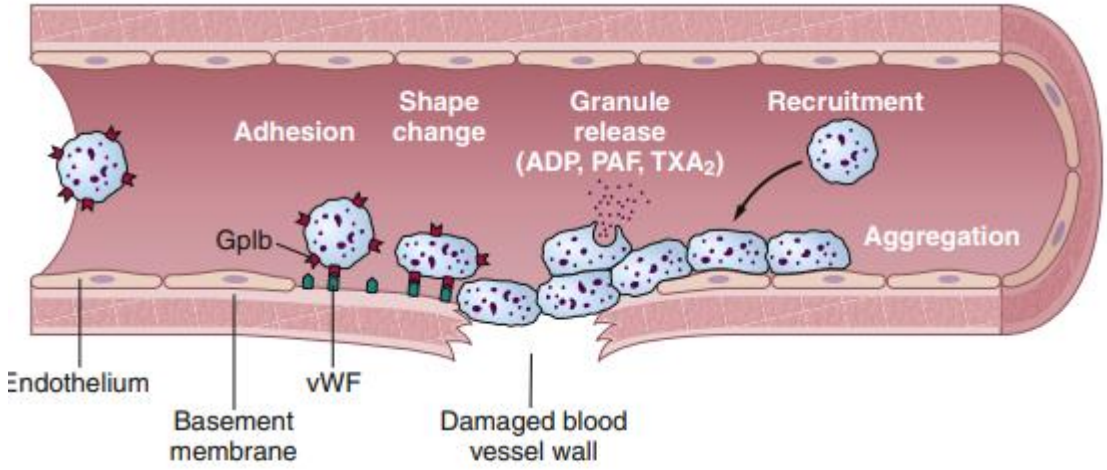
Events in Hemostasis

Vascular Constriction

- Local myogenic spasm-most effective
- Local autacoid factors
- Nervous reflexes-from pain receptors

Formation of a Platelet Plug

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



Platelet Plug Formation

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

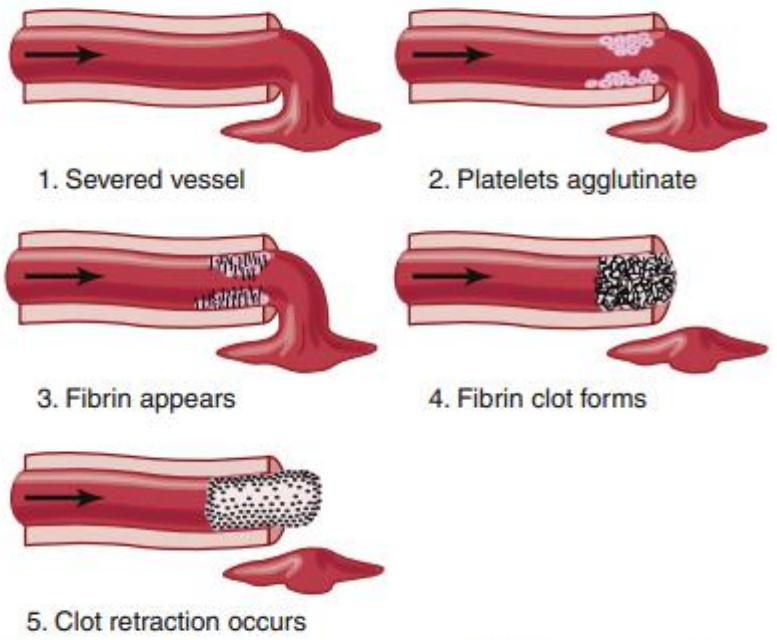
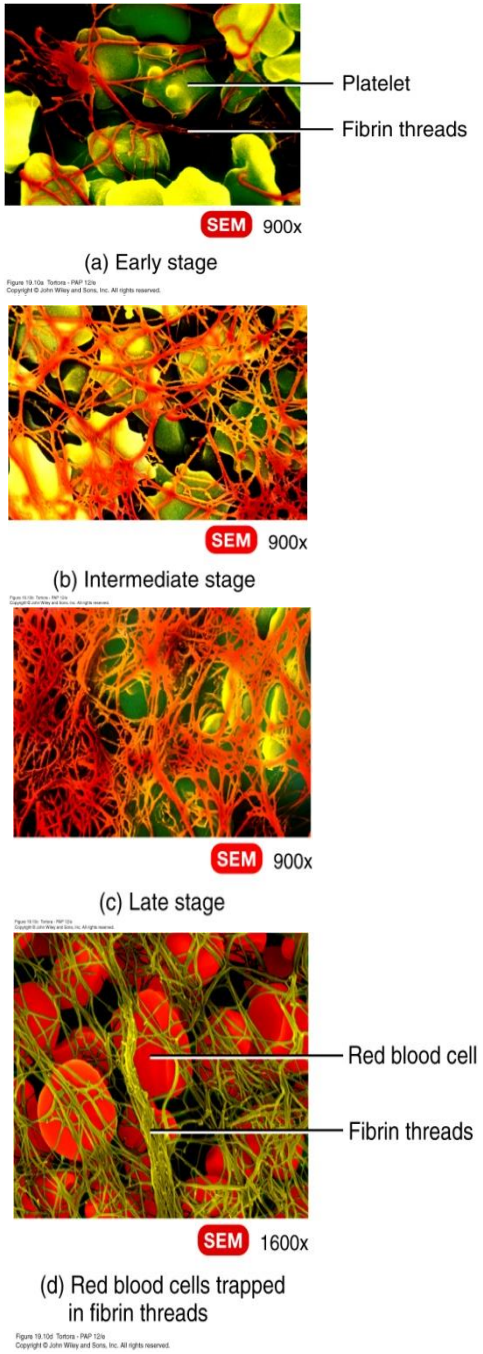


Figure 37-2. Clotting process in a traumatized blood vessel. *(Modified from Seegers WH: Hemostatic Agents. Springfield, IL: Charles C Thomas, 1948.)*

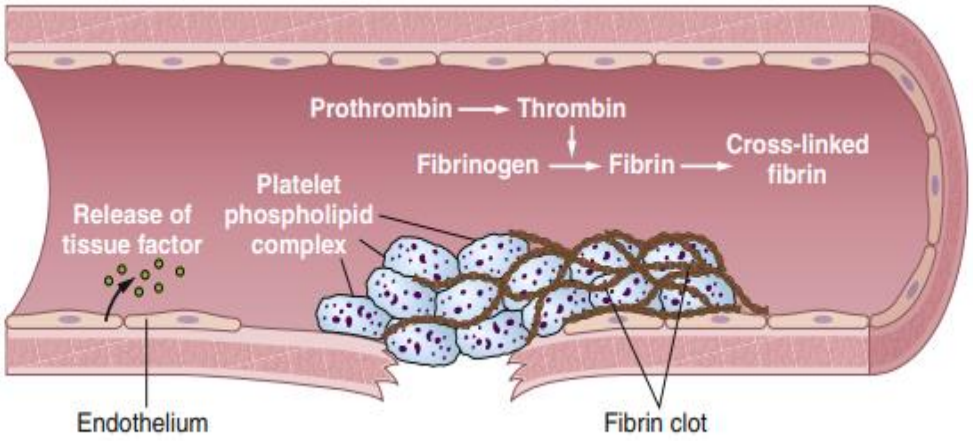
Blood Clotting

3. Blood clotting
   - Serum is blood plasma minus clotting proteins
   - Clotting – 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



Blood Clotting

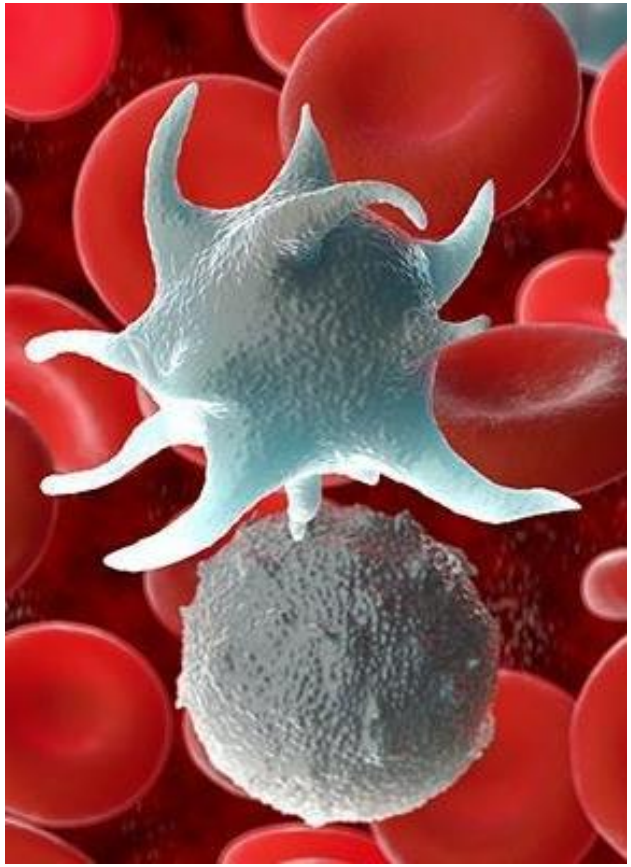
- Exposure of blood to vasc wall- release of TF (III or thromboplastin) from endo cells , phospholipids, thrombin activation- ----------Fibrin



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)
  - Mito-Produce ATP
  - Release prostaglandins
  - Release endothelial cell growth factor
  - Surface glycoproteins for adherence to damaged

    Vessels
  - Half-live of 8-12 days



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
  d. Damaged wall activates increasing numbers of platelets
  e. Important in closing small tears or ruptures in very small vessels (petechiae)

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

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.

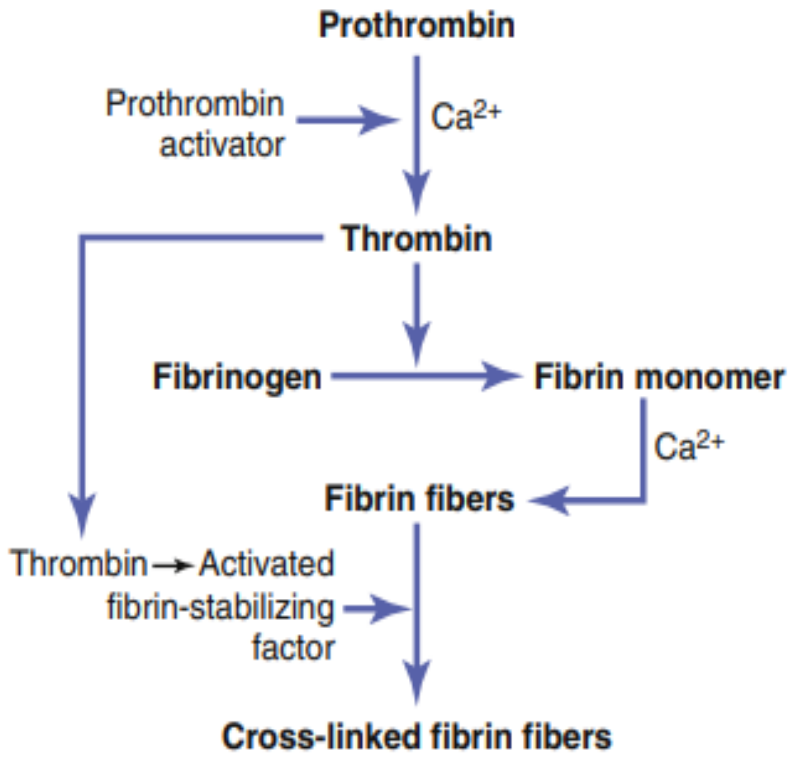


Figure 37-3 Schema for conversion of prothrombin to thrombin

3 Stages of Clotting

1. Extrinsic or intrinsic pathwa lead to formation of prothrombinase
2. Prothrombinase converts prothrombin into thrombin
3. Thrombin converts fibrinog (soluble) into fibrin (insolub forming the threads of the

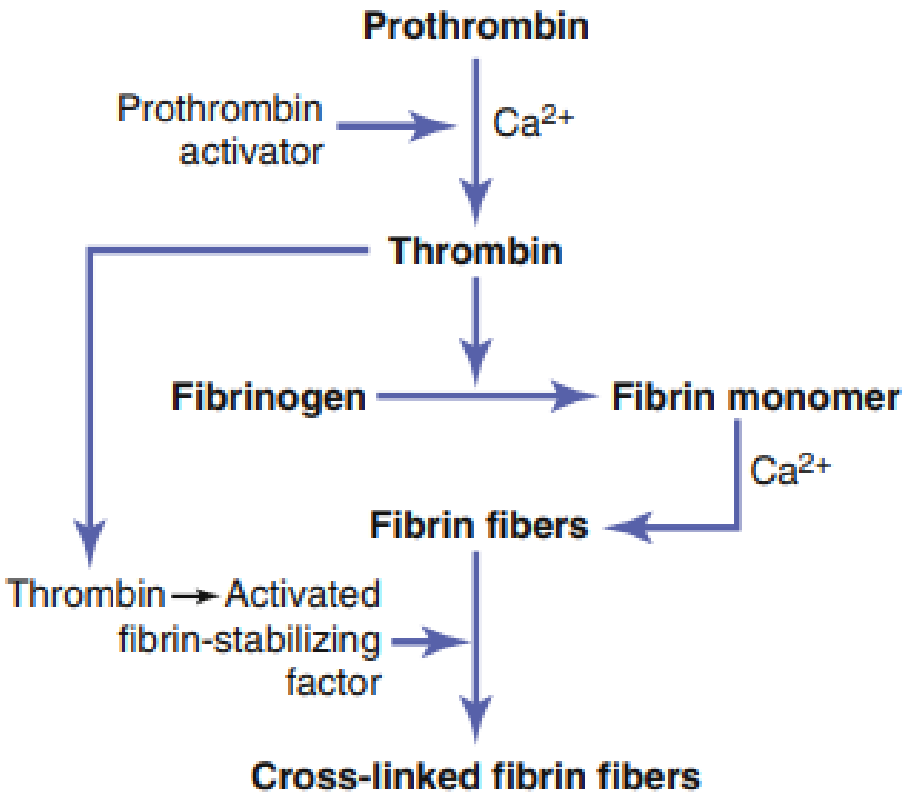


Figure 37-3 Schema for conversion of prothrombin to thrombin

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

Hemostasis: Prevention of Blood Loss

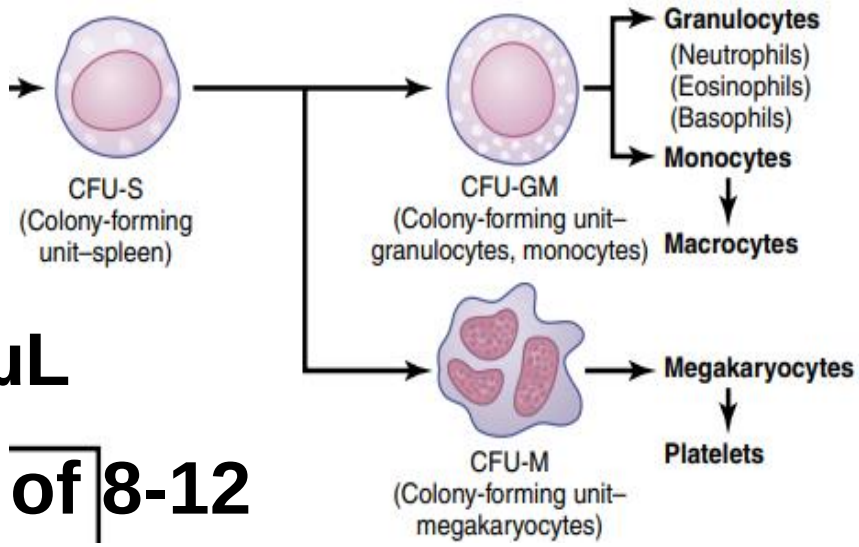
- Vascular constriction
- Formation of a platelet plug
- Formation of a blood clot
- Healing of vascular damage ± re-canalization

Vascular Constriction

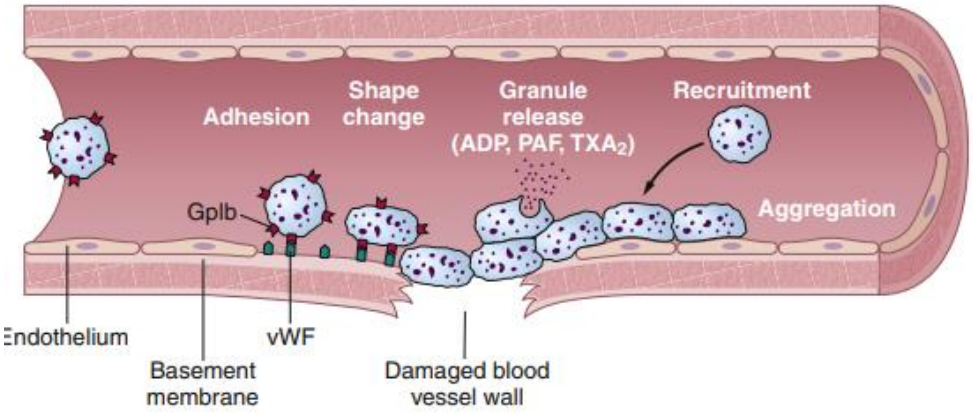
- **Myogenic spasm**
- **Local autocoid factors from damaged tissues and platelets**
- **Nervous reflexes**
- **Smaller vessels: thromboxane A_2 released by platelets**

Platelets (Thrombocytes)

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

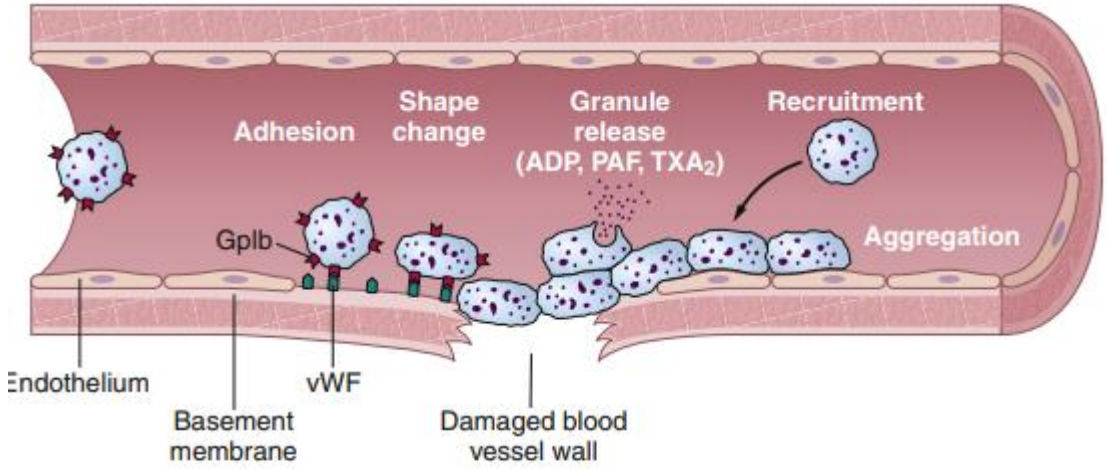


Platelet Functions



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

  fibrin-stabilizing factor, PDGF, store Ca^{++}
- **Mitochondria / enzymes**
  - **produce ATP, ADP**



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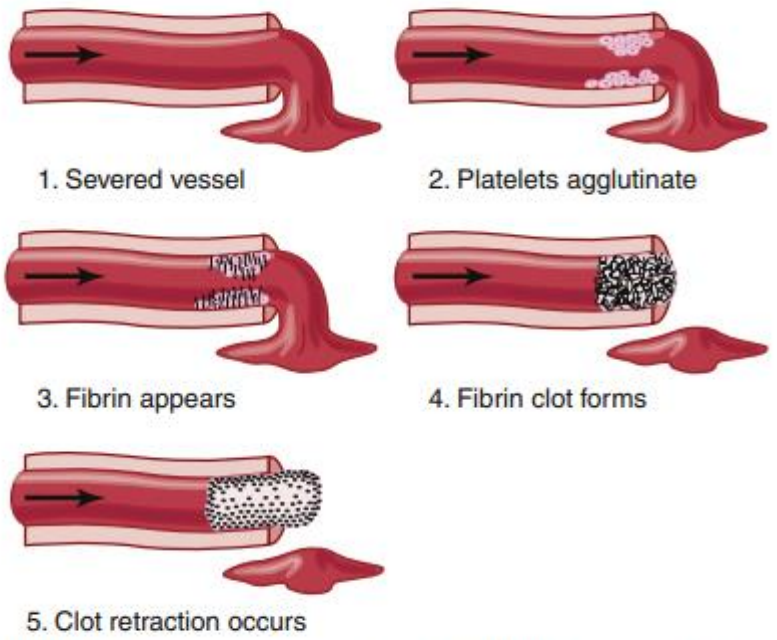


Figure 37-2. Clotting process in a traumatized blood vessel. *(Modified from Seegers WH: Hemostatic Agents. Springfield, IL: Charles C Thomas, 1948.)*

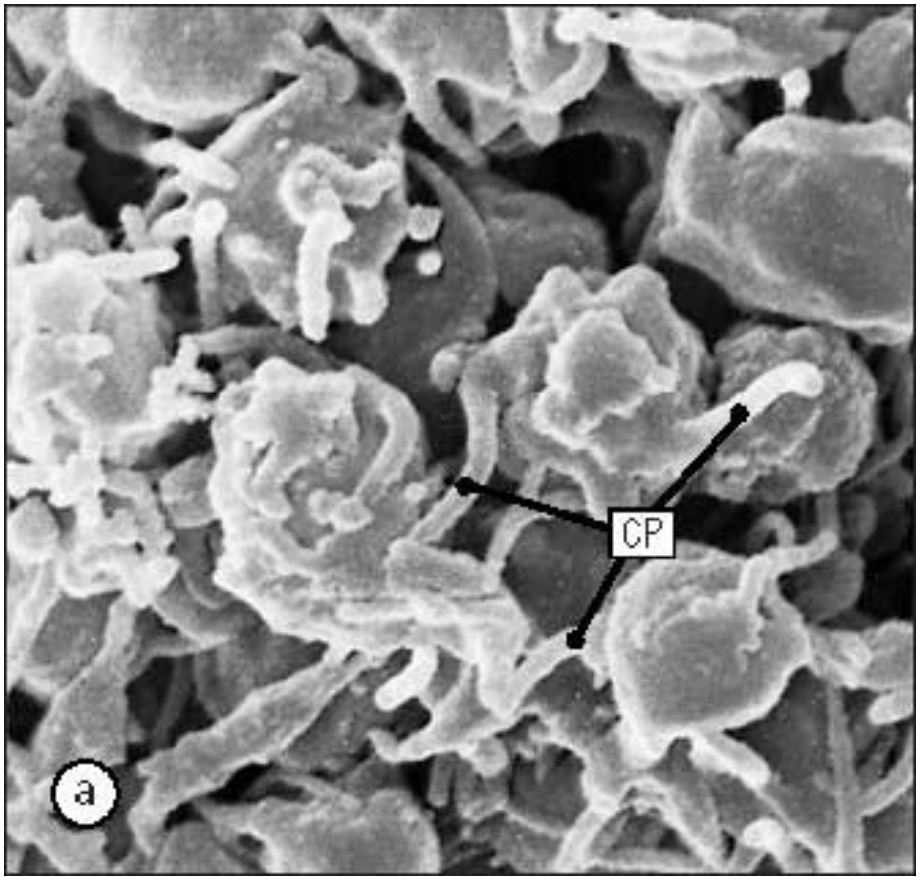
Platelet Membranes

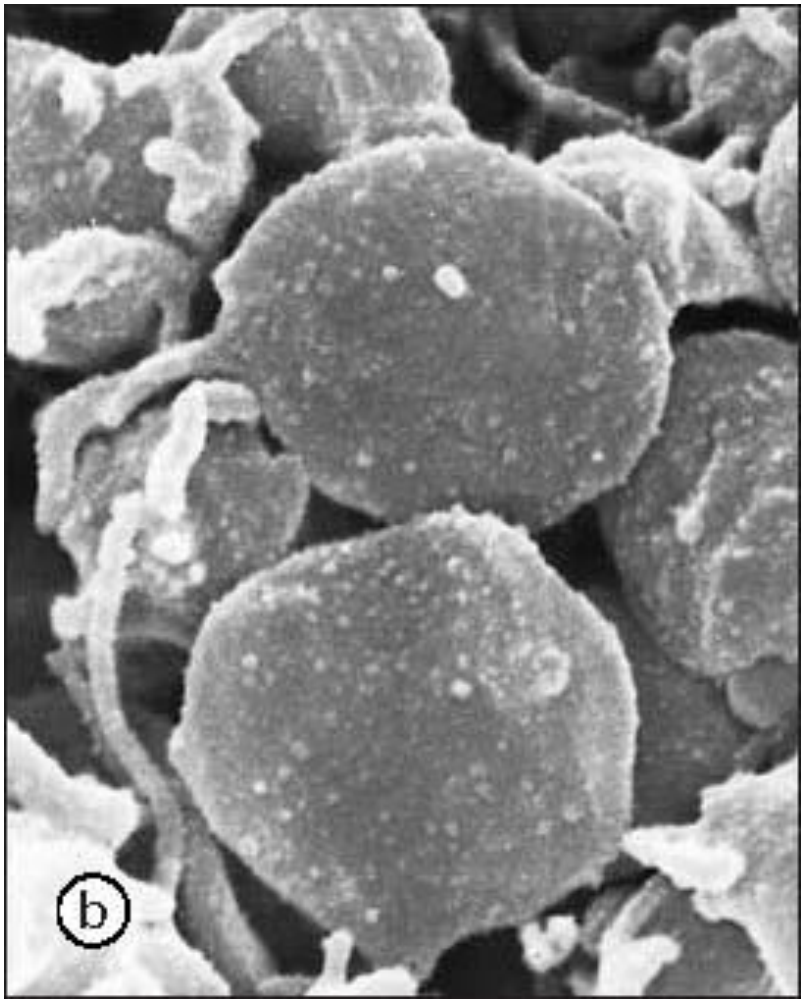
- **Surface glycoprotein**
  - **Repels intact endothelium**
  - **Adheres to injured endothelium and exposed collagen**
- **Membrane phospholipids**
  - **Activate blood clotting**

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





Figs. 7.15a and 7.14b, *Stevens & Lowe Human Histology,* 4th edition

Clot Formation and Progression

Begins in 15- 20 seconds in severe vascular trauma

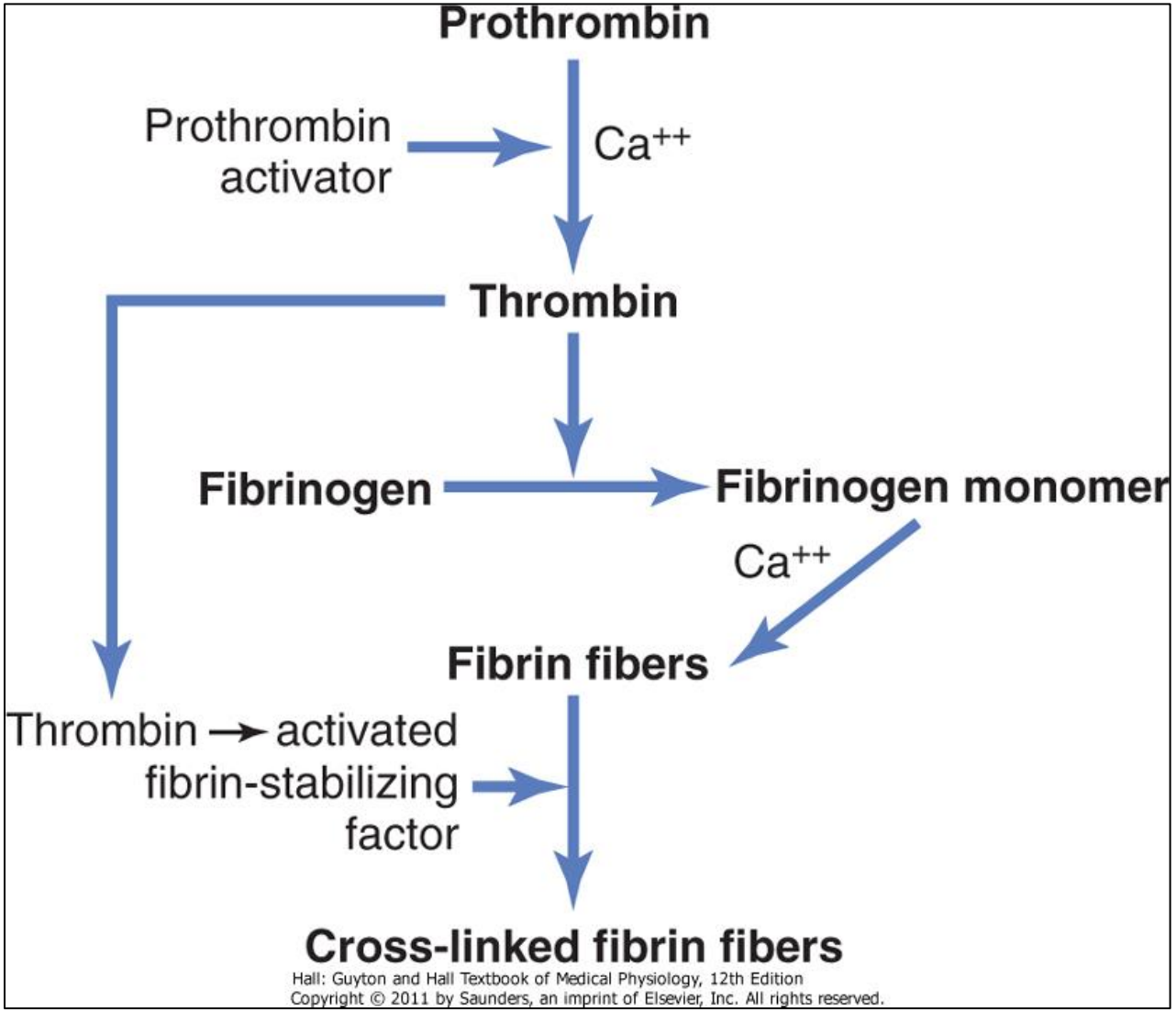
Occlusive clot within 3-6 minutes unless very large vascular defect

20-60 minutes: Clot retraction

1- 2 weeks : Invasion by fibroblasts

Organization into fibrous tissue

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**
- **Fibrinogen**
  - **MW 340,000; 100-700 mg/dl in plasma**
  - **Synthesized in the liver (acute phase reactant)**
  - **Usually intravascular; can extravasate with increased vascular permeability**

Fibrin Production

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

  → fibrin monomer → spontaneous polymerization

- **Long fibers form clot reticulum**

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

Clot Extension

- **Thrombin 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**

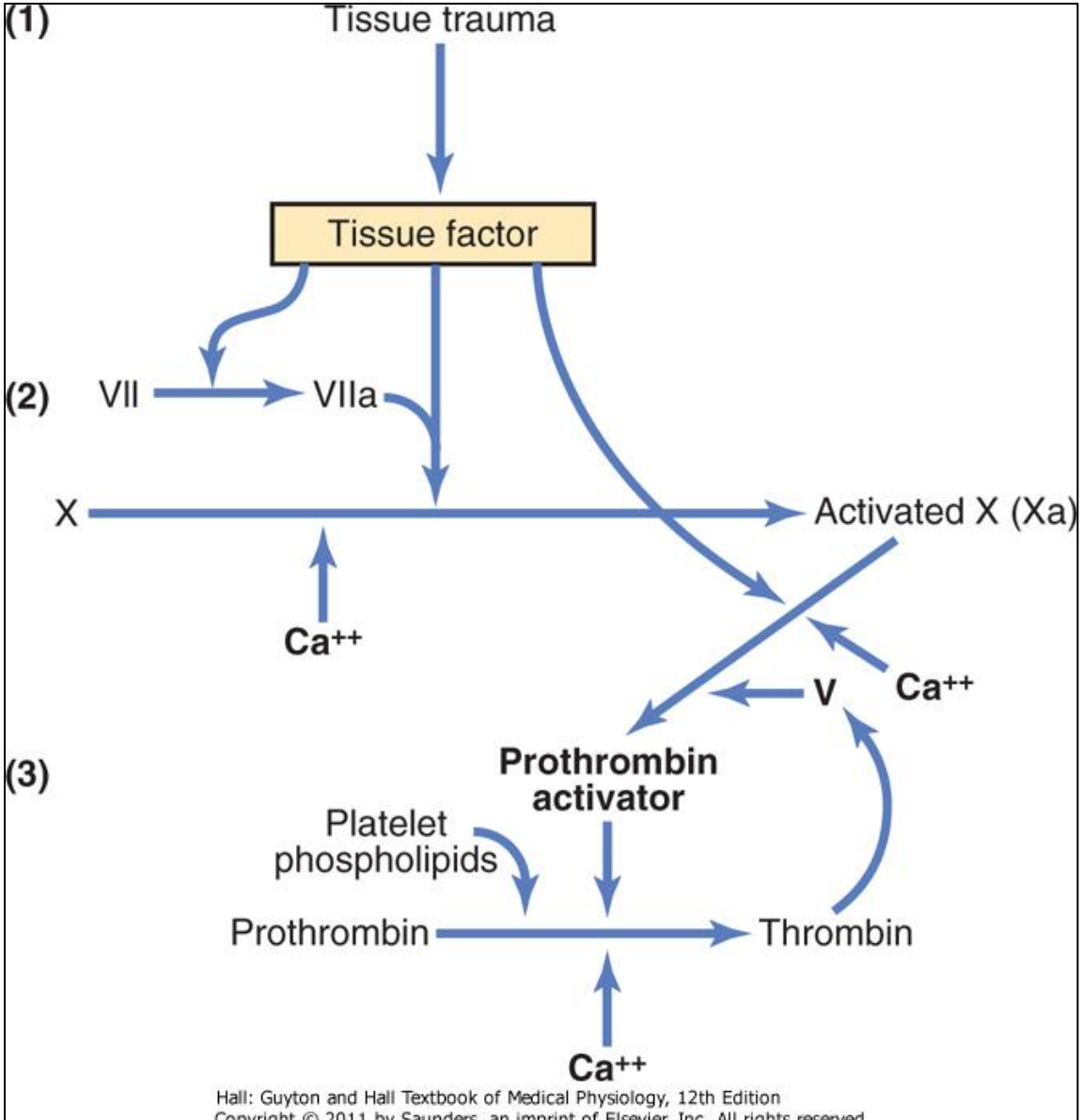
Clot Retraction

- **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**

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**

Extrinsic Pathway of Blood Clotting



Blood Coagulation

- **Extrinsic Pathway**

  a. Release of tissue factor

  b. Activation of Factor X- role of Factor VII and tissue factor

  c. Effect of Xa to form prothrombin activator -role of Factor V in the presence of calcium and phospholipids to split prothrombin to thrombin

Blood Coagulation

- **Intrinsic Pathway**

  a. Blood trauma causes activation Factor XII and release of platelet phospholipids

  b. Activation of Factor XI

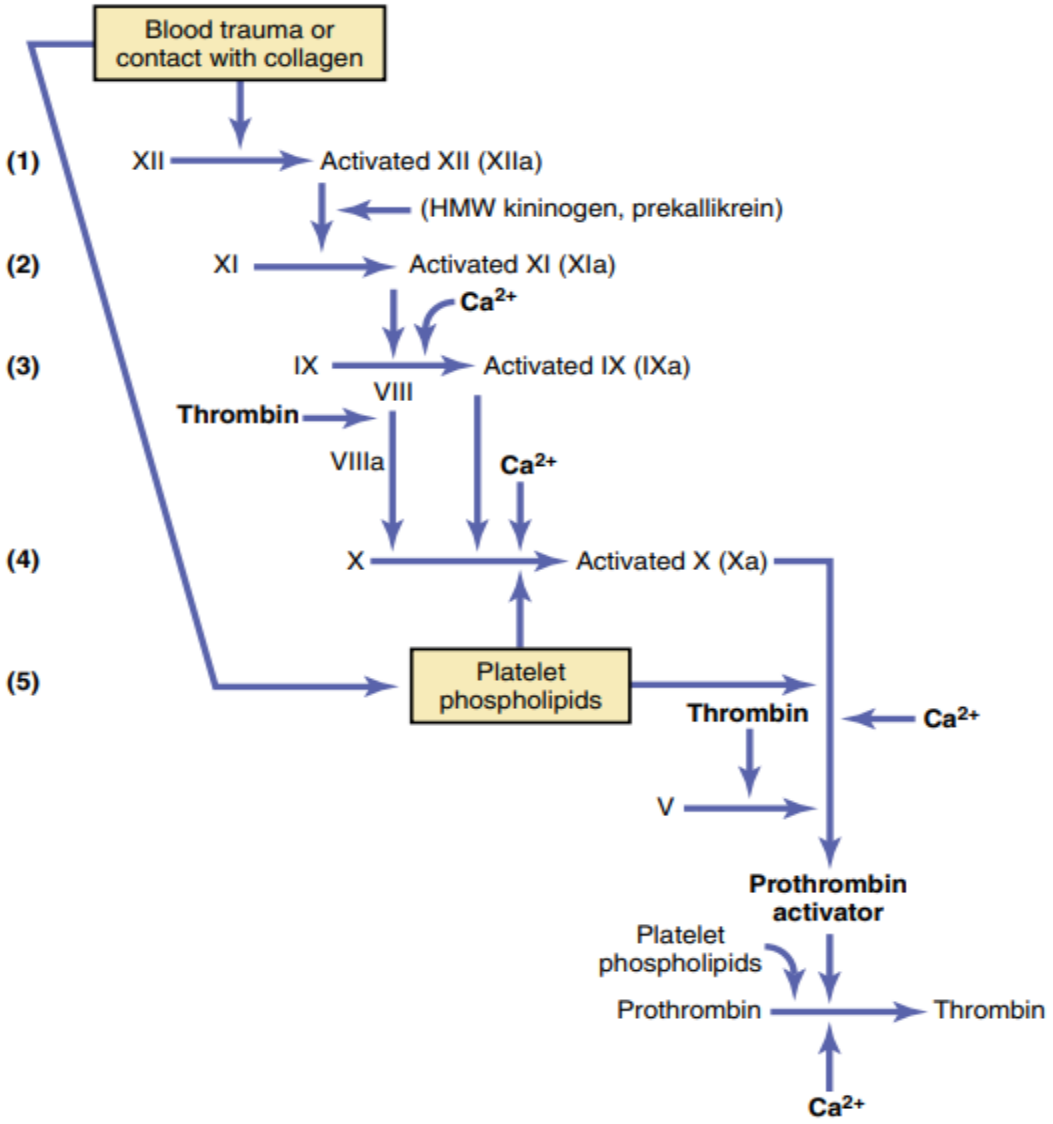
  c. Activation of Factor IX by activated XI

  d. Activation of Factor X-role of Factor VIII

  e. Action of activated Factor X to form prothrombin activator-role of Factor V

Intrinsic Pathway of Blood Clotting

VIII or platelets if def, 4 is def



Synergy between the Intrinsic and Extrinsic Pathways

- **Tissue injury…**
  - **Tissue factor activates the Extrinsic Pathway**
  - **Exposure of Factor XII and platelets to collagen activates the Intrinsic Pathway**
- **Extrinsic pathway can be explosive, with clotting in < 15 seconds**
- **The Intrinsic pathway is slower**

  → 1 – 6 minutes

Prevention of Clotting

- **Smoothness of the endothelial surface**
- **Mucopolysaccharide coating (glycocalyx) repels platelets and clotting factors**
- **Thrombomodulin bound to endothelium binds (competes for) thrombin**
- **Thrombin-thrombomodulin activates Protein C→ inactivates factors V and VIII**
- **Damage to glycocalyx activates factor XII, platelets (intrinsic pathway). If collagen is exposed→ even more robust**

Negative Feedback

- **Fibrin fibers bind 85-90% of thrombin and localize it to the clot**
- **Antithrombin III combines with the remainder and inactivates it over 12-20 minutes**

Heparin

- **Physiologically, availability is limited**
- **Used therapeutically**
- **Highly negatively charged**
- **Binds anti-thrombin III and increases its effectiveness 100- to 1000-fold**
- **Heparin-antithrombin III removes free thrombin from the blood almost instantly**
- **Also removes XIIa, XIa, Xa, and IXa**
- **Mast cells, basophils particularly abundant in pericapillary regions of liver and lung**

Clot Lysis

- **Plasminogen is trapped in the clot**
- **Over several days, injured tissues release tissue plasminogen activator (tPA)**
- **Plasminogen is activated to plasmin, a protease resembling trypsin**
- **Plasmin digests fibrin fibers and several other clotting factors**
- **Often results in re-opening repaired small blood vessels**

Causes of Excessive Bleeding

- **Hepatocellular disease**
- **Vitamin K deficiency**
- **Hemophilia**
- **Low platelet count (thrombocytopenia)**

Vitamin K Deficiency

- **Essential to carboxylate glutamic acid in five important clotting factors:**
  - **prothrombin and factors VII, IX, X, and protein C**
- **In this process vitamin K is oxidized and inactivated**
- **Vitamin K epoxide reductase complex 1 (VKOR c1) reduces vitamin K and reactivates it**

Vitamin K

- **Produced in the intestine by bacteria**
- **Fat-soluble: malabsorption of fats can lead to deficiency**
- **Lack of bile production or delivery can cause fat malabsorption and vitamin K deficiency**
- **In patients with liver or biliary disease, vitamin K can be injected 4-8 hours before surgery**

Hemophilia

- **Hemophilia A – Deficiency of factor VIII**
  - **85% of hemophilia cases**
  - **1 / 10,000 males**
- **Hemophilia B – Deficiency of factor IX**
  - **15% of cases**
  - **About 1 / 60,000 males**
- **Both impair Intrinsic Pathway activation**
- **Both genes are on the X chromosome (males only get one copy)**
- **Clinically: Bleeding after minor trauma**

Factor VIII Deficiency

- **Factor VIII has two components…**
  - **Large: MW > 10^6**
  - **Small: MW ~ 230,000**
- **Deficiency of the small component causes hemophilia A**

  → treat bleeding with factor VIII replacement
- **Deficiency of the large component causes von Willebrand disease (resembles decreased platelet function)**

Thrombocytopenia

- **Low numbers of platelets**
- **Bleeding from small venules or capillaries**
- **Petechaiae, thrombocytopenic purpura**
- **Often idiopathic**
  - **< 50,000 platelets / μL – usually modest bleeding**
  - **< 10,000 platelets / μL – life-threatening**
- **Treated with platelet infusions**
  - **→ effective for 1 – 4 days each time**

Thrombi and Emboli

- An abnormal clot is a thrombus
- When it floats it's an embolus
- Caused by…
  - Endothelial roughening (e.g. atherosclerosis)
  - Slow flow (e.g. prolonged air travel)
- Treatment…
  - tPA
  - Embolectomy

Pulmonary Embolus

- **Usually from deep leg veins**
- **Part of thrombus disengages ~10% of the time**
- **Occludes pulmonary arteries—potentially fatal**
- **tPA can be life-saving**

Disseminated Intravascular Coagulation (DIC)

- **Occurs in the setting of massive tissue damage or sepsis**
- **Wide-spread coagulation in small vessels**
- **Manifested as bleeding from multiple sites because of depletion of clotting factors**

Clinically Useful Anticoagulants

- **Heparin**
  - **Binds, potentiates antithrombin III**
  - **Works rapidly, generally used acutely**
- **Coumarins**
  - **Inhibit VKOR c1**
  - **Deplete active vitamin K → deplete active prothrombin, factors VII, IX, X**
  - **Slower acting (days); used chronically**
  - **Over-anticoagulation – Treat with FFP and vitamin K**

In vitro Anti-coagulation

- **Siliconized containers prevent activation of factor VII and platelets**
- **Heparin – used in blood collection, heart-lung and kidney machines**
- **Calcium chelators (citrate, EDTA) used in blood collection, blood storage**

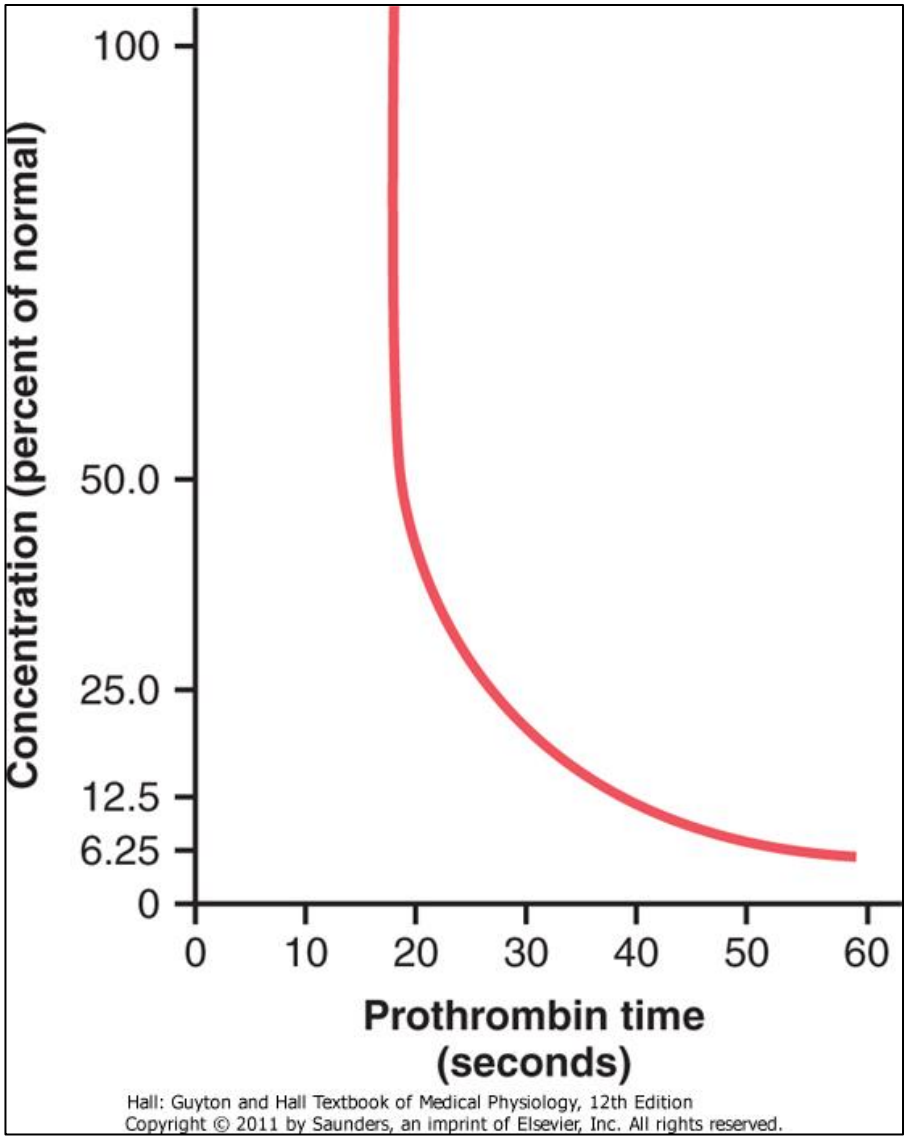
Blood Coagulation Tests

- **Bleeding Time (from small cut)**
  - **normally 1 - 6 minutes**
  - **Largely reflects platelet function**
- **Clotting time**
  - **Invert tube every 30 seconds**
  - **Normally 6 – 10 minutes**
  - **Not reproducible, generally not used**

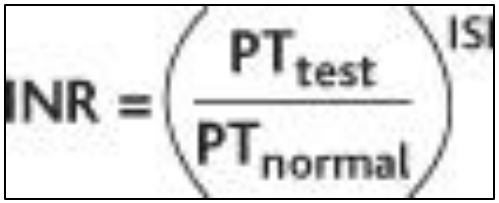
Prothrombin Time

- **Add excess calcium and tissue factor to oxylated blood, measure time to clot**
- **Assesses Extrinsic and Common Pathways**
- **Usually about 12 seconds**
- **Tissue factor batches have to be standardized (activity expressed as “International Sensitivity Index (ISI)”)**

Prothrombin Concentration and Function



International Normalized Ratio (INR)

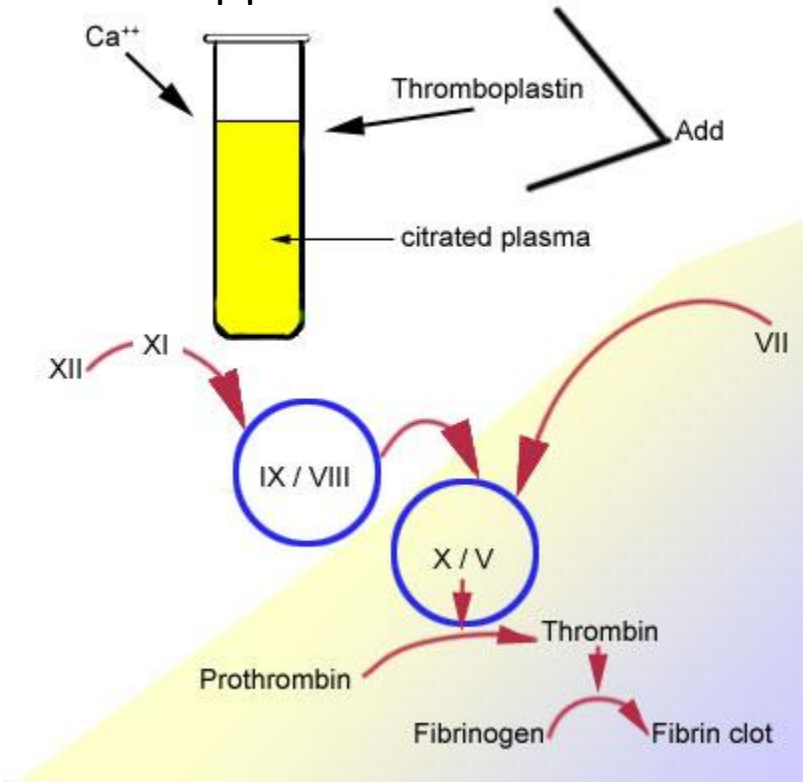


- **Normal INR: 0.9 – 1.3**
- **Therapeutic range: 2.0 - 3.0**

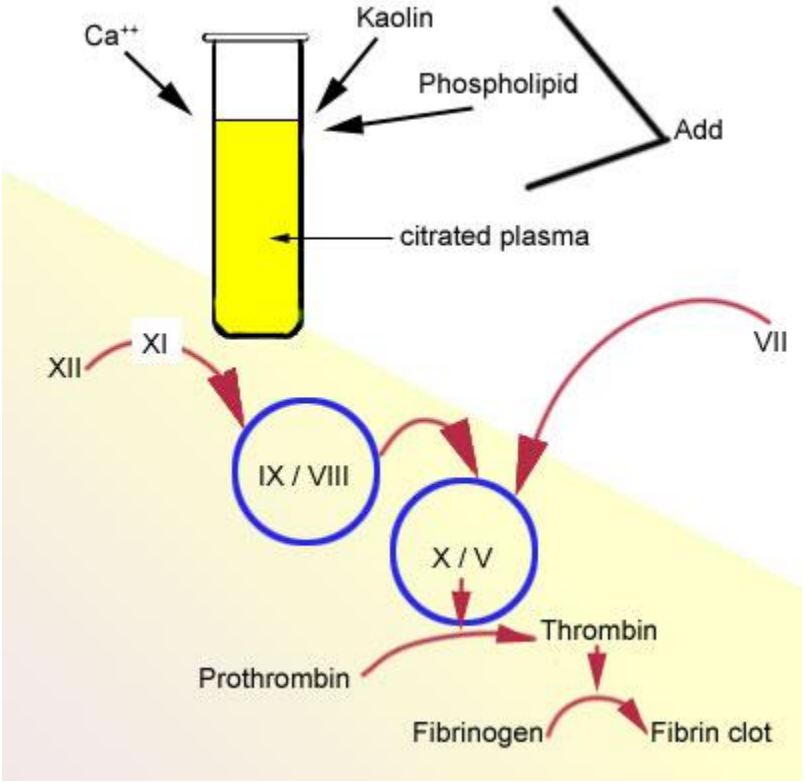
Tests of Other Clotting Factors

- **Mix the patient's plasma with a large excess of all needed components except the factor being tested**
- **Compare time to coagulation with that for pooled plasma of healthy volunteers**

PT


Ca++
Thromboplastin
Add
citrated plasma
XII
XI
VII
IX / VIII
X / V
Thrombin
Prothrombin
Fibrinogen
Fibrin clot

aPT


Ca++
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Phospholipid
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XI
VII
IX / VIII
X / V
Thrombin
Prothrombin
Fibrinogen
Fibrin clot

aPTT

- The activated partial thromboplastin time (aPTT) is a test performed to investigate bleeding disorders and to monitor patients taking an anticlotting drug such as heparin which inhibits factors X and thrombin, while activating anti-thrombin.

The aPTT test uses blood which is decalcified to prevent clotting before the test begins. The plasma is separated by centrifugation. (Ionized) Calcium and activating substances are added to the plasma to start the intrinsic pathway of the coagulation cascade. The substances are: kaolin (hydrated aluminum silicate) and cephalin. Kaolin serves to activate the contact-dependent Factor XII, and cephalin substitutes for platelet phospholipids.

- The partial thromboplastin time is the time it takes for a clot to form, measured in seconds. Normally, the sample will clot in 35 seconds.

PTT measures the integrity of the intrinsic system (Factors XII, XI, VIII, IX) and common clotting pathways.

Increased levels in a person with a bleeding disorder indicate a clotting factor may be missing or defective. At this point, further investigation is needed and warrants the use of sensitive assays for specific coagulation factors. Liver disease decreases production of factors, increasing the PTT.