Circulatory System

- **circulatory system** consists of the heart, blood vessels and blood

- **cardiovascular system** refers only to the heart and blood vessels

- **hematology** – the study of blood

- **functions of circulatory system**
  - **transport**
    - O$_2$, CO$_2$, nutrients, wastes, hormones, and stem cells
  - **protection**
    - inflammation, limit spread of infection, destroy microorganisms and cancer cells, neutralize toxins, and initiates clotting
  - **regulation**
    - fluid balance, stabilizes pH of ECF, and temperature control
Components and General Properties of Blood

• adults have 4-6 L of blood

• a liquid connective tissue consisting of cells and extracellular matrix
  – plasma – matrix of blood
    • a clear, light yellow fluid
  – formed elements - blood cells and cell fragments
    • red blood cells, white blood cells, and platelets
Components and General Properties of Blood

- seven kinds of formed elements
  - **erythrocytes** - red blood cells (RBCs)
  - **platelets**
    - cell fragments from special cell in bone marrow
  - **leukocytes** - white blood cells (WBCs)
    - **five leukocyte types** divided into **two categories**:
      - granulocytes (with granules)
        - **neutrophils**
        - **eosinophils**
        - **basophils**
      - agranulocytes (without granules)
        - **lymphocytes**
        - **monocytes**
Formed Elements of Blood

Figure 18.1
Separating Plasma From Formed Elements of Blood

- **hematocrit** - centrifuge blood to separate components
  - *erythrocytes* are heaviest and settle first
    - 37% to 52% total volume
  - *white blood cells* and *platelets*
    - 1% total volume
    - buffy coat
  - **plasma**
    - the remainder of volume
    - 47% - 63%
    - complex mixture of water, proteins, nutrients, electrolytes, nitrogenous wastes, hormones, and gases

Figure 18.2
Plasma and Plasma Proteins

- **plasma** – liquid portion of blood
  - **serum** – remaining fluid when blood clots and the solids are removed
    - identical to plasma except for the *absence of fibrinogen*

- 3 major categories of plasma proteins
  - **albumins** – smallest and most abundant
    - contributes to viscosity and osmolarity, influences blood pressure, flow and fluid balance
  - **globulins** (antibodies)
    - provide immune system functions
    - alpha, beta and gamma globulins
  - **fibrinogen**
    - precursor of fibrin threads that help form blood clots

- **plasma proteins** formed by liver
  - except globulins (produced by plasma cells)
Nonprotein Components of Plasma

• nitrogenous compounds
  – free amino acids
    • from dietary protein or tissue breakdown
  – nitrogenous wastes (urea)
    • toxic end products of catabolism
    • normally removed by the kidneys

• nutrients
  – glucose, vitamins, fats, cholesterol, phospholipids, and minerals

• dissolved $O_2$, $CO_2$, and nitrogen

• electrolytes
  – $Na^+$ makes up 90% of plasma cations
Properties of Blood

- **viscosity** - resistance of a fluid to flow, resulting from the cohesion of its particles
  - whole blood 4.5 - 5.5 times as viscous as water
  - plasma is 2.0 times as viscous as water

- **osmolarity** of blood - the total molarity of those dissolved particles that cannot pass through the blood vessel wall
  - if too high, blood absorbs too much water, increasing the blood pressure
  - if too low, too much water stays in tissue, blood pressure drops and edema occurs
  - optimum osmolarity is achieved by bodies regulation of sodium ions, proteins, and red blood cells.
Starvation and Plasma Proteins

• hypoproteinemia
  – deficiency of plasma proteins
    • extreme starvation
    • liver or kidney disease
    • severe burns

• kwashiorkor
  – children with severe protein deficiency
    • fed on cereals once weaned
      – thin arms and legs
      – swollen abdomen
Hemopoiesis

• adult production of 400 billion platelets, 200 billion RBCs and 10 billion WBCs every day

• **hemopoiesis** – the production of blood, especially its formed elements

• **hemopoietic tissues** produce blood cells
  – spleen remains involved with lymphocyte production
  – red bone marrow produces all seven formed elements
    • **pluripotent stem cells (PPSC)**
      – formerly called hemopoietic stem cells
    • **colony forming units** – specialized stem cells only producing one class of formed element of blood
    • **myeloid hemopoiesis** – blood formation in the bone marrow
    • **lymphoid hemopoiesis** – blood formation in the lymphatic organs
Erythrocytes

- two principal functions:
  - carry oxygen from lungs to cell tissues
  - pick up carbon dioxide from tissues and bring to lungs

- insufficient RBCs may kill in few minutes due to lack of oxygen to tissues
Erythrocytes (RBCs)

- disc-shaped cell with thick rim
  - 7.5 \( \mu \)M diameter and 2.0 \( \mu \)m thick at rim
  - lose nearly all organelles during development
    - lack mitochondria
      - anaerobic fermentation to produce ATP
    - lack of nucleus and DNA
      - no protein synthesis or mitosis
- blood type determined by surface glycoprotein and glycolipids
- cytoskeletal proteins (spectrin and actin) give membrane durability and resilience
  - stretch and bend as squeeze through small capillaries

Figure 18.4a
RBC Form and Function

• **gas transport** - major function
  – increased surface area/volume ratio
    • due to loss of organelles during maturation
    • increases diffusion rate of substances
  – 33% of cytoplasm is hemoglobin (Hb)
    • 280 million hemoglobin molecules on one RBC
    • \( \text{O}_2 \) delivery to tissue and \( \text{CO}_2 \) transport to lungs

– **carbonic anhydrase** (CAH) in cytoplasm
  • produces carbonic acid from \( \text{CO}_2 \) and water
  • important role in gas transport and pH balance
Hemoglobin (Hb) Structure

• each Hb molecule consists of:
  – four protein chains – globins
  – four heme groups

• heme groups
  – nonprotein moiety that binds $O_2$ to ferrous ion ($Fe^{2+}$) at its center

• globins - four protein chains
  – two alpha and two beta chains
  – 5% $CO_2$ in blood is bound to globin moiety

• adult vs. fetal hemoglobin
Erythrocytes and Hemoglobin

- RBC count and hemoglobin concentration indicate amount of $O_2$ blood can carry
  - **hematocrit** (packed cell volume) – percentage of whole blood volume composed of red blood cells
    - men 42-52% cells; women 37-48% cells
  - **hemoglobin concentration** of whole blood
    - men 13-18g/dL; women 12-16g/dL
  - **RBC count**
    - men 4.6-6.2 million/µL; women 4-2-5.4 million/µL
- values are lower in women
  - androgens stimulate RBC production
  - women have periodic menstrual losses
  - hematocrit is inversely proportional to percentage of body fat
Erythrocyte Production (Erythropoiesis)

- 2.5 million RBCs are produced per second
- average lifespan of about 120 days
- development takes 3-5 days
  - reduction in cell size, increase in cell number, synthesis of hemoglobin and loss of nucleus
- first committed cell - erythrocyte colony forming unit
  - has receptors for erythropoietin (EPO) from kidneys
- erythroblasts multiply and synthesize hemoglobin
- nucleus discarded to form a reticulocyte
  - named for fine network of endoplasmic reticulum
  - 0.5 to 1.5% of circulating RBCs are reticulocytes

Figure 18.6
Iron Metabolism

1. Mixture of Fe\(^{2+}\) and Fe\(^{3+}\) is ingested
2. Stomach acid converts Fe\(^{3+}\) to Fe\(^{2+}\)
3. Fe\(^{2+}\) binds to gastroferritin
4. Gastroferritin transports Fe\(^{2+}\) to small intestine and releases it for absorption
5. In blood plasma, Fe\(^{2+}\) binds to transferrin
6. In liver, some transferrin releases Fe\(^{2+}\) for storage
7. Fe\(^{2+}\) binds to apoferritin to be stored as ferritin
8. Remaining transferrin is distributed to other organs where Fe\(^{2+}\) is used to make hemoglobin, myoglobin, etc.
Nutritional Needs for Erythropoiesis

• iron - key nutritional requirement
  – lost daily through urine, feces, and bleeding
    • men 0.9 mg/day and women 1.7 mg/day
  – low absorption rate of iron requires consumption of 5-20 mg/day
    • dietary iron: ferric (Fe$_3^+$) and ferrous (Fe$_2^+$)

- bone marrow for **hemoglobin**, muscle for **myoglobin**, and all cells use for **cytochromes** in mitochondria
Nutritional Needs for Erythropoiesis

- Vitamin $\text{B}_12$ and folic acid
  - rapid cell division and DNA synthesis that occurs in erythropoiesis

- Vitamin C and copper
  - cofactors for enzymes synthesizing hemoglobin
Erythrocyte Homeostasis

• **negative feedback** control
  – drop in RBC count causes liver and kidney hypoxemia
  – Liver and kidney produce erythropoietin - stimulates bone marrow
  – RBC count increases in 3 - 4 days

• stimuli for increasing erythropoiesis
  – low levels $O_2$ (hypoxemia)
  – high altitude
  – increase in exercise
  – loss of lung tissue in emphysema
Hypoxemia (inadequate O₂ transport)

Sensed by liver and kidneys

Secretion of erythropoietin

Increased O₂ transport

Increased RBC count

Accelerated erythropoiesis

Stimulation of red bone marrow
Erythrocytes Death and Disposal

• RBCs lyse in narrow channels in **spleen**
  • macrophages in spleen
    – digest membrane bits
    – separate heme from globin
      • **globins** hydrolyzed into **amino acids**
      • **iron** removed from **heme**
        – heme pigment converted to **biliverdin** (green)
        – biliverdin converted to **bilirubin** (yellow)
        – released into blood plasma (kidneys - yellow urine)
        – liver removes bilirubin and secretes into bile
  - concentrated in gall bladder: released into small intestine; bacteria create **ubrobilinogen** (brown feces)
Erythrocytes Recycle/Disposal

Figure 18.9
Erythrocyte Disorders

• polycythemia - an excess of RBCs
  – primary polycythemia (polycythemia vera)
    • cancer of erythropoietic cell line in red bone marrow
      – RBC count as high as 11 million/µL; hematocrit 80%
  – secondary polycythemia
    • from dehydration, emphysema, high altitude, or physical conditioning
      – RBC count up to 8 million/µL

• dangers of polycythemia
  – increased blood volume, pressure, viscosity
    • can lead to embolism, stroke or heart failure
Anemia

- **causes** of anemia fall into three categories:
  - inadequate erythropoiesis or hemoglobin synthesis
    - kidney failure and insufficient erythropoietin
    - iron-deficiency anemia
    - inadequate vitamin B\textsubscript{12} from poor nutrition or lack of intrinsic factor (*pernicious anemia*)
    - hypoplastic anemia – slowing of erythropoiesis
    - aplastic anemia - complete cessation of erythropoiesis
  - hemorrhagic anemias from bleeding
  - hemolytic anemias from RBC destruction
Anemia

- anemia has three potential consequences:
  - tissue hypoxia and necrosis
    - patient is lethargic
    - shortness of breath upon exertion
    - life threatening necrosis of brain, heart, or kidney
  - blood osmolarity is reduced producing tissue edema
  - blood viscosity is low
    - heart races and pressure drops
    - cardiac failure may ensue
Sickle-Cell Disease

- hereditary hemoglobin defects that occur mostly among people of African descent
- caused by a recessive allele that modifies the structure of the hemoglobin molecule (HbS)
  - differs only on the sixth amino acid of the beta chain
  - HbS does not bind oxygen well
  - RBCs become rigid, sticky, pointed at ends
  - clump together and block small blood vessels causing intense pain
  - can lead to kidney or heart failure, stroke, rheumatism or paralysis
Blood Types

• blood types and transfusion compatibility are a matter of interactions between plasma proteins and erythrocytes

• Karl Landsteiner discovered blood types A, B and O in 1900
  – won Nobel Prize

• blood types are based on interactions between antigens and antibodies
Blood Antigens and Antibodies

- **antigens**
  - complex molecules on surface of cell membrane that are unique to the individual
    - used to distinguish self from foreign
    - foreign antigens generate an immune response
    - **agglutinogens** – antigens on the surface of the RBC that is the basis for blood typing

- **antibodies**
  - proteins (gamma globulins) secreted by plasma cells
    - part of immune response to foreign matter
    - bind to antigens and mark them for destruction
    - forms **antigen-antibody complexes**
    - **agglutinins** – antibodies in the plasma that bring about transfusion mismatch

- **agglutination**
  - antibody molecule binding to antigens
  - causes clumping of red blood cells
Blood Types

• RBC antigens called agglutinogens
  – called antigen A and B
  – determined by carbohydrate moieties found on RBC surface

• antibodies called agglutinins
  – found in plasma
  – anti-A and anti-B

Figure 18.12
ABO Group

• your ABO blood type is determined by presence or absence of antigens (agglutinogens) on RBCs
  – blood type A person has A antigens
  – blood type B person has B antigens
  – blood type AB has both A and B antigens
  – blood type O person has neither antigen
  • most common - type O
  • rarest - type AB
ABO Blood Typing

Figure 18.14
Plasma Antibodies

- antibodies (agglutinins); anti-A and anti-B
- appear 2-8 months after birth; at maximum concentration at 10 yr.
  - antibody-A and/or antibody-B (both or none) are found in plasma
    - you do not form antibodies against your antigens
- agglutination
  - each antibody can attach to several foreign antigens on several different RBCs at the same time
- responsible for mismatched transfusion reaction
  - agglutinated RBCs block small blood vessels, hemolyze, and release their hemoglobin over the next few hours or days
  - Hb blocks kidney tubules and causes acute renal failure
Agglutination of Erythrocytes

Figure 18.13

Antibodies (agglutinins)
Transfusion Reaction

Figure 18.15

Blood from type A donor

Type B (anti-A) recipient

Donor RBCs agglutinated by recipient plasma

Agglutinated RBCs block small vessels
Universal Donors and Recipients

• universal donor
  – **Type O** – most common blood type
  – lacks RBC antigens
  – donor’s plasma may have both antibodies against recipient’s RBCs (anti-A and anti-B)
    • may give packed cells (minimal plasma)

• universal recipient
  – **Type AB** – rarest blood type
  – lacks plasma antibodies; no anti- A or B
Rh Group

• Rh (C,D,E) agglutinogens discovered in rhesus monkey in 1940
  – Rh D is the most reactive and a patient is considered blood type Rh⁺ if they have D antigen (agglutinogens) on RBCs
  – Rh frequencies vary among ethnic groups

• Anti-D agglutinins not normally present
  – form in Rh⁻ individuals exposed to Rh⁺ blood
    • Rh⁻ woman with an Rh⁺ fetus or transfusion of Rh⁺ blood
    • no problems with first transfusion or pregnancy
Hemolytic Disease of Newborn

• occurs if Rh⁻ mother has formed antibodies and is pregnant with second Rh⁺ child
  – Anti-D antibodies can cross placenta

• prevention
  – RhoGAM given to pregnant Rh⁻ women
    • binds fetal agglutinogens in her blood so she will not form Anti-D antibodies
Hemolytic Disease of Newborn

- Rh antibodies attack fetal blood causing severe anemia and toxic brain syndrome.

Figure 18.16
Leukocytes (WBCs)

• least abundant formed element
  – 5,000 to 10,000 WBCs/µL

• protect against infectious microorganisms and other pathogens

• conspicuous nucleus

• spend only a few hours in the blood stream before migrating to connective tissue

• retain their organelles for protein synthesis

• granules
  – all WBCs have **lysosomess** called nonspecific (azurophilic) granules – inconspicuous so cytoplasm looks clear
  – granulocytes have **specific granules** that contain enzymes and other chemicals employed in defense against pathogens
Types of Leukocytes

• **granulocytes**
  – **neutrophils** (60-70%)-polymorphonuclear leukocytes
    • barely-visible granules in cytoplasm; 3 to 5 lobed nucleus
  – **eosinophils** (2-4%)
    • large rosy-orange granules; bilobed nucleus
  – **basophils** (<1%)
    • large, abundant, violet granules (obscure a large S-shaped nucleus)

• **agranulocytes**
  – **lymphocytes** (25-33%)
    • variable amounts of bluish cytoplasm (scanty to abundant); ovoid/round, uniform dark violet nucleus
  – **monocytes** (3-8%)
    • largest WBC; ovoid, kidney-, or horseshoe- shaped nucleus
Granulocytes

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Figure TA 18.1

Figure TA 18.2

Figure TA 18.3

all: © Ed Reschke
Agranulocytes

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Figure TA 18.4

Lymphocyte

10 µm

Figure TA 18.5

Monocyte

10 µm

both: Michael Ross/Photo Researchers, Inc.
Granulocyte Functions

• **neutrophils** - increased numbers in bacterial infections
  – phagocytosis of bacteria
  – release antimicrobial chemicals

• **eosinophils** - increased numbers in parasitic infections, collagen diseases, allergies, diseases of spleen and CNS
  – phagocytosis of antigen-antibody complexes, allergens, and inflammatory chemicals
  – release enzymes to destroy large parasites

• **basophils** - increased numbers in chicken pox, sinusitis, diabetes)
  – secrete histamine (vasodilator) – speeds flow of blood to an injured area
  – secrete heparin (anticoagulant) – promotes the mobility of other WBCs in the area
Agranulocyte Functions

• **lymphocytes** - increased numbers in diverse infections and immune responses
  – destroy cells (cancer, foreign, and virally infected cells)
  – “present” antigens to activate other immune cells
  – coordinate actions of other immune cells
  – secrete antibodies and provide immune memory

• **monocytes** - increased numbers in viral infections and inflammation
  – leave bloodstream and transform into macrophages
    • phagocytize pathogens and debris
    • “present” antigens to activate other immune cells - **antigen presenting cells (APCs)**
Complete Blood Count

- Hematocrit
- Hemoglobin concentration
- Total count for RBCs, reticulocytes, WBCs, and platelets
- Differential WBC count
- RBC size and hemoglobin concentration per RBC
Leukocyte Life Cycle

- **leukopoiesis** – production of white blood cells
  - pluripotent stem cells – (PPSCs)
    - myeloblasts – form neutrophils, eosinophils, basophils
    - monoblasts - form monocytes
    - lymphoblasts give rise to all forms of lymphocytes
      - T lymphocytes complete development in thymus

- red bone marrow stores and releases granulocytes and monocytes

- circulating WBCs do not stay in bloodstream
  - granulocytes leave in 8 hours and live 5 days longer
  - monocytes leave in 20 hours, transform into macrophages and live for several years
  - lymphocytes provide long-term immunity (decades) being continuously recycled from blood to tissue fluid to lymph and back to the blood
Leukopoiesis

Figure 18.18
Leukocyte Disorders

- **leukopenia** - low WBC count below 5000/µL
  - causes: radiation, poisons, infectious disease
  - effects: elevated risk of infection

- **leukocytosis** - high WBC count above 10,000/µL
  - causes: infection, allergy and disease
  - differential WBC count – identifies what percentage of the total WBC count consist of each type of leukocyte

- **leukemia** - cancer of hemopoietic tissue that usually produces an extraordinary high number of circulating leukocytes and their precursors
  - **myeloid leukemia** – uncontrolled granulocyte production
  - **lymphoid leukemia** - uncontrolled lymphocyte or monocyte production
  - **acute leukemia** – appears suddenly, progresses rapidly, death within months
  - **chronic leukemia** – undetected for months, survival time three years
  - effects - normal cell percentages disrupted; impaired clotting; opportunistic infections
Normal and Leukemic Blood

Figure 18.19 a-b
Hemostasis

• **hemostasis** – the cessation of bleeding
  – stopping potentially fatal leaks
  – hemorrhage – excessive bleeding

• **three hemostatic mechanisms**
  – vascular spasm
  – platelet plug formation
  – blood clotting (coagulation)

• **platelets** play an important role in all three
Platelets

- **platelets** - small fragments of **megakaryocyte** cells
  - 2-4 µm diameter; contain “granules”
  - amoeboid movement and phagocytosis

- normal platelet count - **130,000 to 400,000** platelets/µL

- **functions**
  - secrete vasoconstrictors that help reduce blood loss
  - stick together to form **platelet plugs** to seal small breaks
  - secrete **procoagulants** or clotting factors promote clotting
  - initiate formation of **clot-dissolving enzyme**
  - chemically attract neutrophils and monocytes to sites of inflammation
  - phagocytize and destroy bacteria
  - secrete **growth factors** that stimulate mitosis to repair blood vessels
Figure 18.20 a-b
Platelet Production - Thrombopoiesis

• stem cells (that develop receptors for thrombopoietin) become megakaryoblasts

• megakaryoblasts
  – repeatedly replicate DNA without dividing
  – forms gigantic cell called megakaryocyte with a multilobed nucleus
    • 100 µm in diameter, remains in bone marrow

• megakaryocytes – live in bone marrow adjacent to blood sinusoids
  – long tendrils of cytoplasm (proplatelets) protrude into the blood sinusoids – blood flow splits off fragments called platelets
  – circulate freely for 10 days
  – 40% are stored in spleen
Hemostasis

(a) Vascular spasm
(b) Platelet plug formation
(c) Coagulation

Vasoconstriction

Vessel injury

Platelet plug

Collagen fibers

Blood clot

Figure 18.21 a-c

all 3 pathways involve platelets
Hemostasis - Vascular Spasm

• **vascular spasm** - prompt constriction of a broken vessel
  - most immediate protection against blood loss

• causes:
  – pain receptors
    • some directly innervate blood vessels to constrict
  – smooth muscle injury
  – platelets release serotonin (vasoconstrictor)

• effects:
  – prompt constriction of a broken vessel
    • pain receptors - short duration (minutes)
    • smooth muscle injury - longer duration
  – provides time for other two clotting pathways
Hemostasis - Platelet Plug Formation

• endothelium smooth, coated with **prostacyclin** – a platelet repellant

• platelet plug formation
  – broken vessel exposes collagen
  – platelet **pseudopods** stick to damaged vessel and other platelets - pseudopods contract and draw walls of vessel together forming a platelet plug
  – platelets **degranulate** releasing a variety of substances
    • serotonin is a vasoconstrictor
    • ADP attracts and degranulates more platelets
    • thromboxane $A_2$, an eicosanoid, promotes platelet aggregation, degranulation and vasoconstriction

– positive feedback cycle is active until break in small vessel is sealed
Hemostasis - Coagulation

• **coagulation** (clotting) – last and most effective defense against bleeding
  – conversion of plasma protein **fibrinogen** into insoluble **fibrin threads** to form framework of clot

• **procoagulants** (clotting factors), usually produced by the liver, are present in plasma
  – activate one factor and it will activate the next to form a **reaction cascade**

• **extrinsic pathway**
  – factors released by damaged tissues begin cascade

• **intrinsic pathway**
  – factors found in blood begin cascade (platelet degranulation)
SEM of Blood Clot

Figure 18.22
Coagulation Pathways

• extrinsic pathway
  – initiated by release of tissue thromboplastin (factor III) from damaged tissue
  – cascade to factor VII, V and X (fewer steps)

• intrinsic pathway
  – initiated by platelets releasing Hageman factor (factor XII)
  – cascade to factor XI to IX to VIII to X

• calcium required for either pathway
Factor X (active) → Prothrombin activator → Factor III, Factor V, Ca^{2+}, PF_{3} → Prothrombin (factor II) → Thrombin → Fibrinogen (factor I) → Fibrin → Fibrin polymer → Factor XIII, Ca^{2+}
Enzyme Amplification in Clotting

rapid clotting - each activated cofactor activates many more molecules in next step of sequence
Completion of Coagulation

- activation of factor X
  - leads to production of prothrombin activator

- prothrombin activator
  - converts prothrombin to thrombin

- thrombin
  - converts fibrinogen into fibrin

- positive feedback - thrombin speeds up formation of prothrombin activator
Fate of Blood Clots

- **clot retraction** occurs within 30 minutes

- **platelet-derived growth factor** secreted by platelets and endothelial cells
  - mitotic stimulant for fibroblasts and smooth muscle to multiply and repair damaged vessel

- **fibrinolysis** - dissolution of a clot
  - factor XII speeds up formation of *kallikrein* enzyme
  - kallikrein converts *plasminogen* into *plasmin*, a fibrin-dissolving enzyme that breaks up the clot
Blood Clot Dissolution

Positive feedback occurs

Plasmin promotes formation of fibrin

Figure 18.25
Prevention of Inappropriate Clotting

• **platelet repulsion**
  – platelets do not adhere to prostacyclin-coating

• **thrombin dilution**
  – by rapidly flowing blood
    • heart slowing in shock can result in clot formation

• **natural anticoagulants**
  – **heparin** (from basophils and mast cells) interferes with formation of prothrombin activator
  – **antithrombin** (from liver) deactivates thrombin before it can act on fibrinogen
Clotting Disorders - Hemophilia

- deficiency of any clotting factor can shut down the coagulation cascade

- **hemophilia** – family of hereditary diseases characterized by deficiencies of one factor or another

- sex-linked recessive (on X chromosome)
  - **hemophilia A** missing factor VIII (83% of cases)
  - **hemophilia B** missing factor IX (15% of cases)

  note: **hemophilia C** missing factor XI (autosomal)

- physical exertion causes bleeding and excruciating pain
  - transfusion of plasma or purified clotting factors
  - factor VIII produced by transgenic bacteria

- **hematomas** – masses of clotted blood in the tissues
Coagulation Disorders

• **thrombosis** - abnormal clotting in unbroken vessel
  – **thrombus** - clot
    • most likely to occur in leg veins of inactive people
  – **pulmonary embolism** - clot may break free, travel from veins to lungs

• **embolus** – anything that can travel in the blood and block blood vessels

• **infarction** (tissue death) may occur if clot blocks blood supply to an organ (MI or stroke)
  – 650,000 Americans die annually of thromboembolism – traveling blood clots
Clinical Management of Clotting

• **goal** - prevent formation of clots or dissolve existing clots

• **preventing clots**
  – Vitamin K is required for formation of clotting factors
    • coumarin (Coumadin) is a vitamin K antagonist
  – **aspirin** suppresses thromboxane $A_2$
  – other anticoagulants discovered in animal research
    • medicinal leeches used since 1884 (hirudin)
    • snake venom from vipers (Arvin)
Clinical Management of Clotting

• dissolving clots that have already formed
  – *streptokinase* – enzyme made by streptococci bacteria
    • used to dissolve clots in coronary vessels
    • digests almost any protein
  – *tissue plasminogen activator* (TPA) – works faster, is more specific, and now made by transgenic bacteria
  – *hementin* – produced by giant Amazon leech