The Circulatory system - Blood

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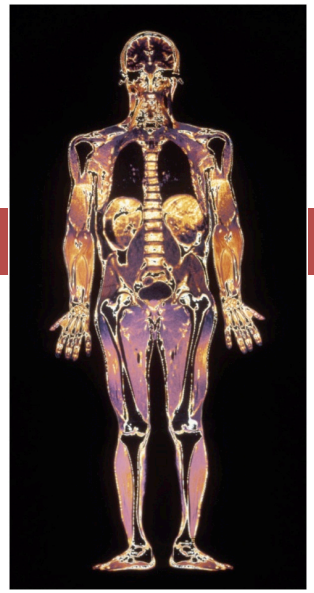

LEARNING OUTCOMES

As a result of the lesson you will be able to:

- *Describe the functions and major components of the circulatory system;*
- *Describe the components and physical properties of blood and blood plasma; and discuss its importance in the body.*
- *Explain the significance of blood viscosity and osmolarity;*
- *Describe the structure and explain the function of red blood cells; characterize the structure and function of hemoglobin;*
- *Define some clinical measurements of RBC and hemoglobin quantities and give some typical values for each;*
- *Discuss the life cycle of erythrocytes;*
- *Explain the molecular basis of blood types and their clinical significance.*
- *Discuss the general function of leukocytes and the specific functions of each individual type*
- *Characterize the appearance and relative abundance of each type of leukocyte;*
- *Describe the life cycle of leukocytes.*
- *Describe the structure and functions of blood platelets;*
- *Describe platelet production*
- *Describe blood clotting and other mechanisms for controlling bleeding.*

Circulatory System

- **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**

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
    - important in circulatory function
- **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.

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
  - **yolk sac** produces stem cells for first blood cells
    - colonize fetal bone marrow, liver, spleen and thymus
  - liver stops producing blood cells at birth
  - spleen remains involved with lymphocyte production
  - red bone marrow produces all seven formed elements
    - **pluripotent stem cells (PPSC)**
      - formerly called hemocytoblasts or 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

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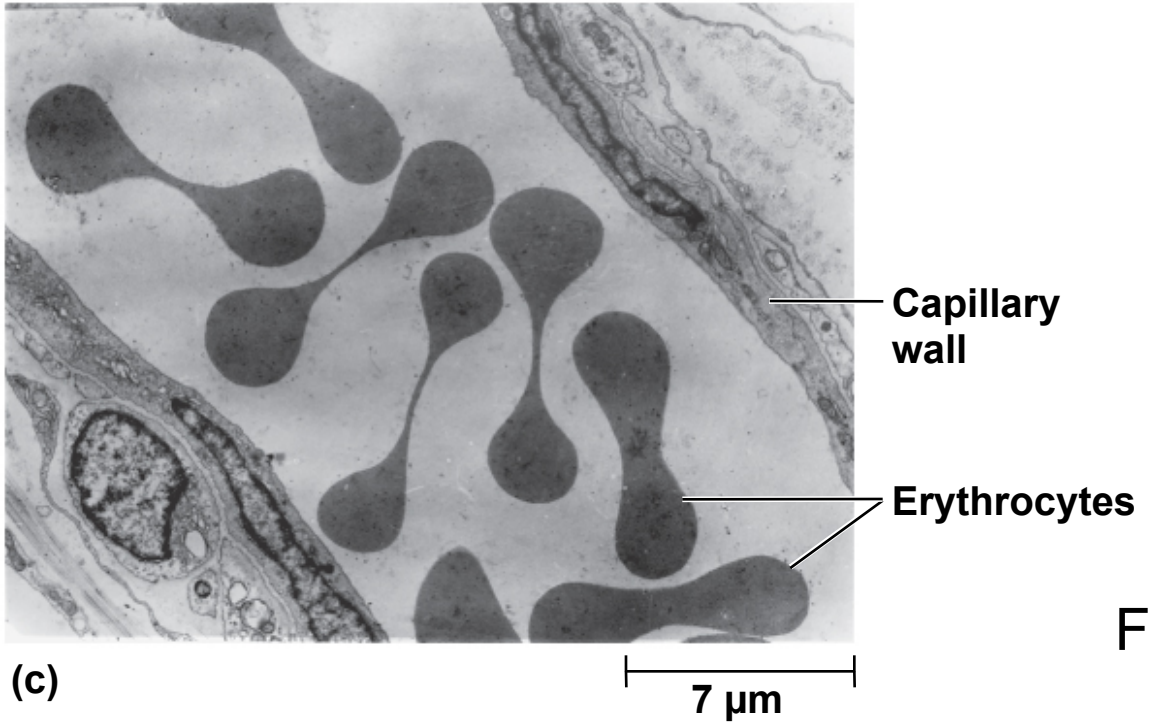

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Figure 18.4c

- **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 μM diameter and 2.0 μm 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

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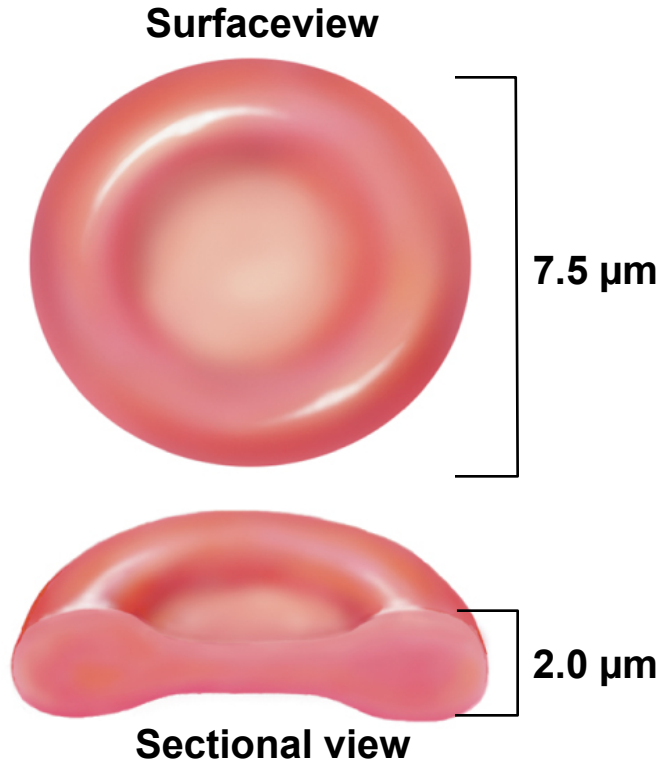

Figure 18.4a

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
    - O_2 delivery to tissue and CO_2 transport to lungs
  - **carbonic anhydrase** (CAH) in cytoplasm
    - produces carbonic acid from 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

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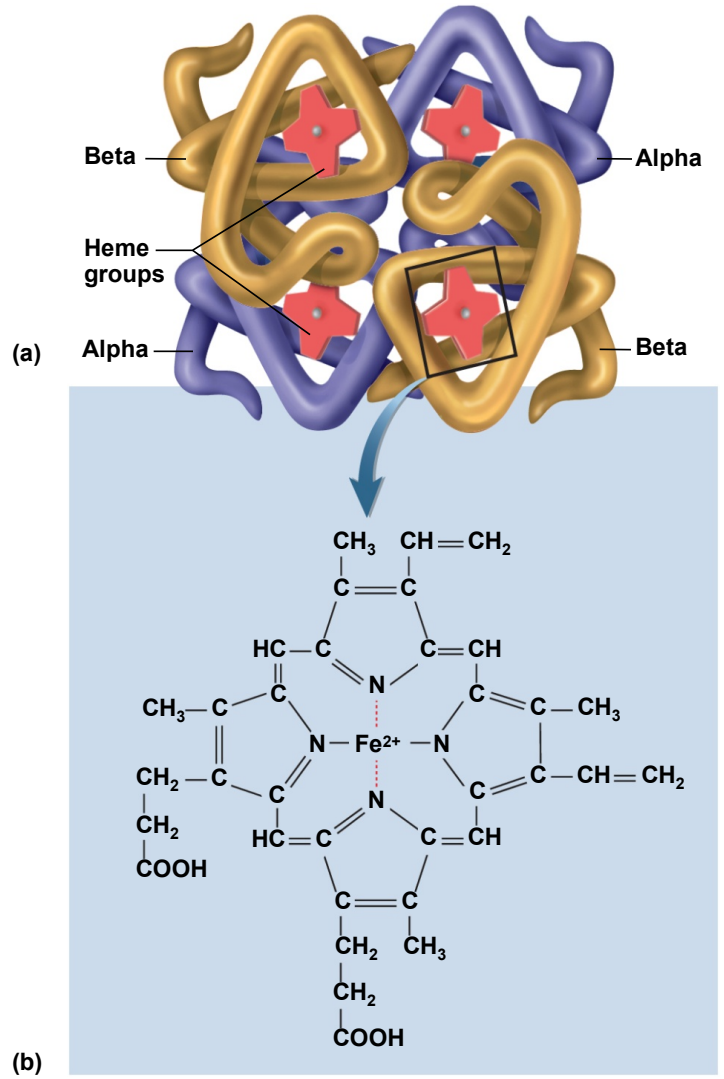

Figure 18.5 a-b

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)

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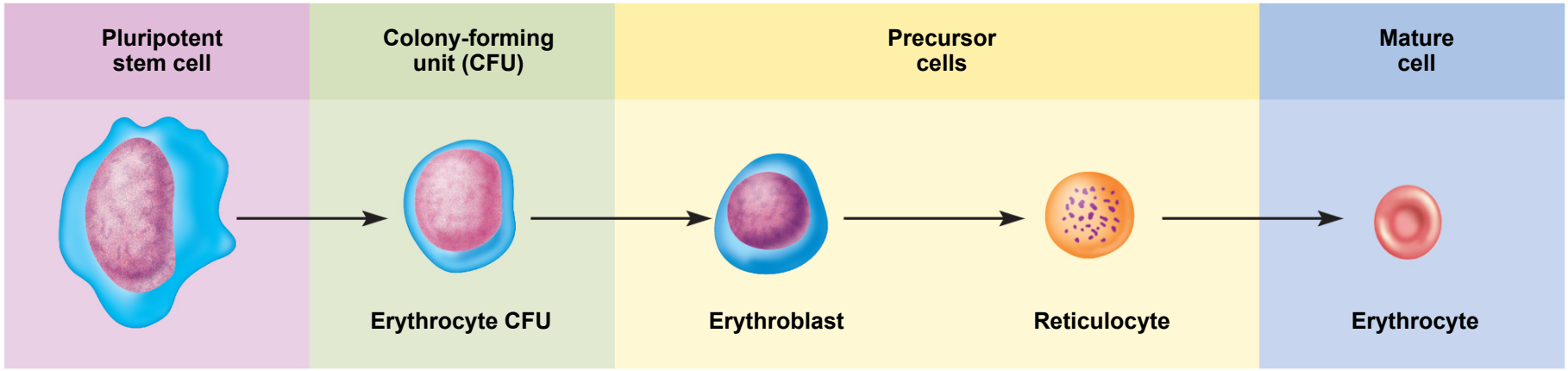

Figure 18.6

- 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 (normoblast) 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

Iron Metabolism

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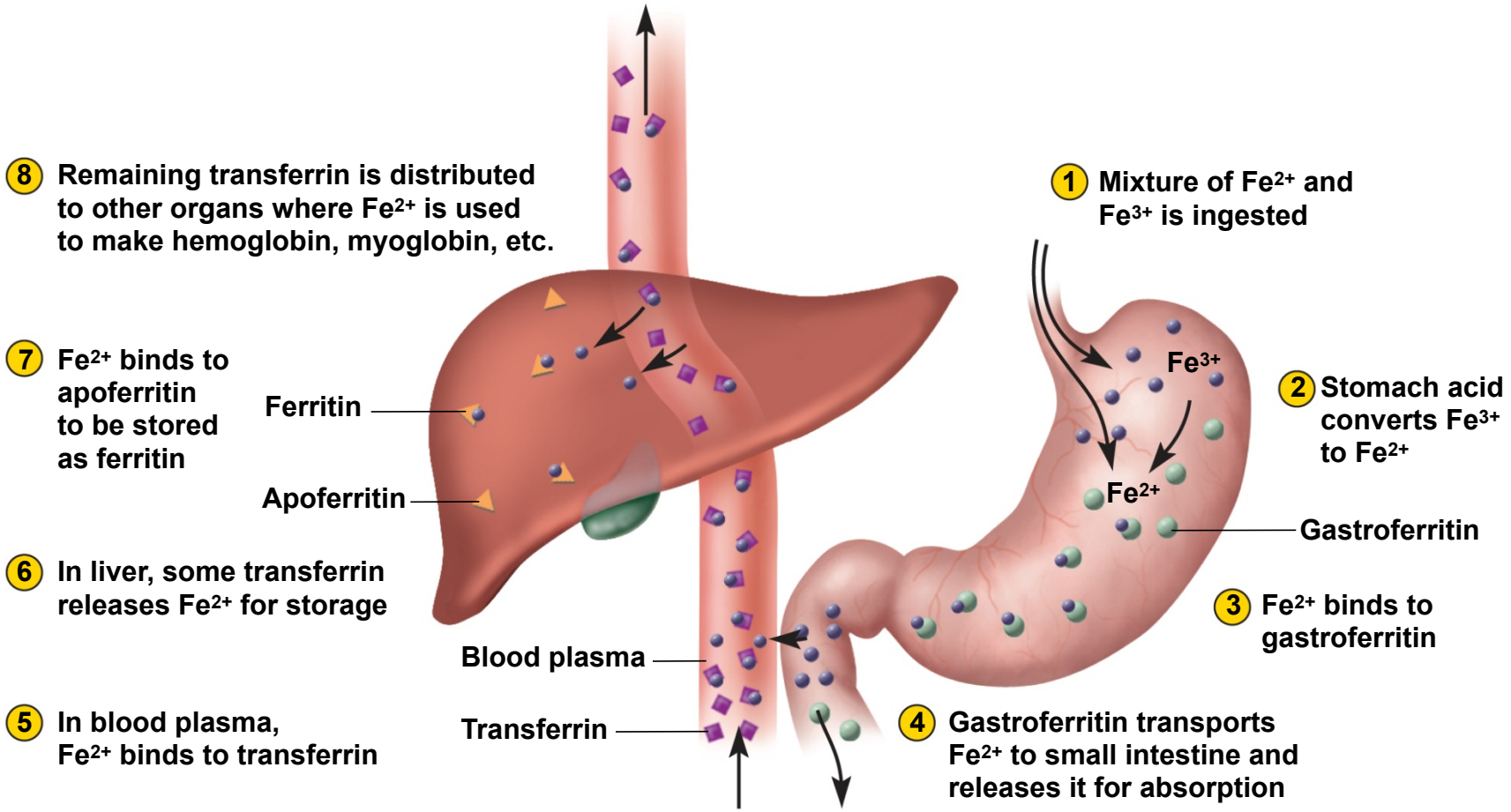

Figure 18.7

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+})
      - stomach acid converts Fe^{3+} to absorbable Fe^{2+}
      - **gastroferritin** binds Fe^{2+} and transports it to small intestine
      - absorbed into blood and binds to **transferrin** for transport to bone marrow, liver, and other tissues
        - bone marrow for **hemoglobin**, muscle for **myoglobin,** and all cells use for **cytochromes** in mitochondria
    - liver **apoferritin** binds to create **ferritin** for storage

Nutritional Needs for Erythropoiesis

- Vitamin B_{12} and folic acid
  - rapid cell division and DNA synthesis that occurs in erythropoiesis

- Vitamin C and copper
  - cofactors for enzymes synthesizing hemoglobin
    - copper is transported in the blood by an alpha globulin called ceruloplasmin

Erythrocyte Homeostasis

- **negative feedback** control
  - drop in RBC count causes kidney **hypoxemia**
  - kidney production of 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

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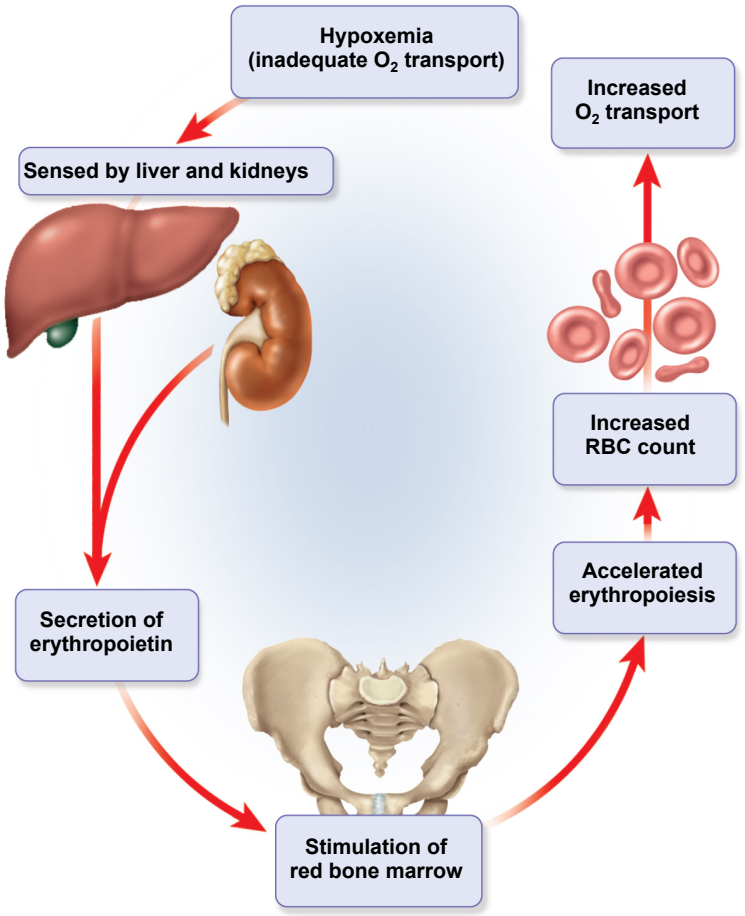

Figure 18.8

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 **urobilinogen** (brown feces)

Erythrocytes Recycle/Disposal

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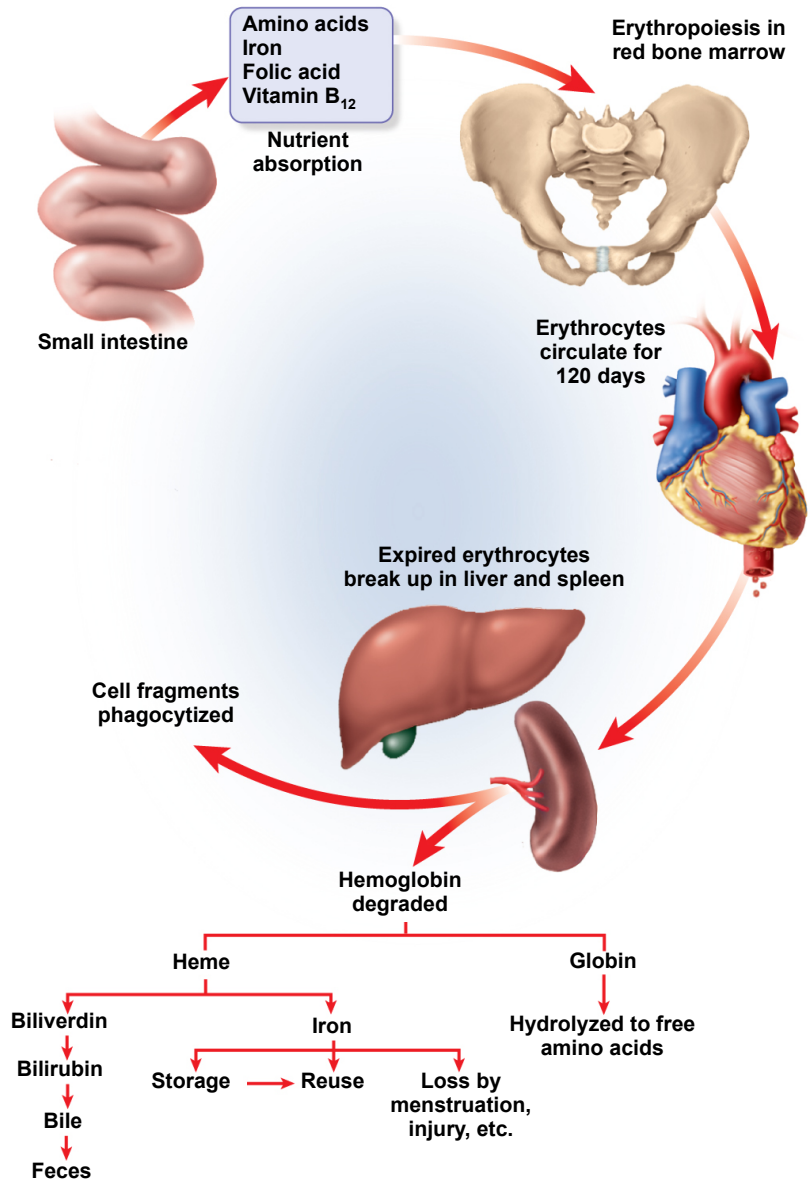

Figure 18.9

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_{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

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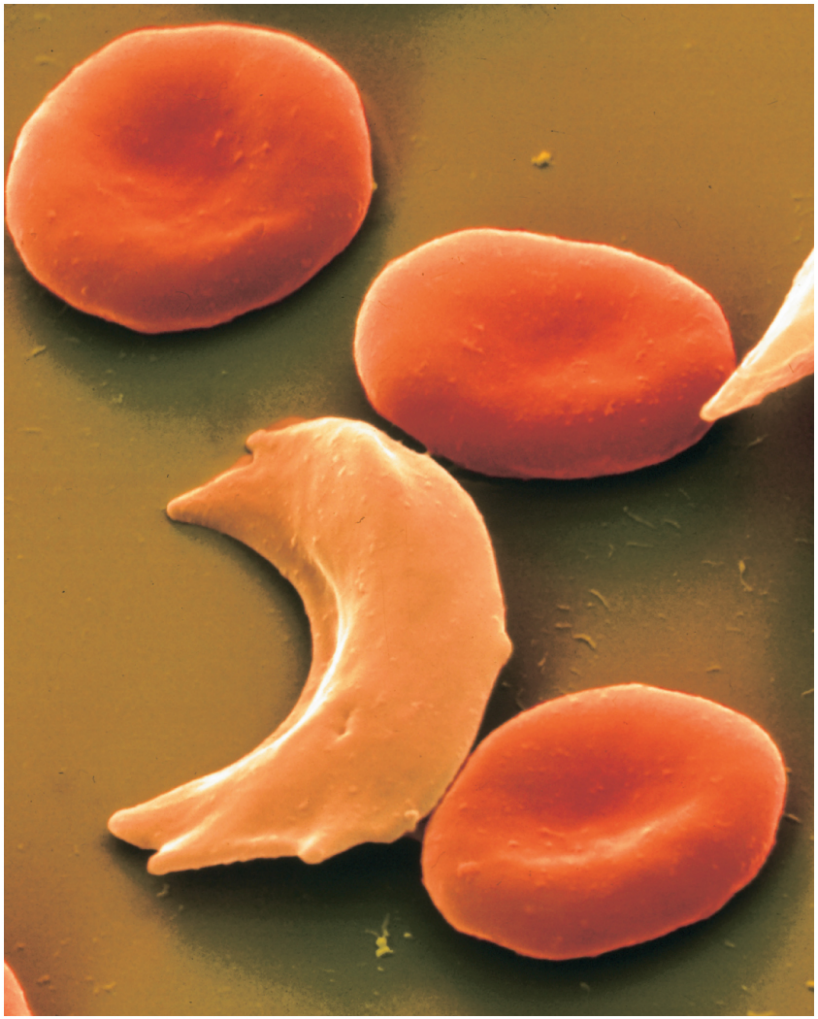

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Figure 18.10

- 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

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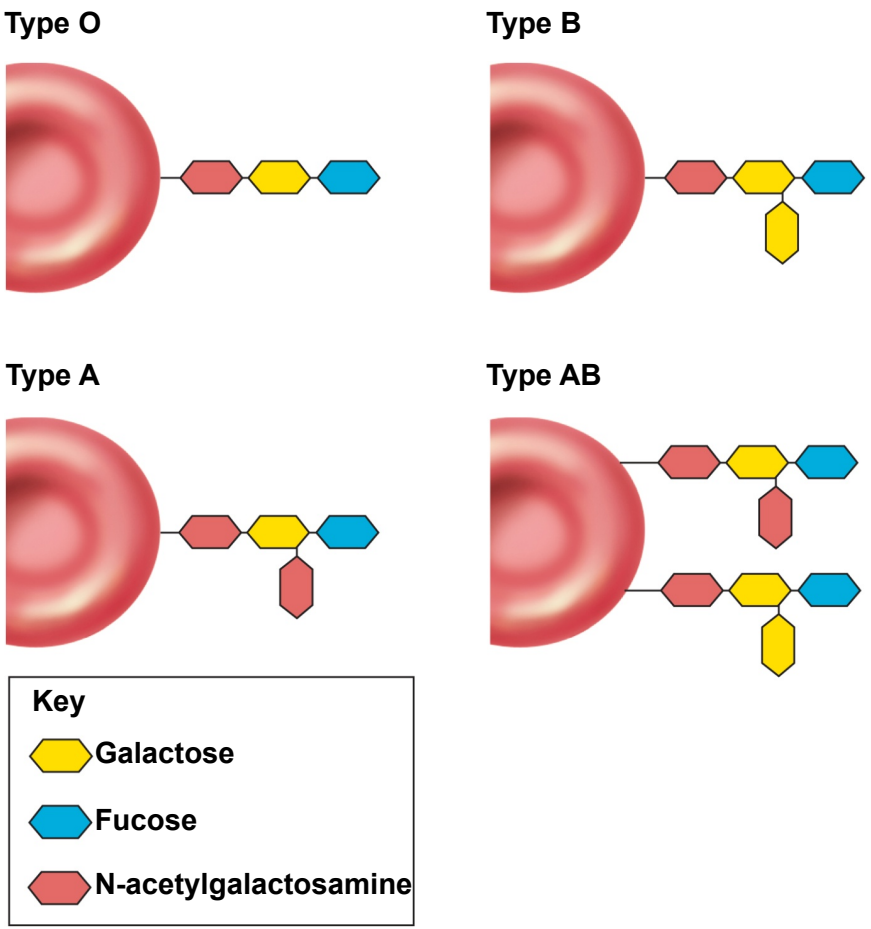

Figure 18.12

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

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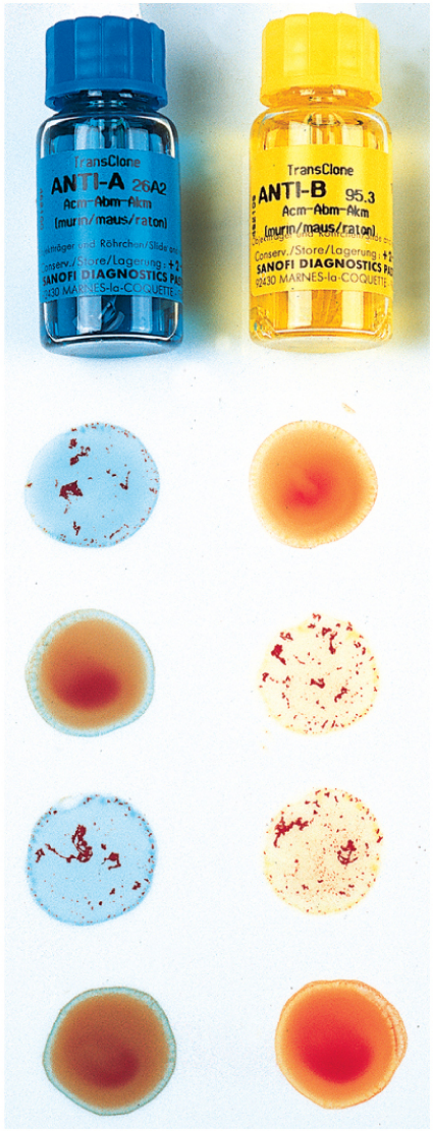

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Figure 18.14

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

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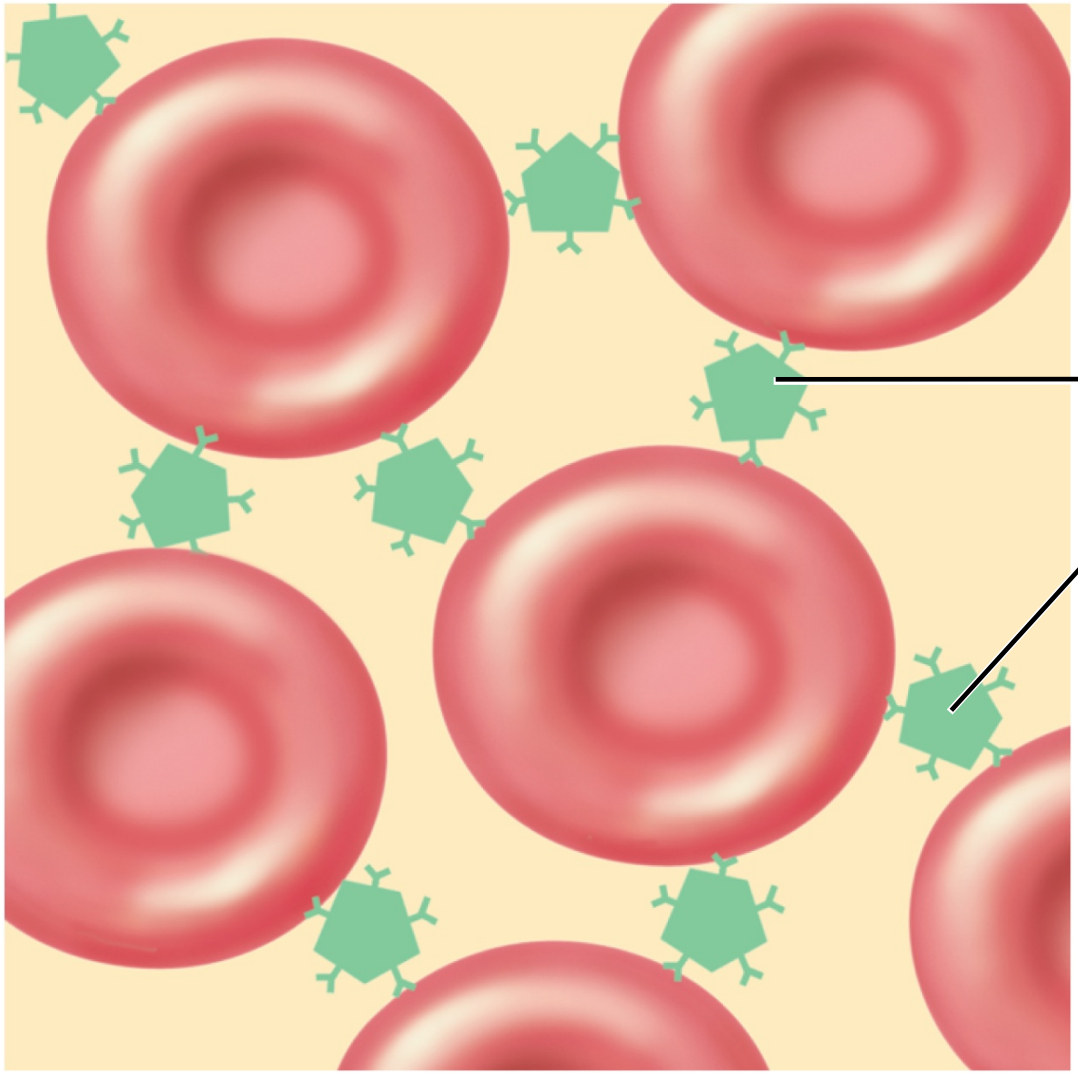

Figure 18.13

Transfusion Reaction

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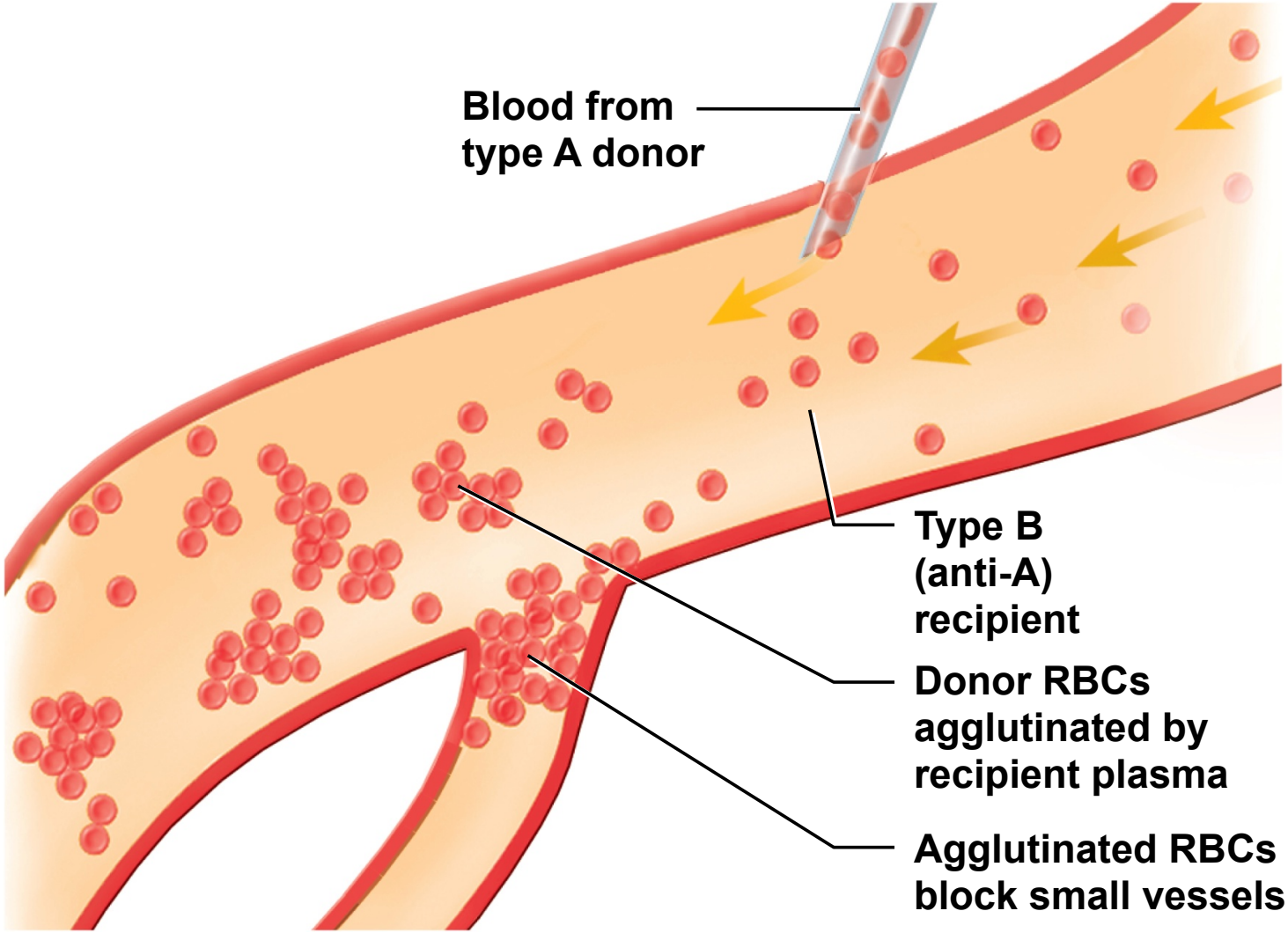

Figure 18.15

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

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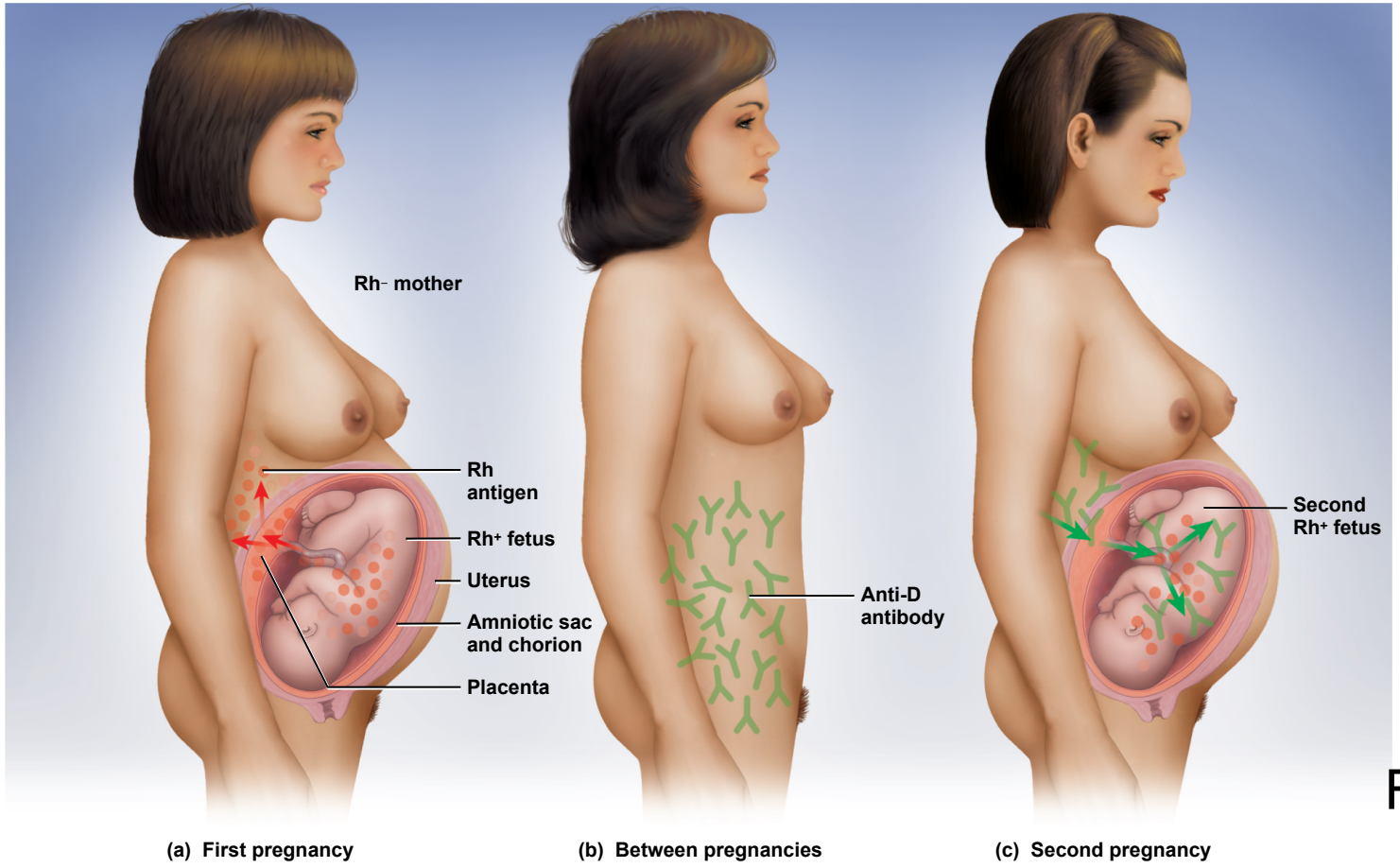

Figure 18.16

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

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 **lysosomes** 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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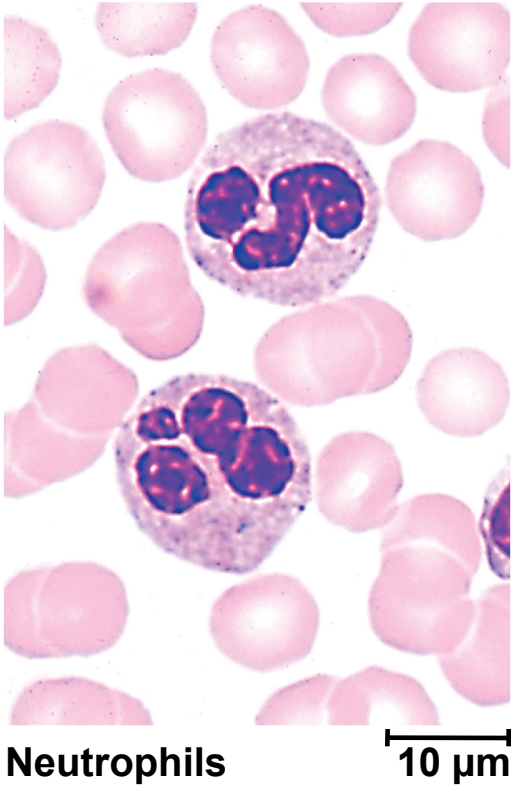

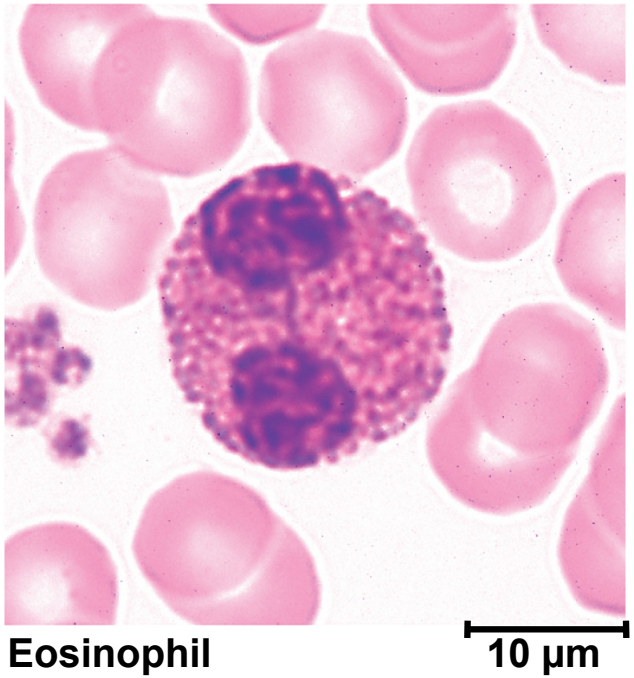

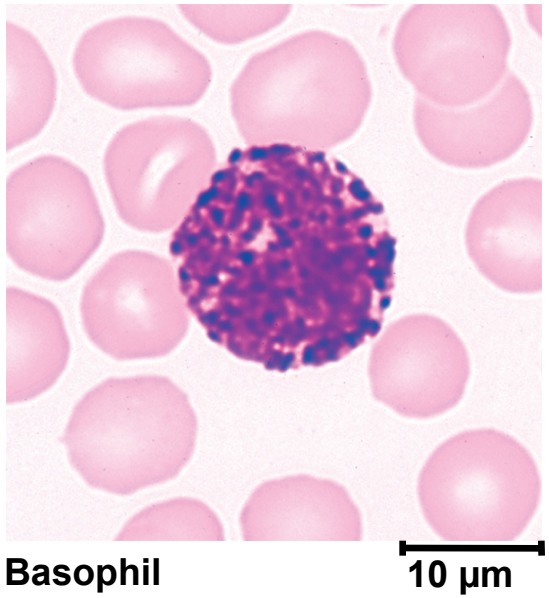

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Figure TA 18.1

Figure TA 18.2

Figure TA 18.3

Agranulocytes

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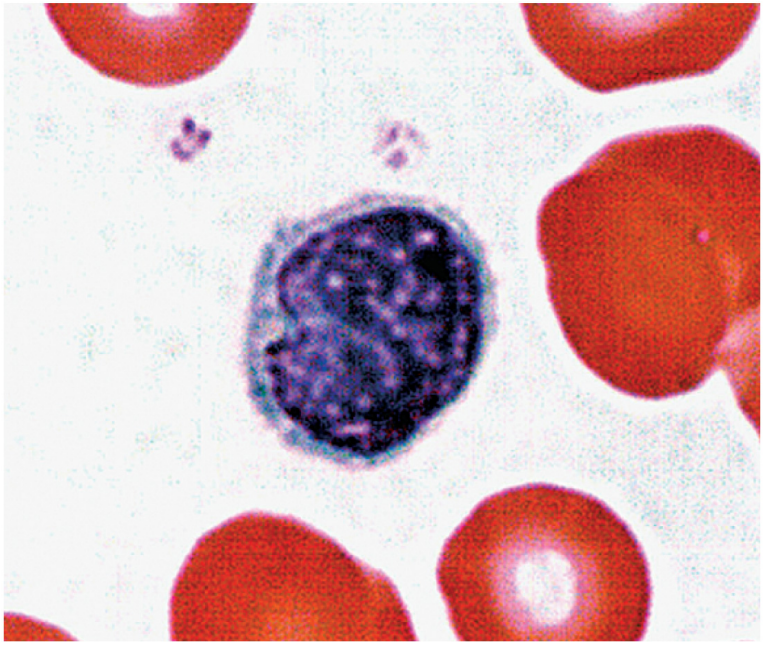

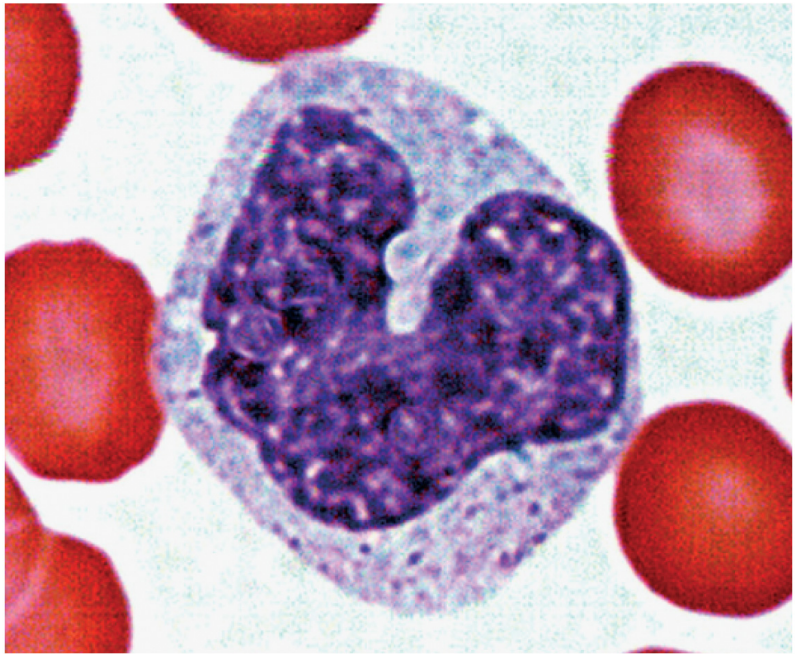

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Figure TA 18.4

Figure TA 18.5

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

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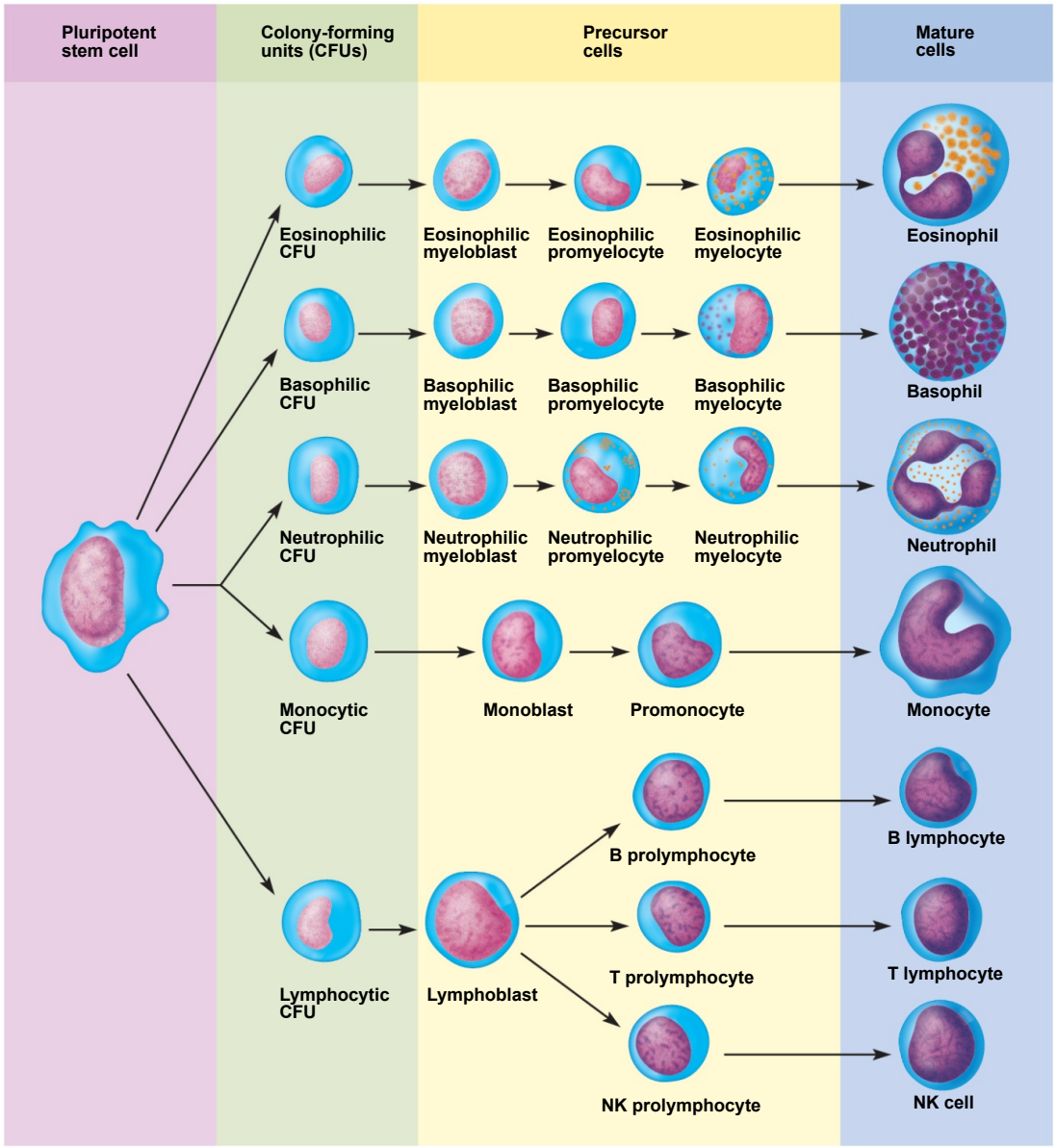

Figure 18.18

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

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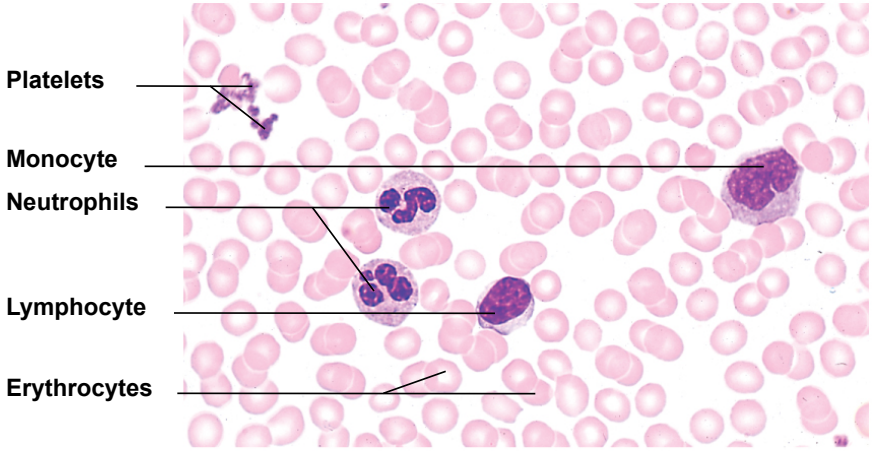

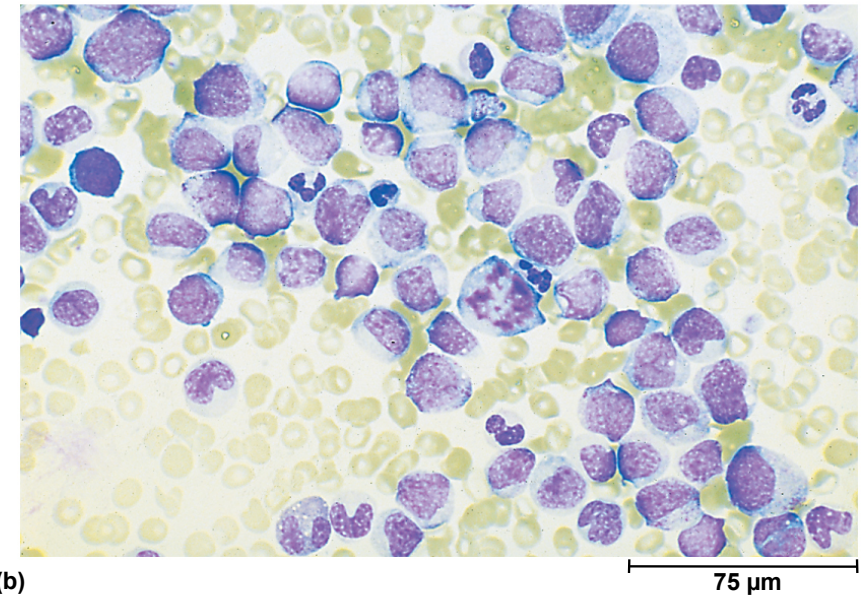

Figure 18.19 a-b

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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"
  - complex internal structure and open **canalicular system**
  - 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

Platelets

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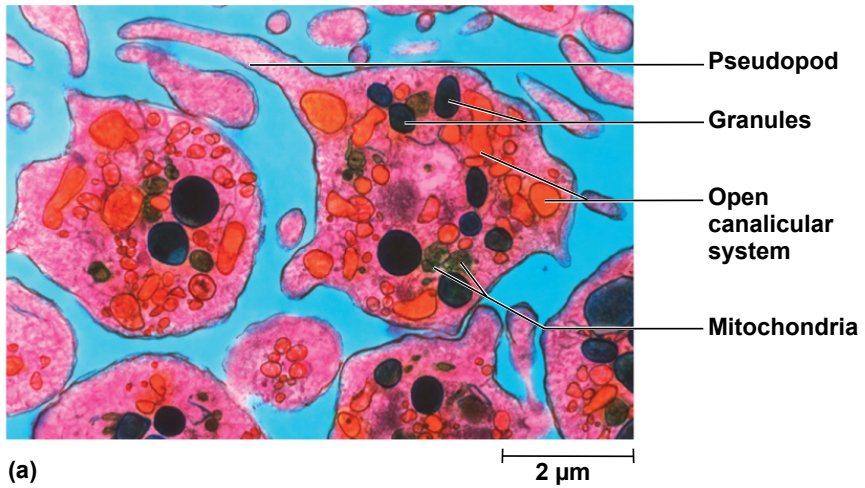

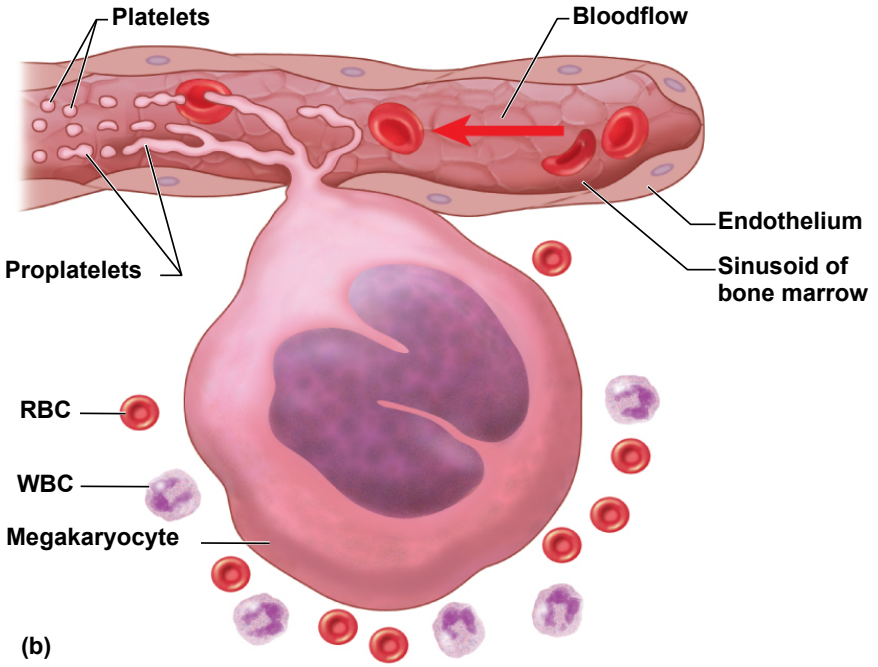

Figure 18.20 a-b

a: NIBSC/Science Photo Library/Photo Researchers, Inc.

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

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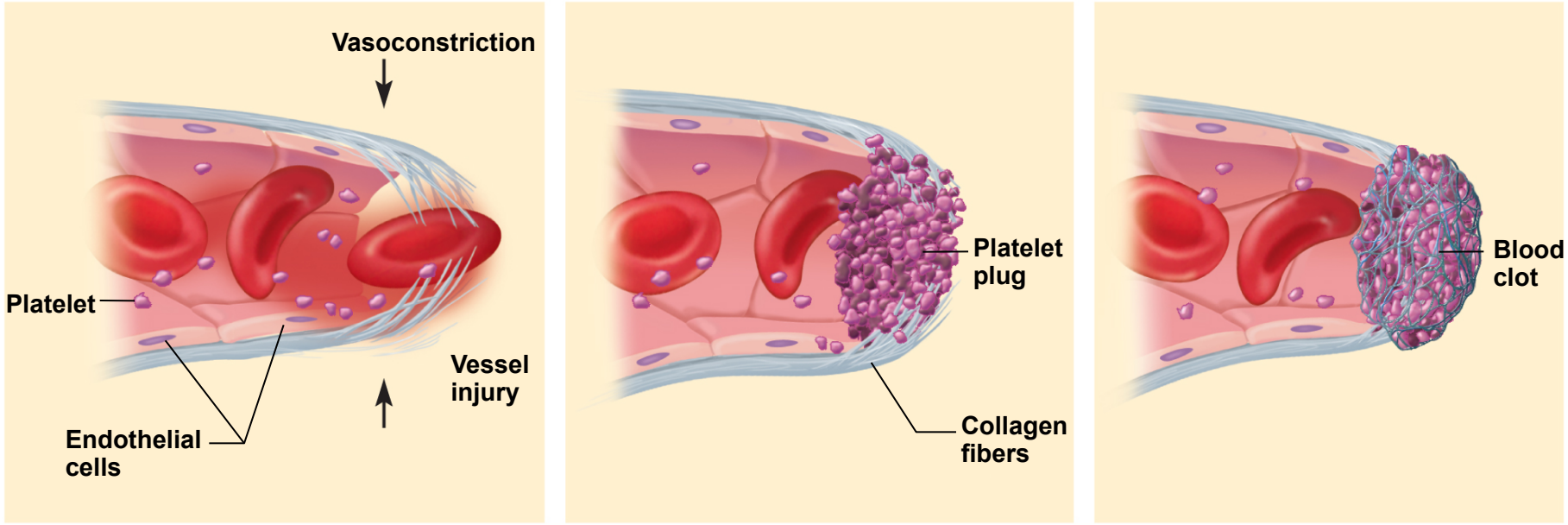

Figure 18.21 a-c

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

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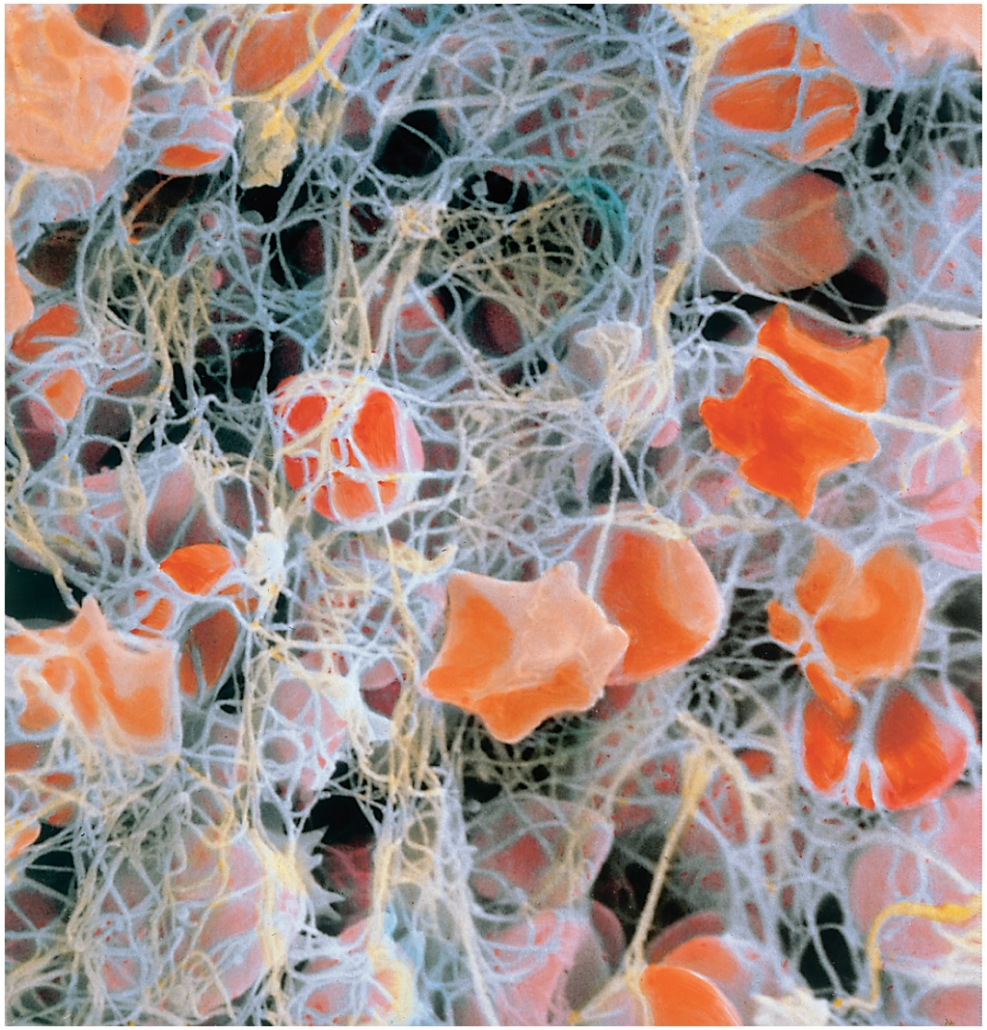
Figure 18.22



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Coagulation Pathways

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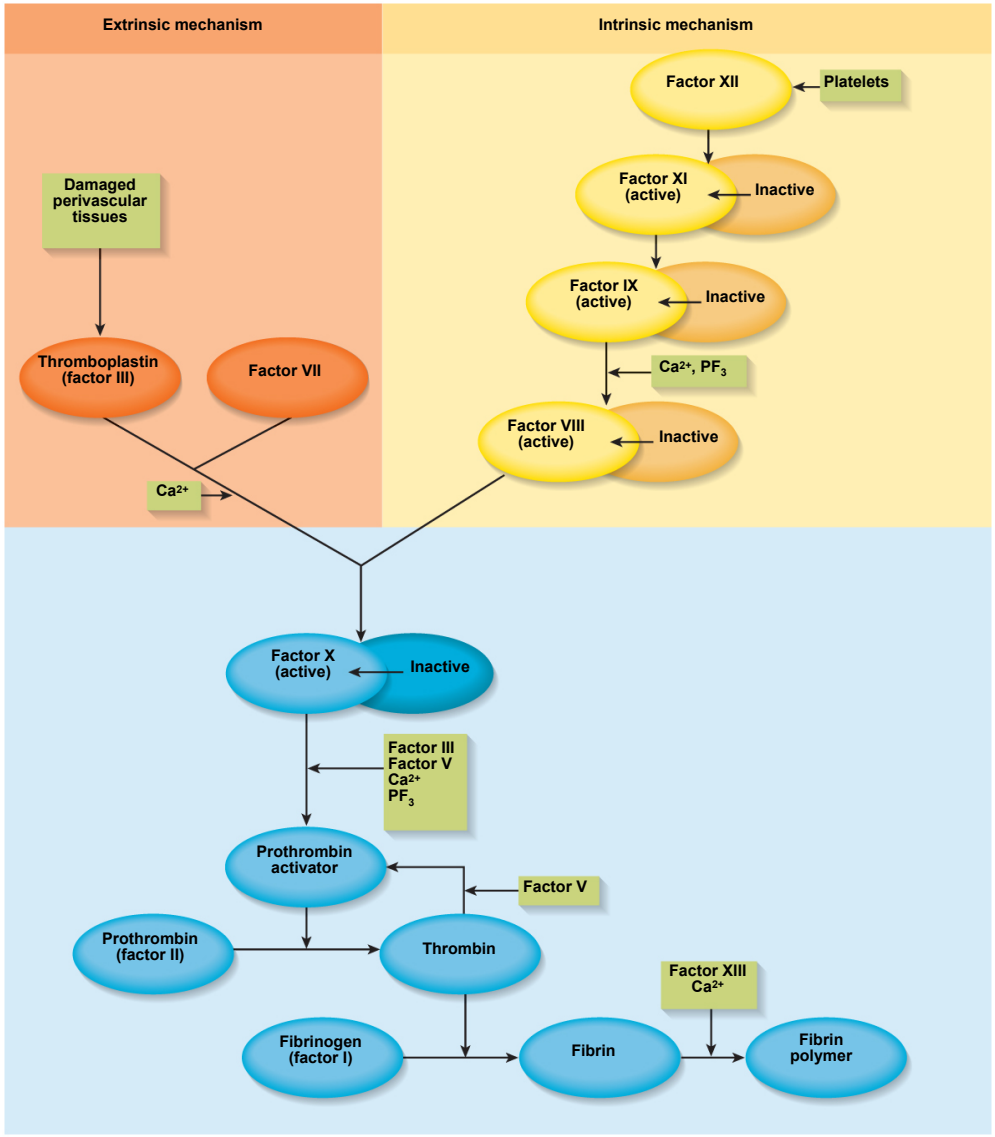

Figure 18.23

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

Enzyme Amplification in Clotting

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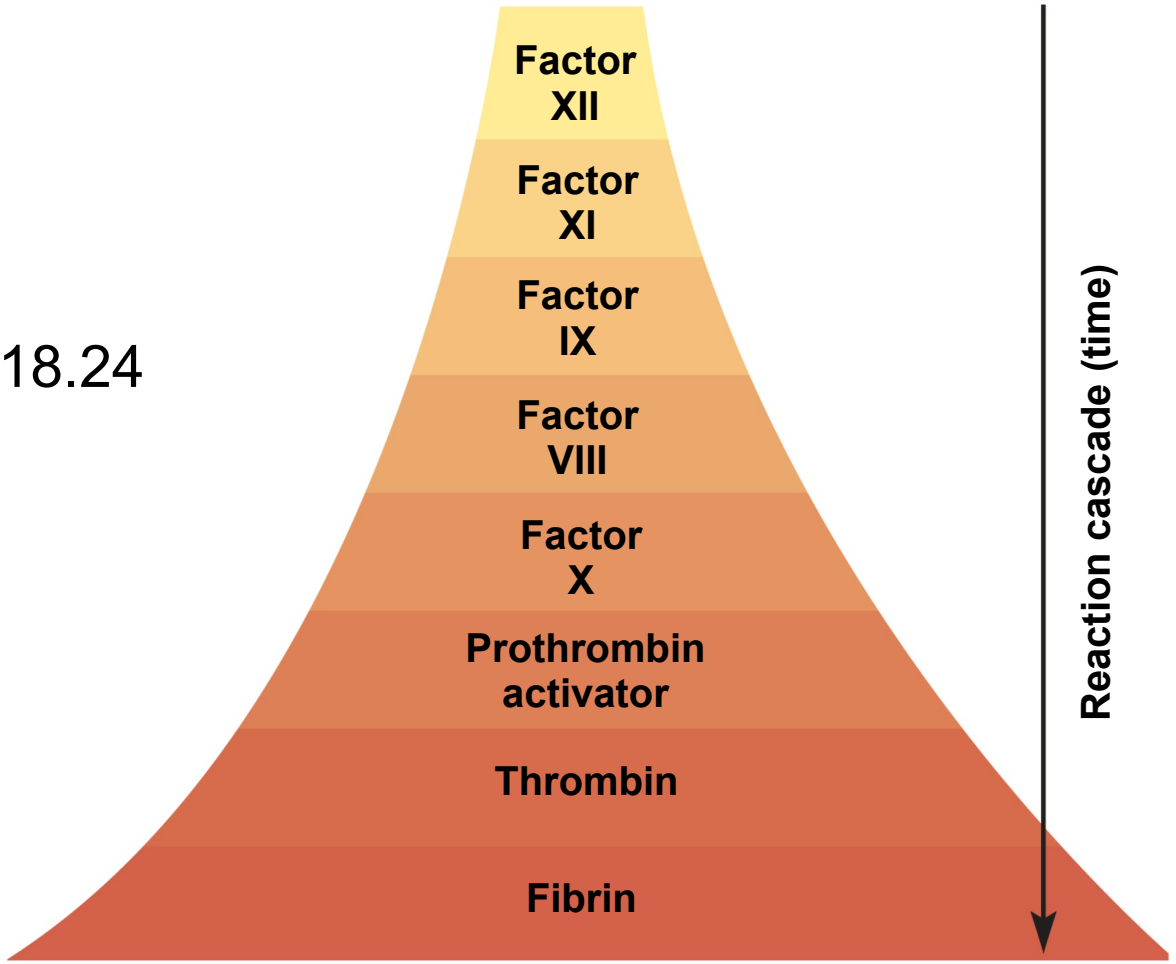
Figure 18.24



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

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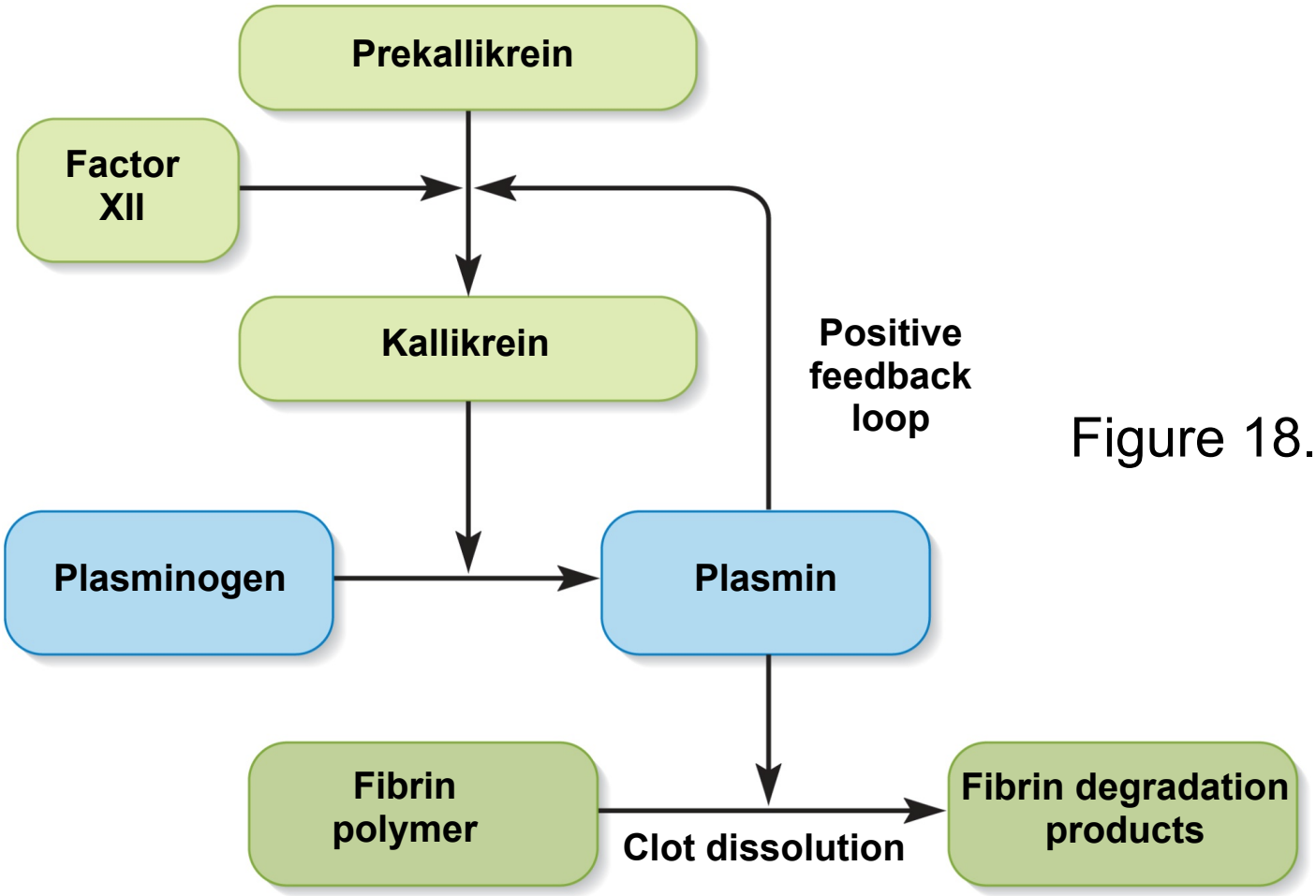

Figure 18.25

- positive feedback occurs
- plasmin promotes formation of fibrin

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

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

- **dissolving clots that have already formed**
  - **streptokinase** – enzyme make 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