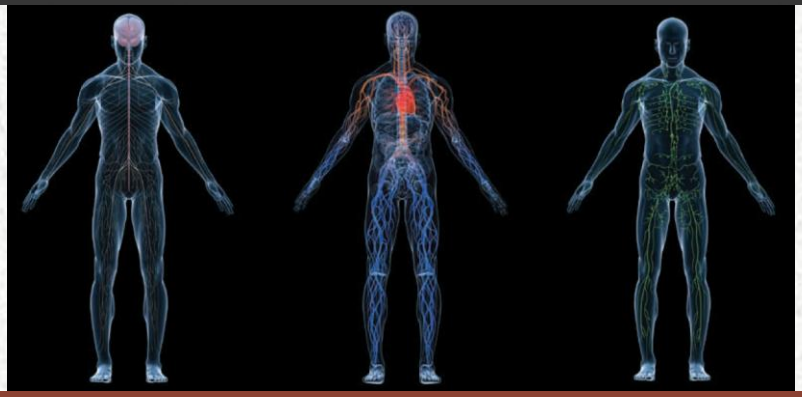
UNIT VI

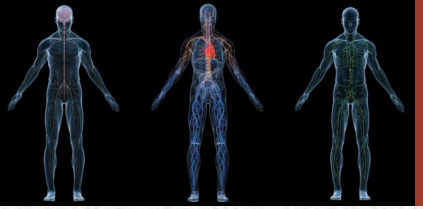
GUYTON AND HALL
TEXTBOOK OF MEDICAL PHYSIOLOGY
THIRTEENTH EDITION



Chapter 37:

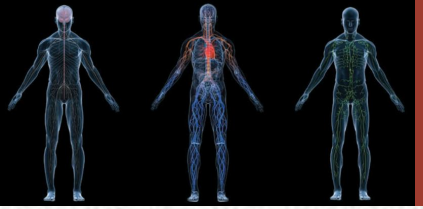
Platelets
Hemostasis and Blood Coagulation

Presented by Dr. Diksha Yadav



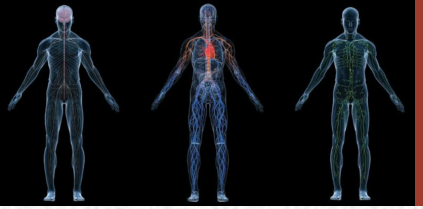
Hemostasis: Prevention of Blood Loss

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



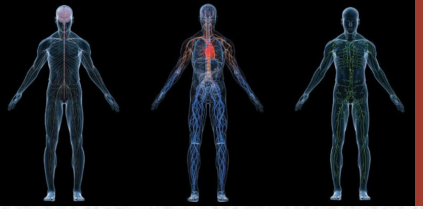
Vascular Constriction

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



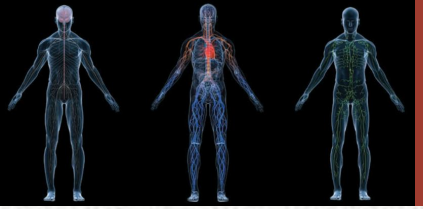
Platelets (Thrombocytes)

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



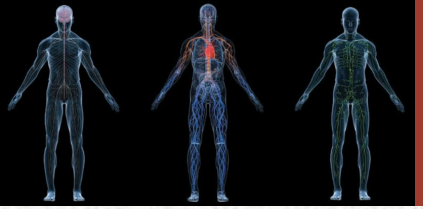
Platelet Functions

- **Contractile capabilities**
  - **actin, myosin, thrombosthenin**
- **Residual ER and Golgi**
  - **synthesize enzymes, prostaglandins, fibrin-stabilizing factor, PDGF, store Ca^{++}**
- **Mitochondria / enzymes**
  - **produce ATP, ADP**



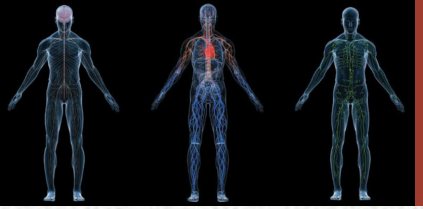
Platelet Membranes

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

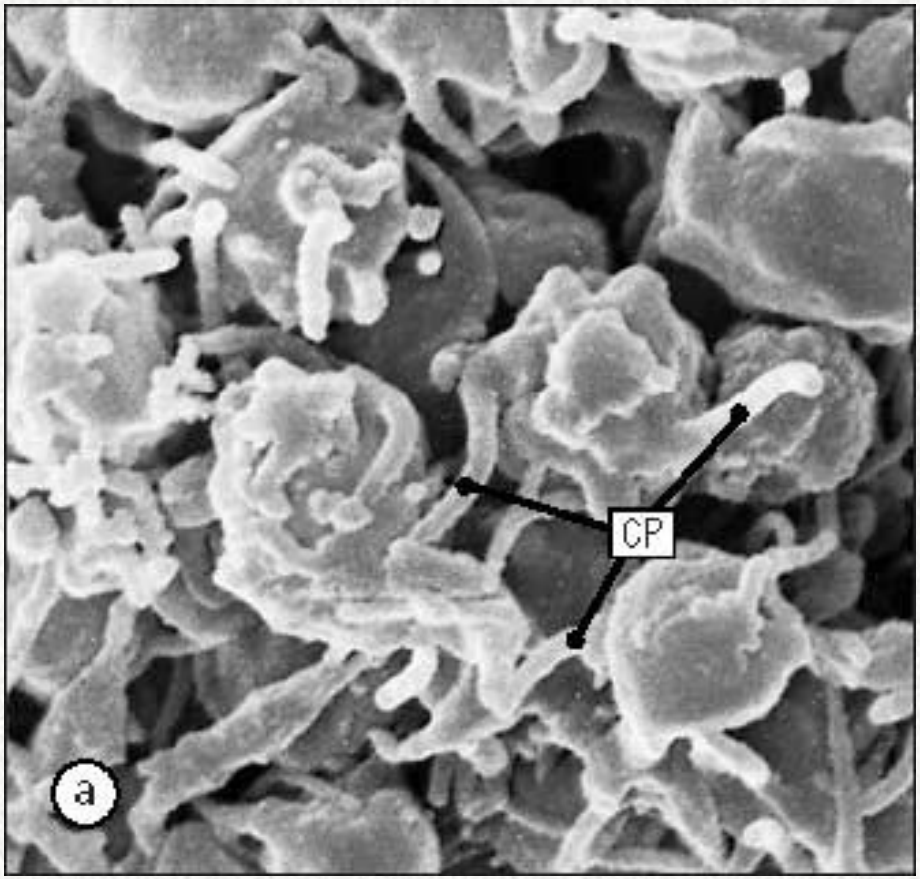


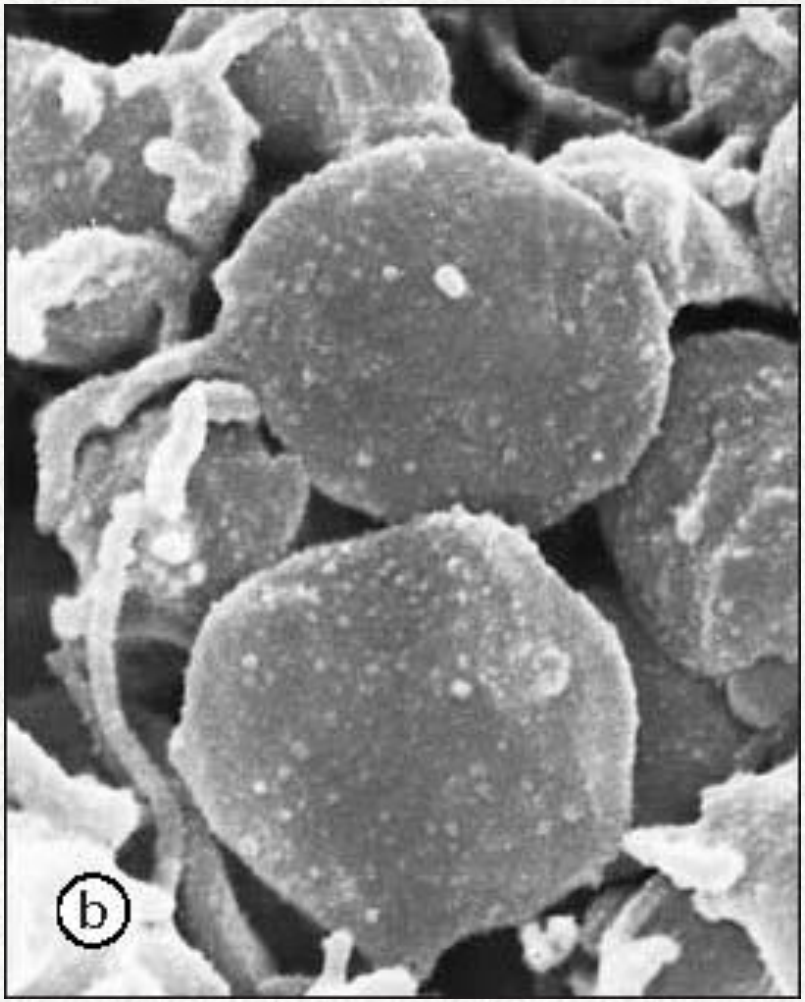
Formation of the Platelet Plug

- **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**

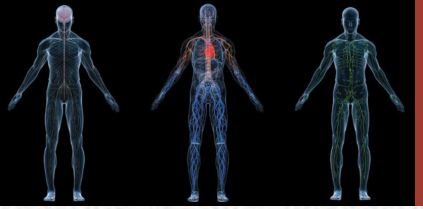


Platelet Plug



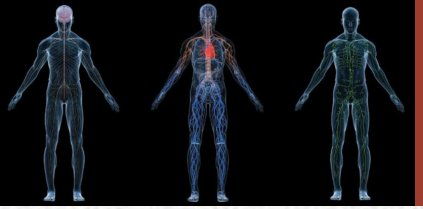


Figs. 7.15a and 7.14b, *Stevens & Lowe Human Histology,* 4th edition

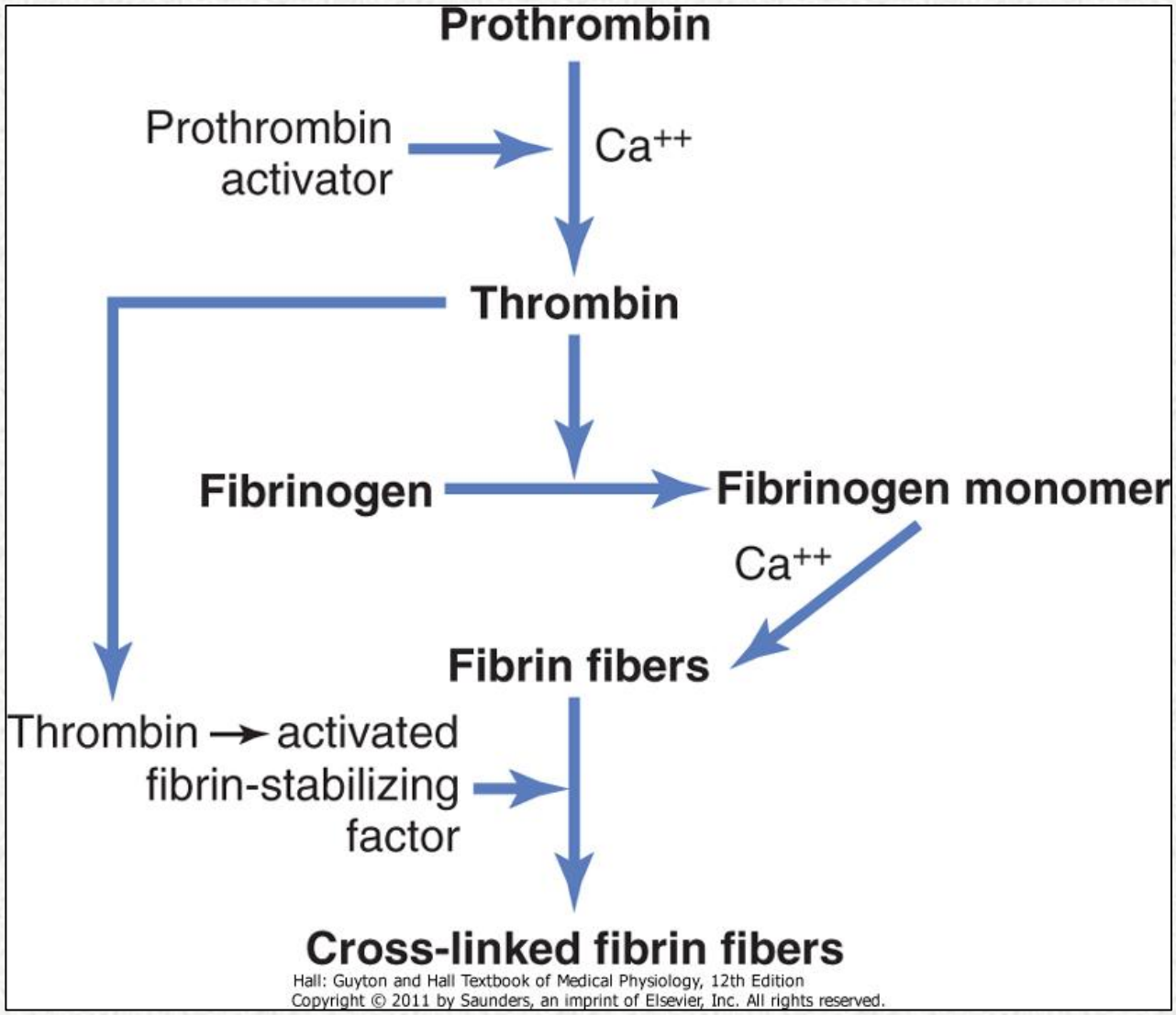


Clot Formation and Progression

- 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



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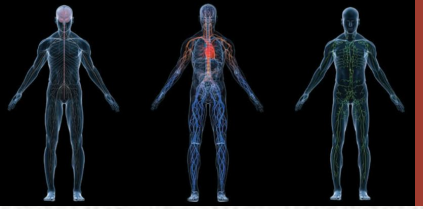
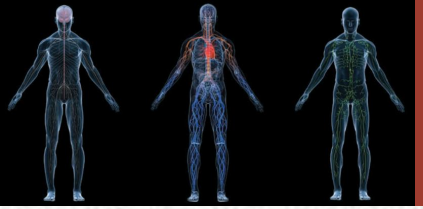


Effector Proteins for Clotting

- **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**

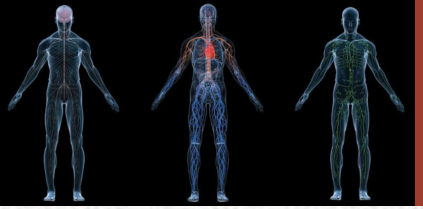


Fibrin Production

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

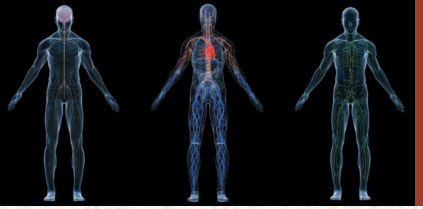
  → fibrin monomer → spontaneous polymerization

- **Long fibers form clot reticulum**
- **Fibrin stabilizing factor**
  - **In plasma and released from platelets**
  - **Activated by thrombin**
  - **Covalent cross-linking of fibrin monomers and adjacent fibrin fibers**



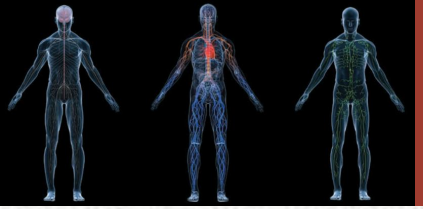
Clot Extension

- 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



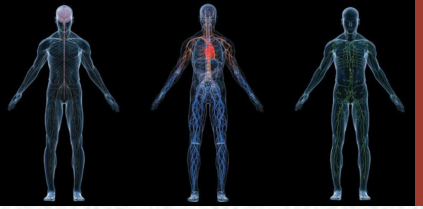
Clot Retraction

- Begins within 20-60 minutes
- Fibrin binds to damaged vessel wall
- Platelets bind to multiple fibrin fibers
  - contract via actin, myosin, thrombosthenin
- Clot tightens, expressing serum, and closing the vascular defect

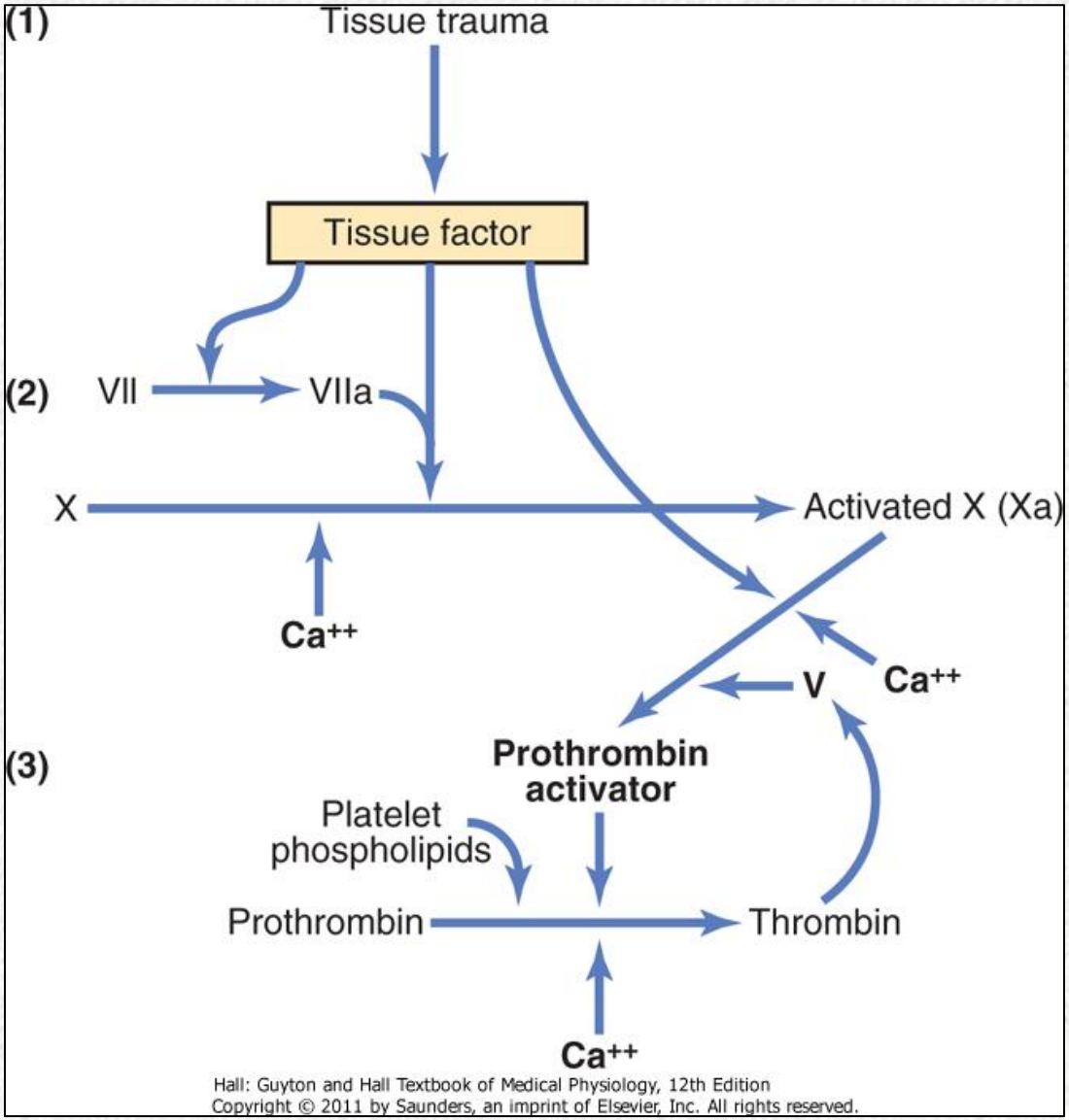


Generating Prothrombin Activator

- **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



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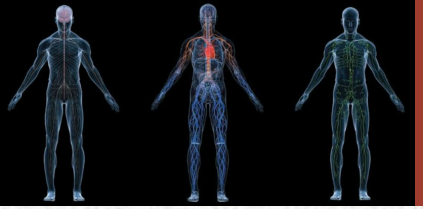
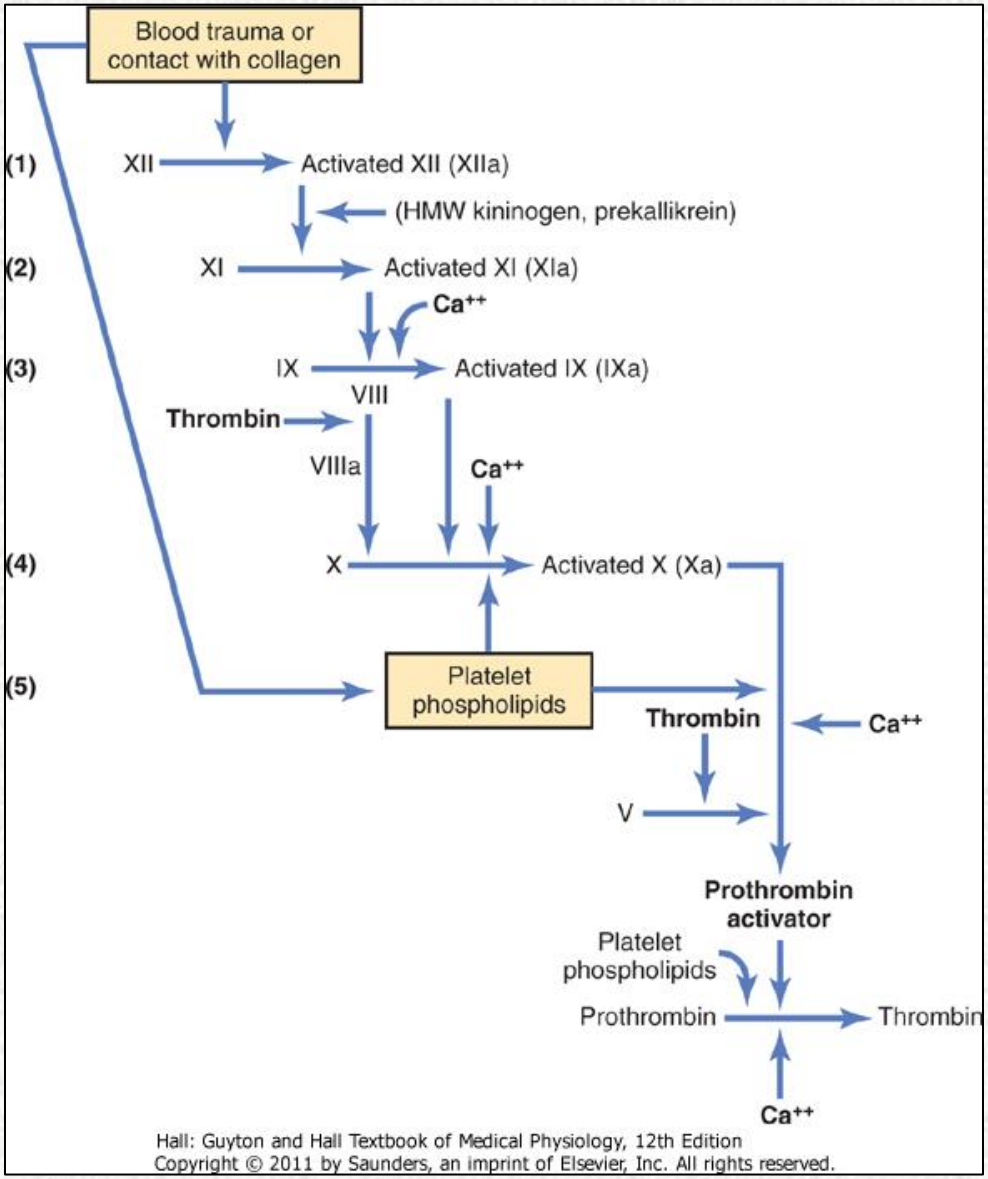


Intrinsic Pathway of Blood Clotting



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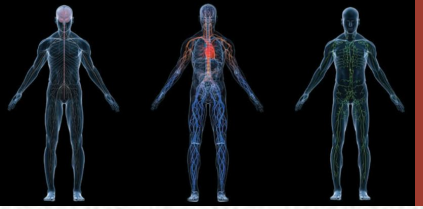
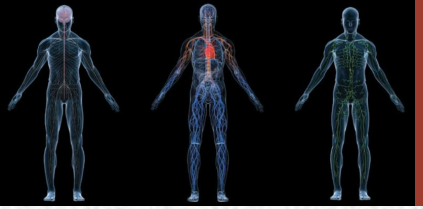


Synergy between the Intrinsic and Extrinsic Pathways

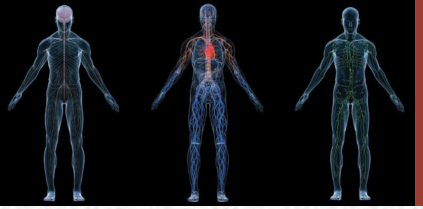
- **Tissue injury…**
  - **Tissue factor activates the Extrinsic Pathway**
  - **Exposure of Factor XII and platelets to collagen activates the Intrinsic Pathway**
- **Extrinsic pathway can be explosive, with clotting in < 15 seconds**
- **The Intrinsic pathway is slower**

  → 1 – 6 minutes



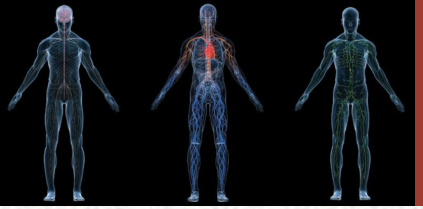
Prevention of Clotting

- 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



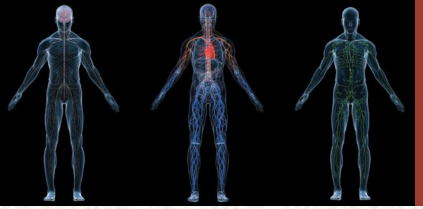
Negative Feedback

- 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



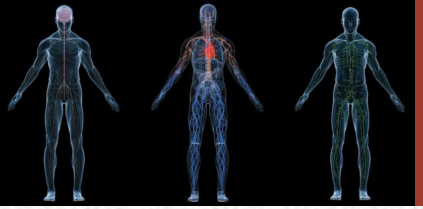
Heparin

- 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



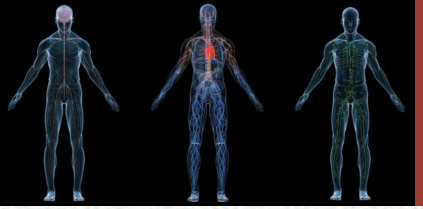
Clot Lysis

- 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



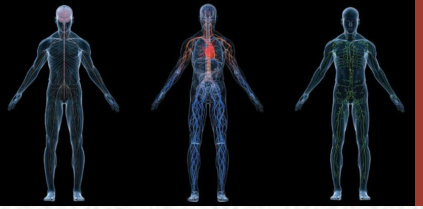
Causes of Excessive Bleeding

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



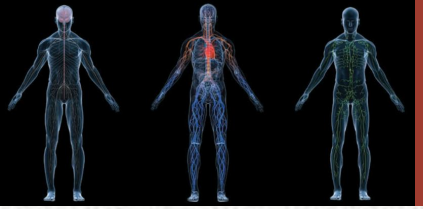
Vitamin K Deficiency

- **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**



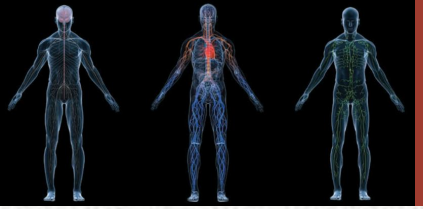
Vitamin K

- 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

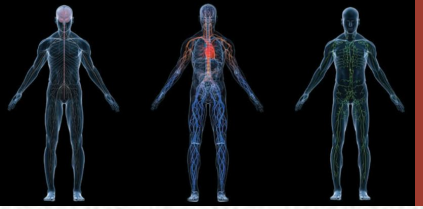
- **Hemophilia A – Deficiency of factor VIII**
  - **85% of hemophilia cases**
  - **1 / 10,000 males**
- **Hemophilia B – Deficiency of factor IX**
  - **15% of cases**
  - **About 1 / 60,000 males**
- **Both impair Intrinsic Pathway activation**
- **Both genes are on the X chromosome (males only get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



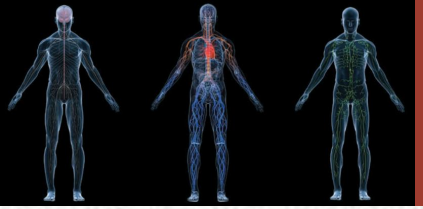
Thrombocytopenia

- Low numbers of platelets
- Bleeding from small venules or capillaries
- Petechaiae, thrombocytopenic purpura
- Often idiopathic

  < 50,000 platelets / μL – usually modest bleeding

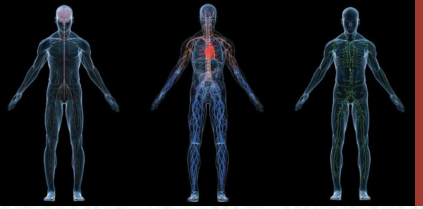
  < 10,000 platelets / μL – life-threatening
- Treated with platelet infusions

  → effective for 1 – 4 days each time



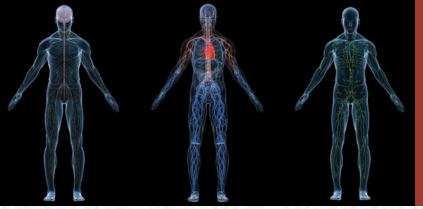
Thrombi and Emboli

- 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



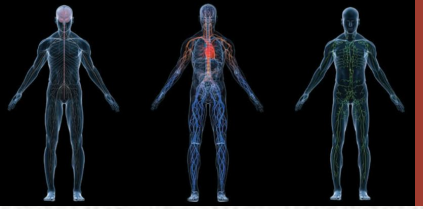
Pulmonary Embolus

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



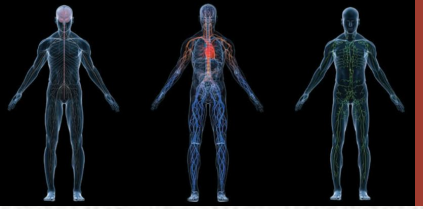
Disseminated Intravascular Coagulation (DIC)

- 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



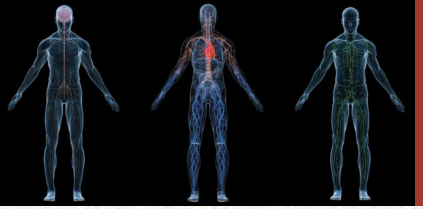
Clinically Useful Anticoagulants

- **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**



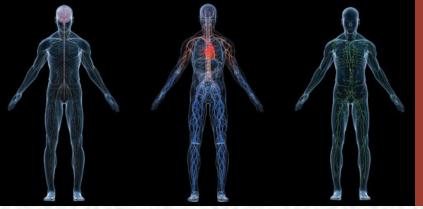
In vitro Anti-coagulation

- 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



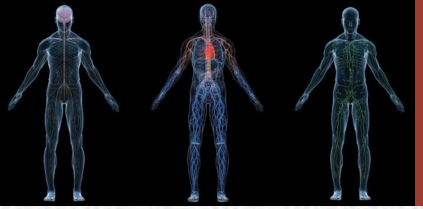
Blood Coagulation Tests

- **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**

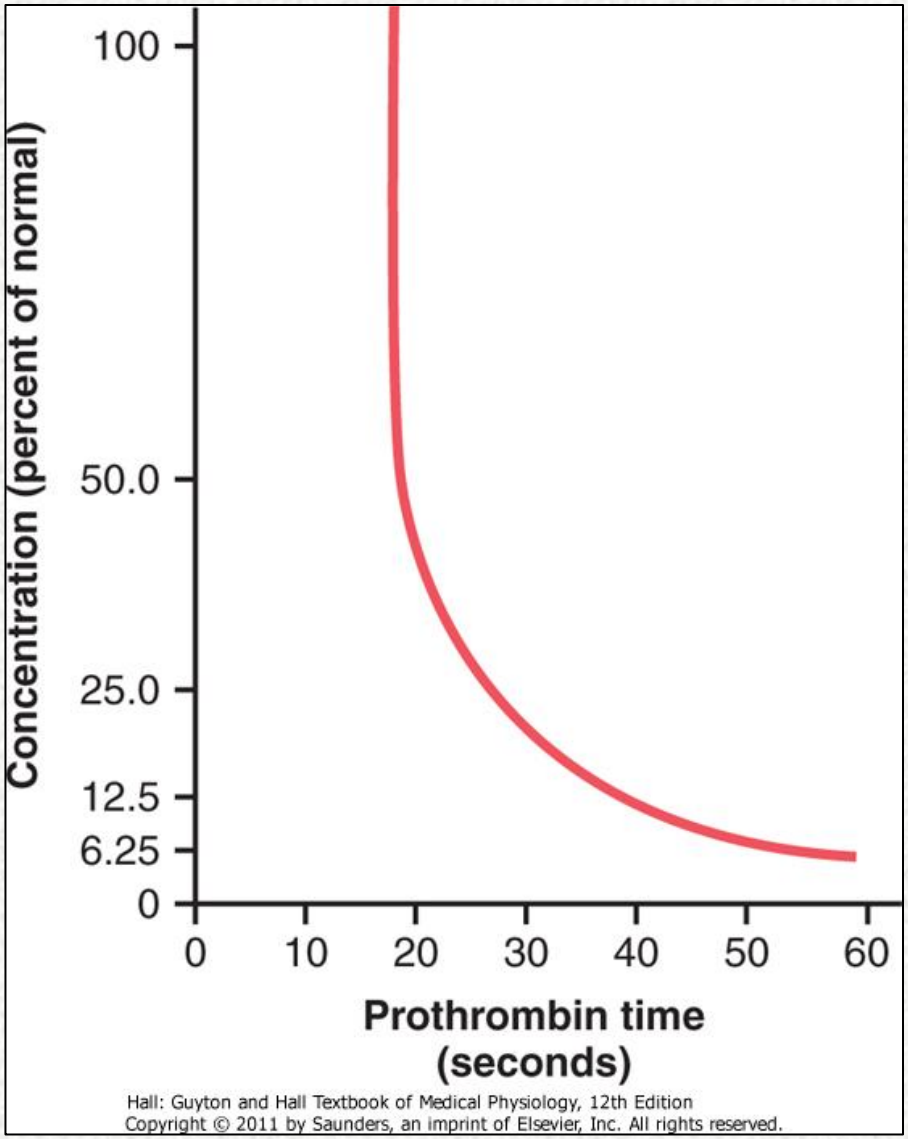


Prothrombin Time

- 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



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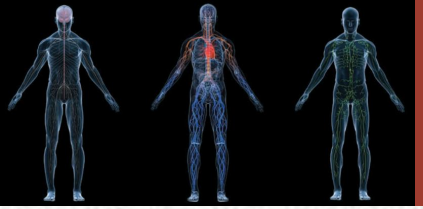
International Normalized Ratio (INR)

$$INR = \left(\frac{PT_{test}}{PT_{normal}} \right)^{ISI}$$

- **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