Circulatory System

-Blood

Al-Farabi Kazakh National University
Higher School of Medicine

◆ PART I

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;***
- ***Describe the composition of blood plasma;***
- ***Explain the significance of blood viscosity and osmolarity;***
- ***describe in general terms how blood is produced***

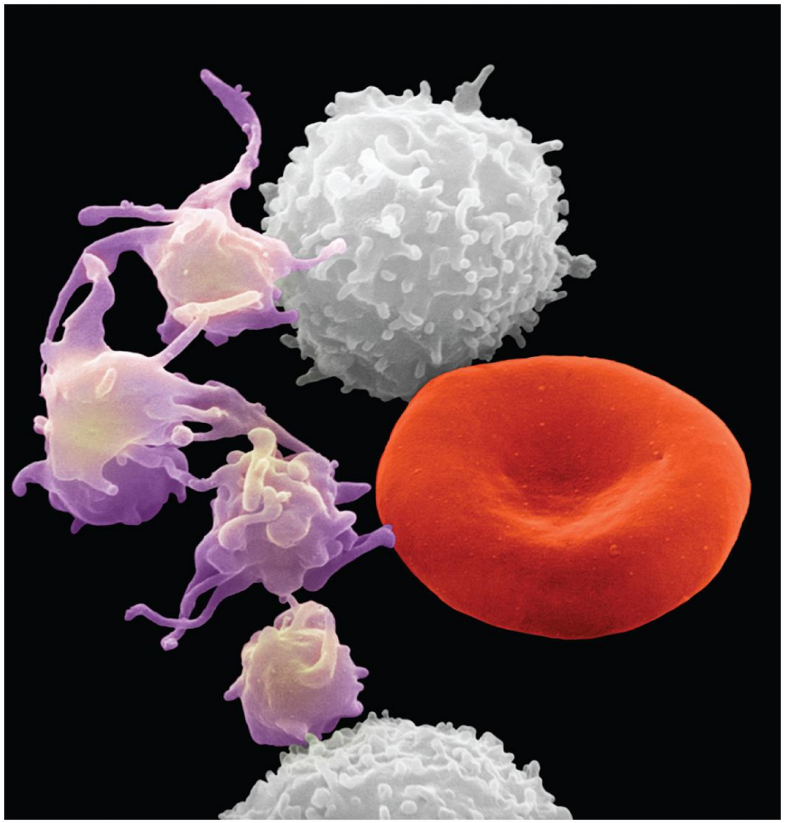
LEARNING OUTCOMES

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

- ***Explain what determines a person's ABO and Rh blood types and how this relates to transfusion compatibility;***
- ***list some blood groups other than ABO and Rh and explain how they may be useful;***
- ***describe the effects of a blood type incompatibility between mother and fetus.***

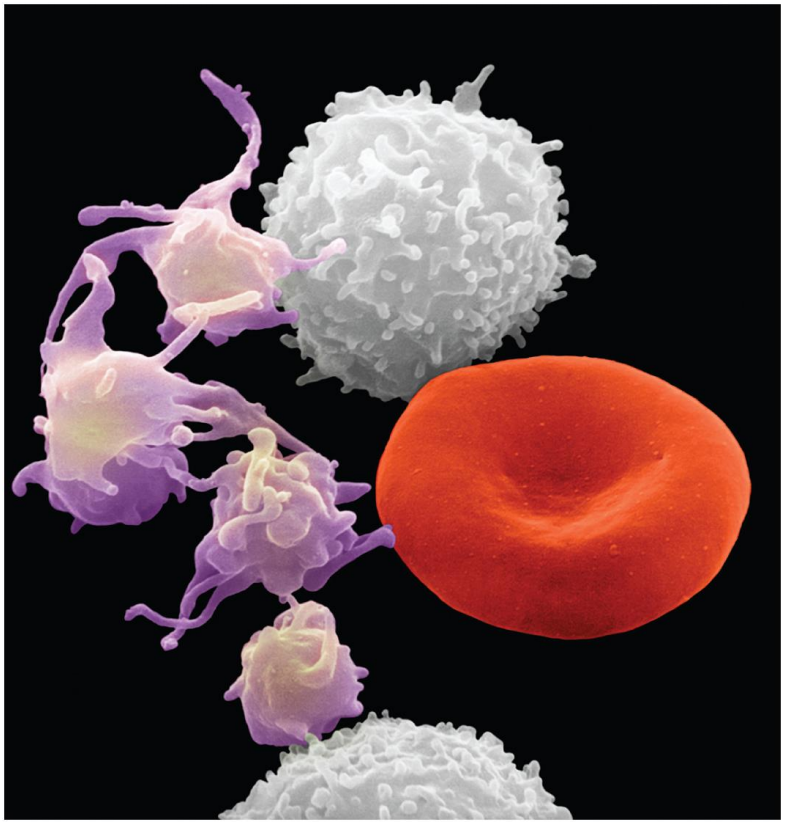
Circulatory System

- **circulatory system** consists of the heart, blood vessels and blood
- **cardiovascular[cardio = heart; vas = vessel] system** refers only to the heart and blood vessels
- **hematology[hem, hemato = blood; logy = study of]** – the study of blood



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



Identify at least two each of the transport, protective, and regulatory functions of the circulatory system

why an excessive loss of blood is quickly fatal

Components and General Properties of Blood

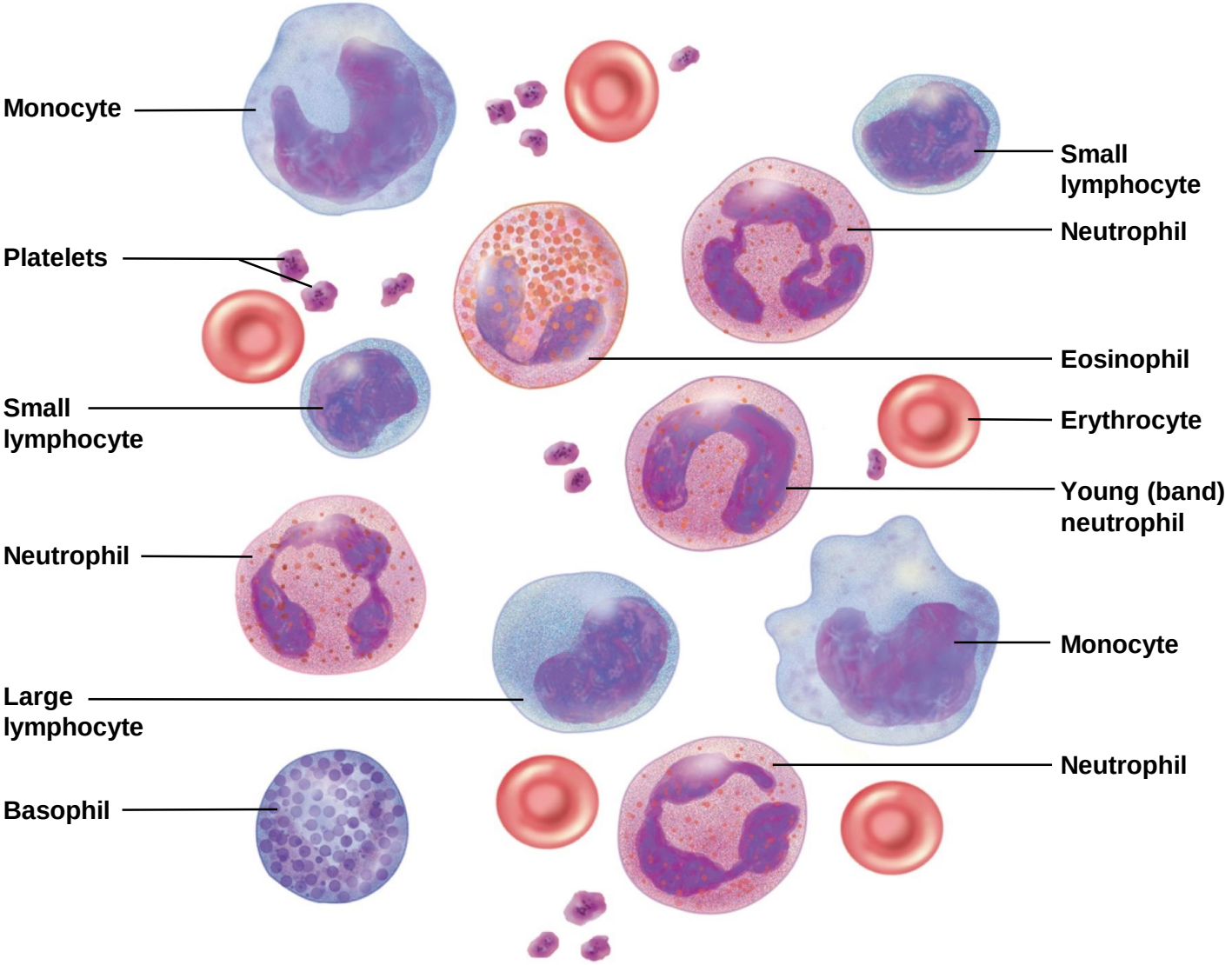
- adults have 4-6 L of blood
- a **liquid connective tissue** consisting of cells and extracellular matrix
  - **plasma** – matrix of blood
    - a clear, light yellow fluid
  - **formed elements** - blood cells and cell fragments
    - red blood cells, white blood cells, and platelets

Components and General Properties of Blood

- seven kinds of formed elements
  - **erythrocytes [erythro = red; cyte = cell] -** red blood cells (RBCs)
  - **platelets**
    - cell fragments from special cell in bone marrow
  - **leukocytes[*leuko* = white; *cyte* = cell] -** 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

What do erythrocytes and platelets lack that the other formed elements have?



Separating Plasma From Formed Elements of Blood

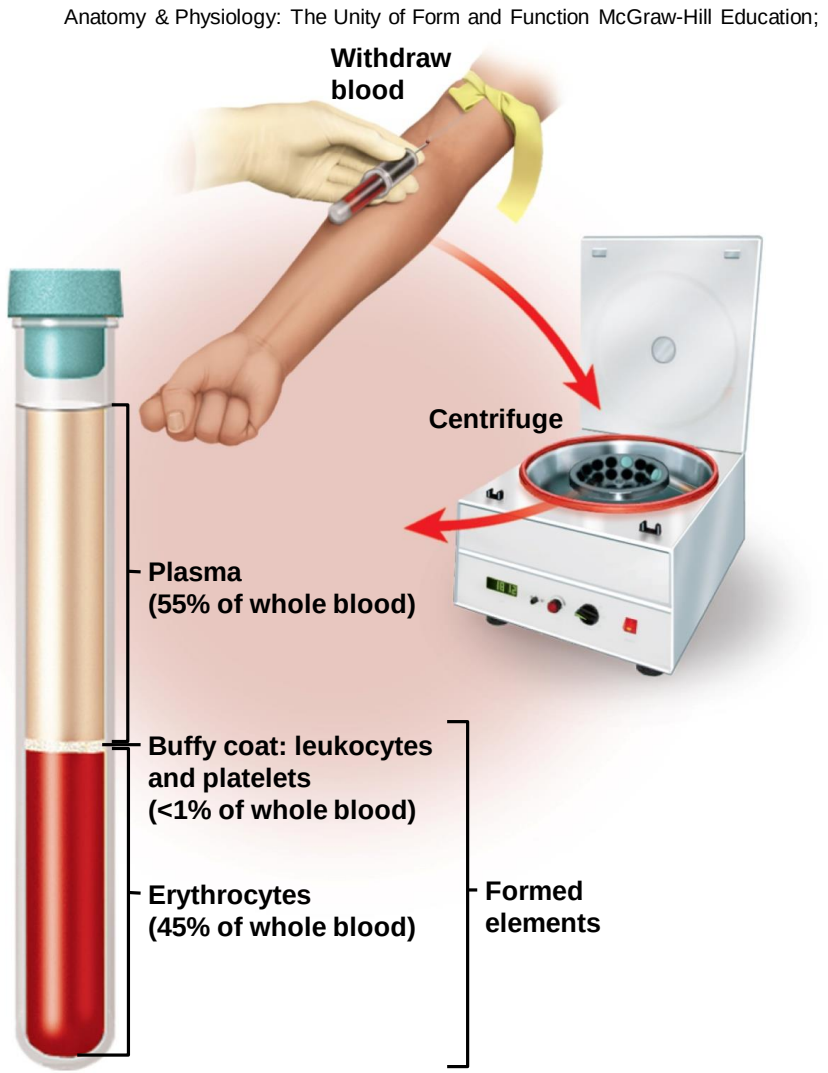


Figure 18.2

- **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

▶▶▶APPLY WHAT YOU KNOW

Based on your body weight, estimate the volume (in liters) and weight (in kilograms) of your own blood

Anatomy & Physiology: The Unity of Form and Function McGraw-Hill Education; 8th Edition

TABLE 18.1 General Properties of Blood

Characteristic	Typical Values for Healthy Adults*
Mean fraction of body weight	8%
Volume in adult body	Female: 4–5 L; male: 5–6 L
Volume/body weight	80–85 mL/kg
Mean temperature	38°C (100.4°F)
pH	7.35–7.45
Viscosity (relative to water)	Whole blood: 4.5–5.5; plasma: 2.0
Osmolarity	280–296 mOsm/L
Mean salinity (mainly NaCl)	0.9%
Hematocrit (packed cell volume)	Female: 37% to 48% Male: 45% to 52%
Hemoglobin	Female: 12–16 g/dL Male: 13–18 g/dL
Mean RBC count	Female: 4.2–5.4 million/μL Male: 4.6–6.2 million/μL
Platelet count	130,000–360,000/μL
Total WBC count	5,000–10,000/μL

*Values vary slightly depending on the testing methods used.

Plasma and Plasma Proteins

▶▶▶APPLY WHAT YOU KNOW
How could a disease such as liver cancer or hepatitis result in impaired blood clotting ?

- **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 gamma 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.

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

DEEPER INSIGHT 18.1

CLINICAL APPLICATION

Starvation and Plasma Protein Deficiency

Several conditions can lead to *hypoproteinemia*, a deficiency of plasma protein: extreme starvation or dietary protein deficiency, liver diseases that interfere with protein synthesis, and protein loss through the urine or body surface in the cases of kidney disease and severe burns, respectively.

FIGURE 18.3 Children of Angola with Kwashiorkor. Note the thin limbs and fluid-distended abdomens.

DEEPER INSIGHT 18.1

CLINICAL APPLICATION

Starvation and Plasma Protein Deficiency

As the protein content of the blood plasma drops, so does its osmolarity. The bloodstream loses more fluid to the tissues than it reabsorbs by osmosis. Thus, the tissues become edematous and a pool of fluid may accumulate in the abdominal cavity—a condition called *ascites* (ah-SY-teez).

DEEPER INSIGHT 18.1

CLINICAL APPLICATION

Starvation and Plasma Protein Deficiency

Children who suffer severe dietary protein deficiencies often exhibit a condition called *kwashiorkor* (KWASH-ee-OR-cor) (fig. 18.3). The arms and legs are emaciated for lack of muscle, the skin is shiny and tight with edema, and the abdomen is swollen by ascites. *Kwashiorkor* is an African word for a “deposed” or “displaced” child who is no longer breast-fed. Symptoms appear when a child is weaned and placed on a diet consisting mainly of rice or other cereals. Children with kwashiorkor often die of diarrhea and dehydration.

What does *hemopoiesis* mean? After birth, what one cell type is the starting point for all hemopoiesis

Hemopoiesis

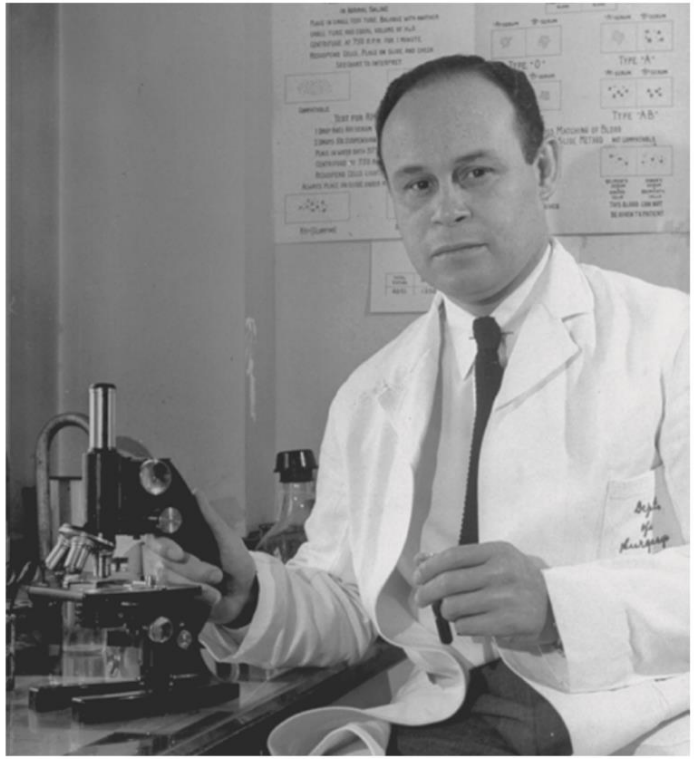
- Adult production of 400 billion platelets, 200 billion RBCs and 10 billion WBCs every day
- **hemopoiesis[*hemo* = blood; *poiesis* = formation]** – the production of blood, especially its formed elements
- **hemopoietic tissues** produce blood cells
  - **yolk sac** produces stem cells for first blood 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 [bone marrow] hemopoiesis** – blood formation in the bone marrow
    - **lymphoid hemopoiesis** – blood formation in the lymphatic organs

DEEPER INSIGHT 18.2

MEDICAL HISTORY

Charles Drew—Blood-Banking Pioneer

Charles Drew was a scientist who lived and died in the grip of irony. After receiving his M.D. from McGill University of Montreal in 1933, Drew became the first black person to pursue the advanced degree of Doctor of Science in Medicine, for which he studied transfusion and blood banking at Columbia University. He became the director of a new blood bank at Columbia Presbyterian Hospital in 1939 and organized numerous blood banks during World War II.

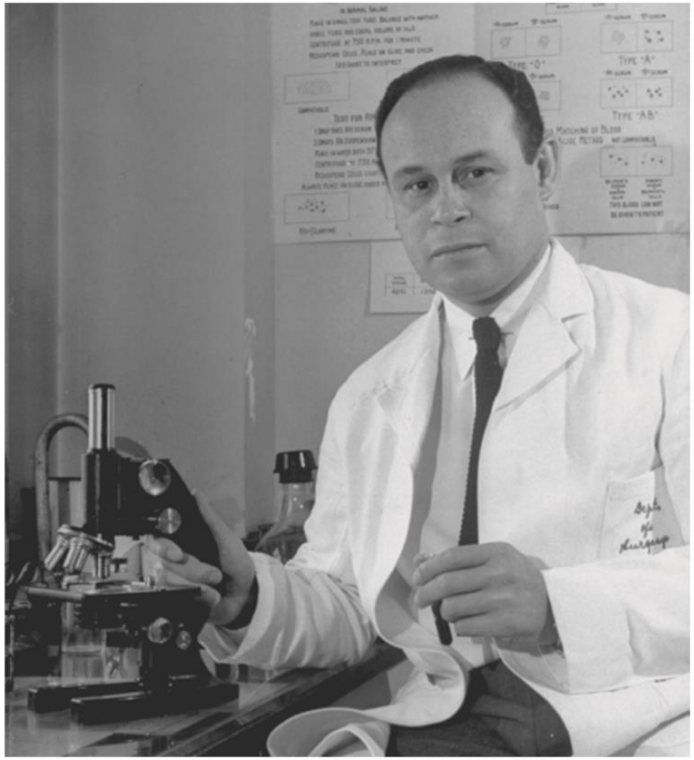


DEEPER INSIGHT 18.2

MEDICAL HISTORY

Charles Drew—Blood-Banking Pioneer

Drew saved countless lives by convincing physicians to use plasma rather than whole blood for battlefield and other emergency transfusions. Whole blood could be stored for only a week and given only to recipients with compatible blood types. Plasma could be stored longer and was less likely to cause transfusion reactions.



DEEPER INSIGHT 18.2

MEDICAL HISTORY

Charles Drew—Blood-Banking Pioneer

When the U.S. War Department issued a directive forbidding the storage of Caucasian and Negro blood in the same military blood banks, Drew denounced the order and resigned his position. He became a professor of surgery at Howard University in Washington, D.C., and later chief of staff at Freedmen's Hospital. He was a mentor for numerous young black physicians and campaigned to get them accepted into the medical community. The American Medical Association, however, refused to admit black members until the 1960s, excluding even Drew himself.

DEEPER INSIGHT 18.2

MEDICAL HISTORY

Charles Drew—Blood-Banking Pioneer

Late one night in 1950, Drew and three colleagues set out to volunteer their medical services to an annual free clinic in Tuskegee, Alabama. Drew fell asleep at the wheel and was critically injured in the resulting accident. Contrary to a myth that Drew was refused emergency treatment because of his race, doctors at the nearest hospital administered blood and attempted to revive him. Yet, for all the lives he saved through his pioneering work in transfusion, Drew himself bled to death at the age of 45.

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

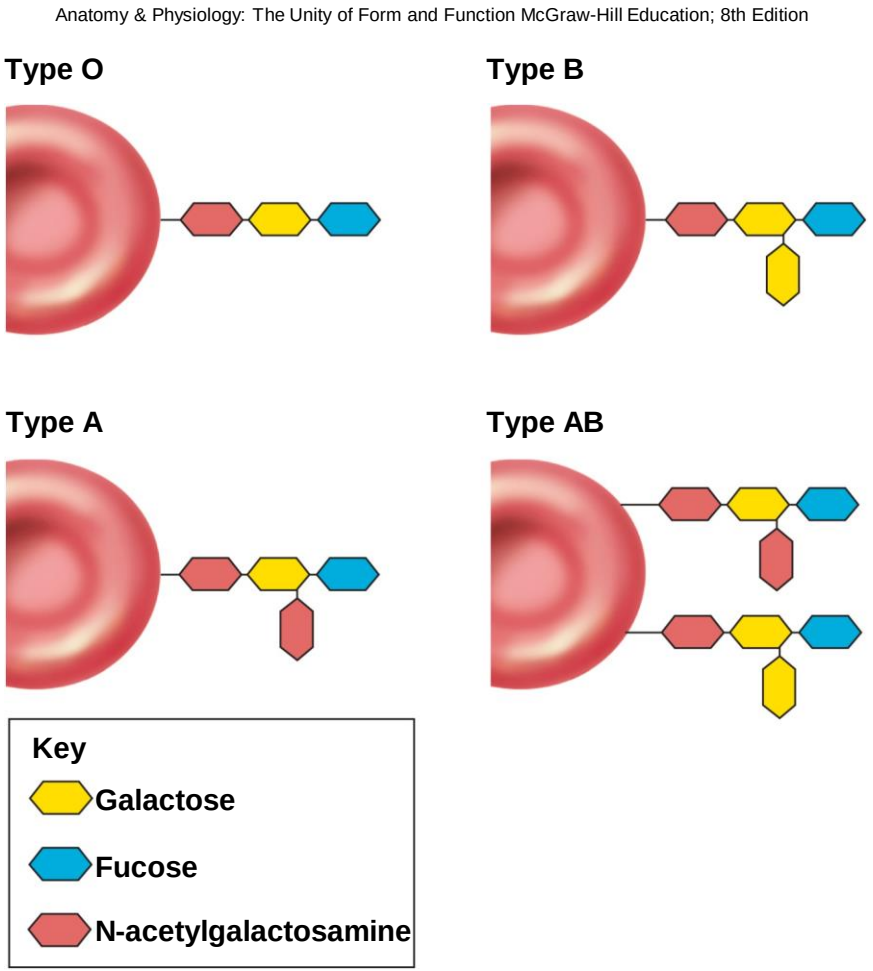


Figure 18.12

What Scientists have developed a method of enzymatically splitting N-acetylgalactosamine off the glycolipid of type A blood cells . What potential benefit do you think they saw as justifying their research effort?

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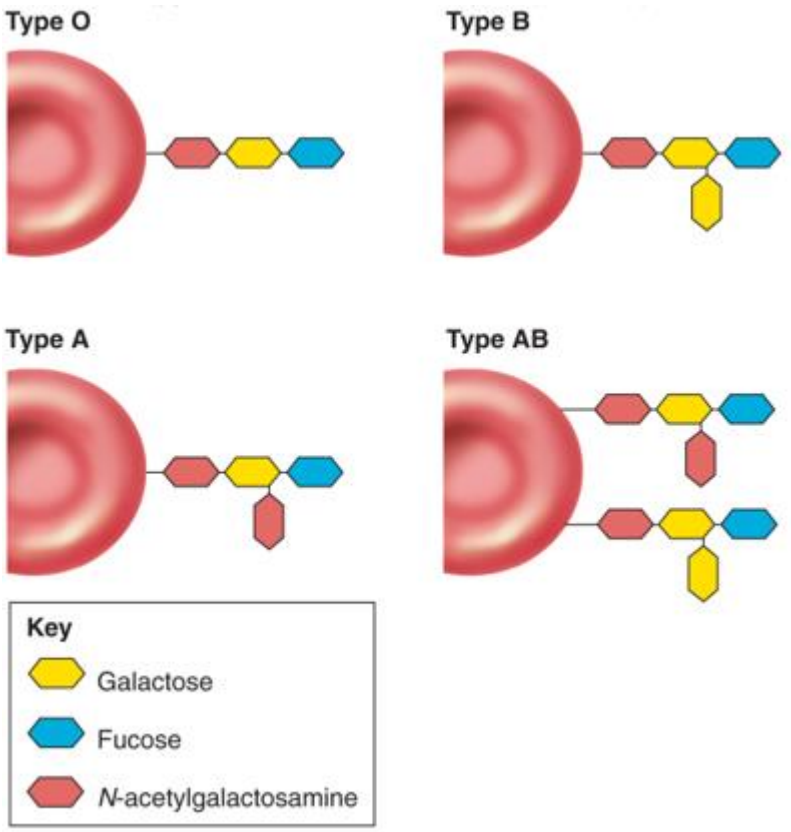

ABO Group

- 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

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

ABO Blood Typing

Anatomy & Physiology: The Unity of Form and Function McGraw-Hill Education; 8th Edition

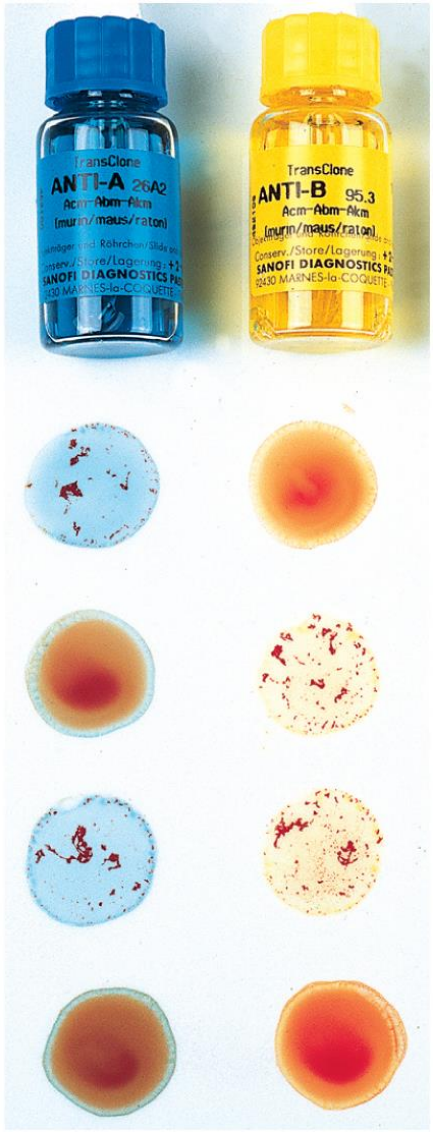

Figure 18.14

Agglutination of Erythrocytes

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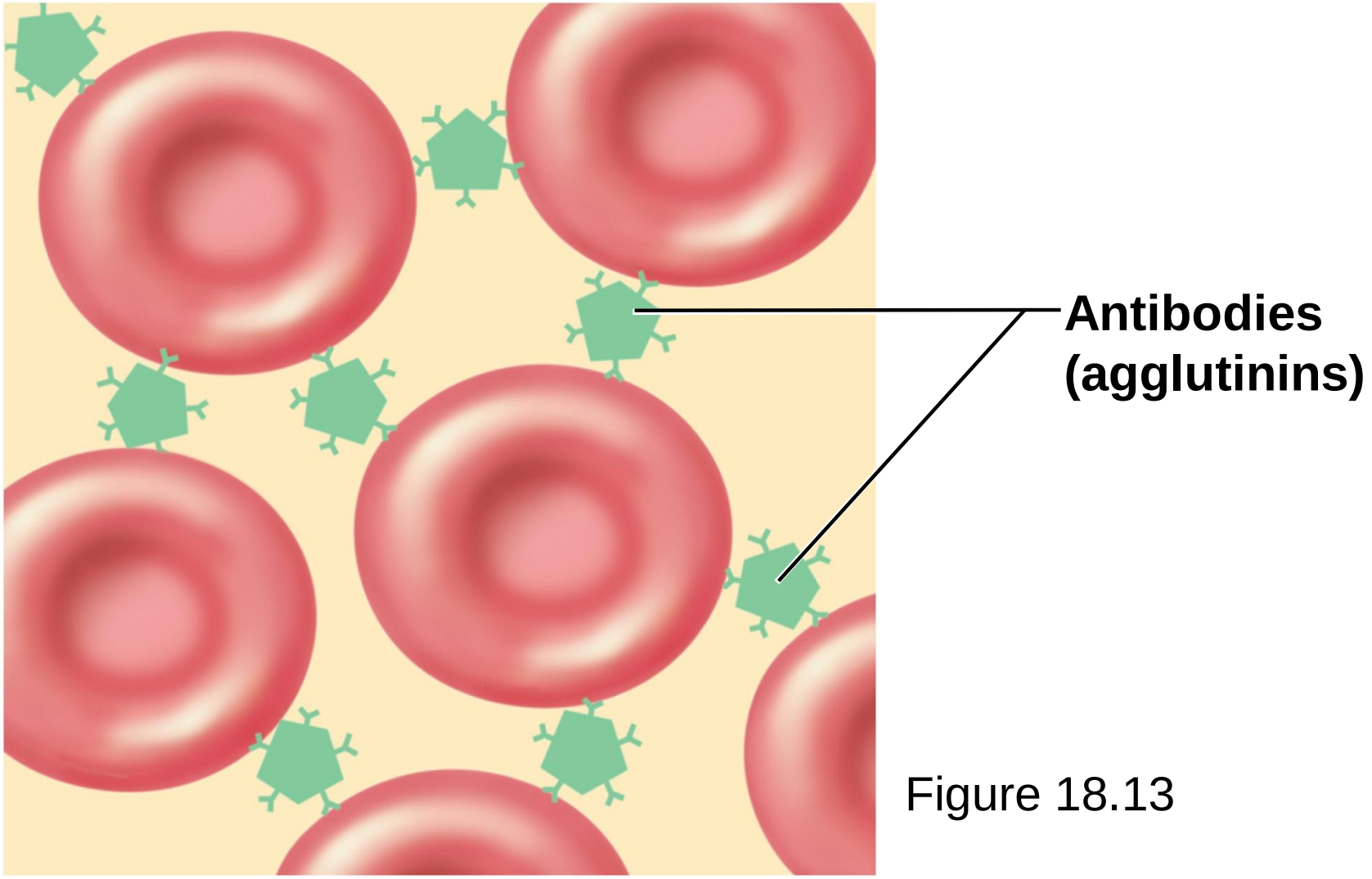

Figure 18.13

Transfusion Reaction

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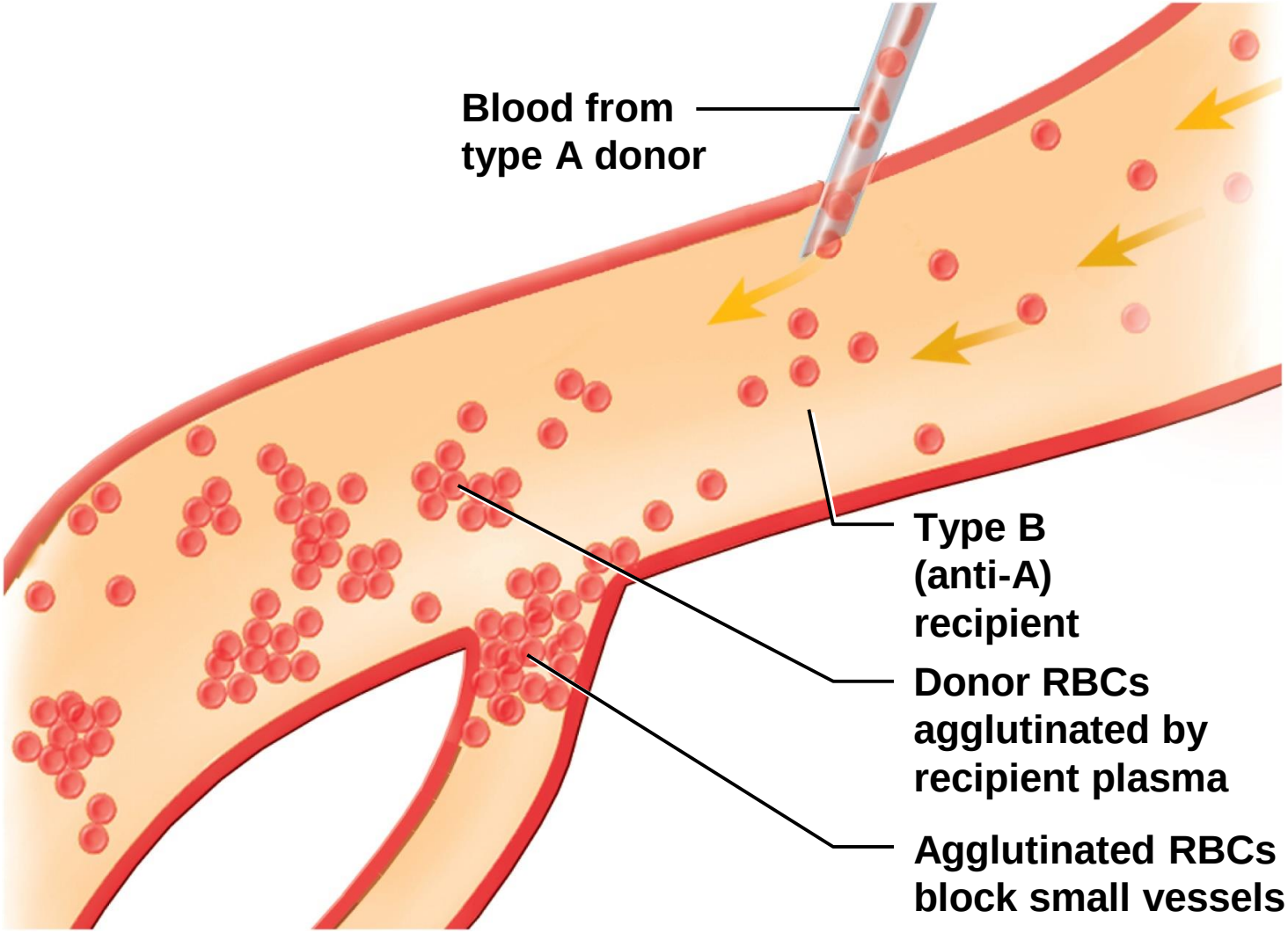


Figure 18.15

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

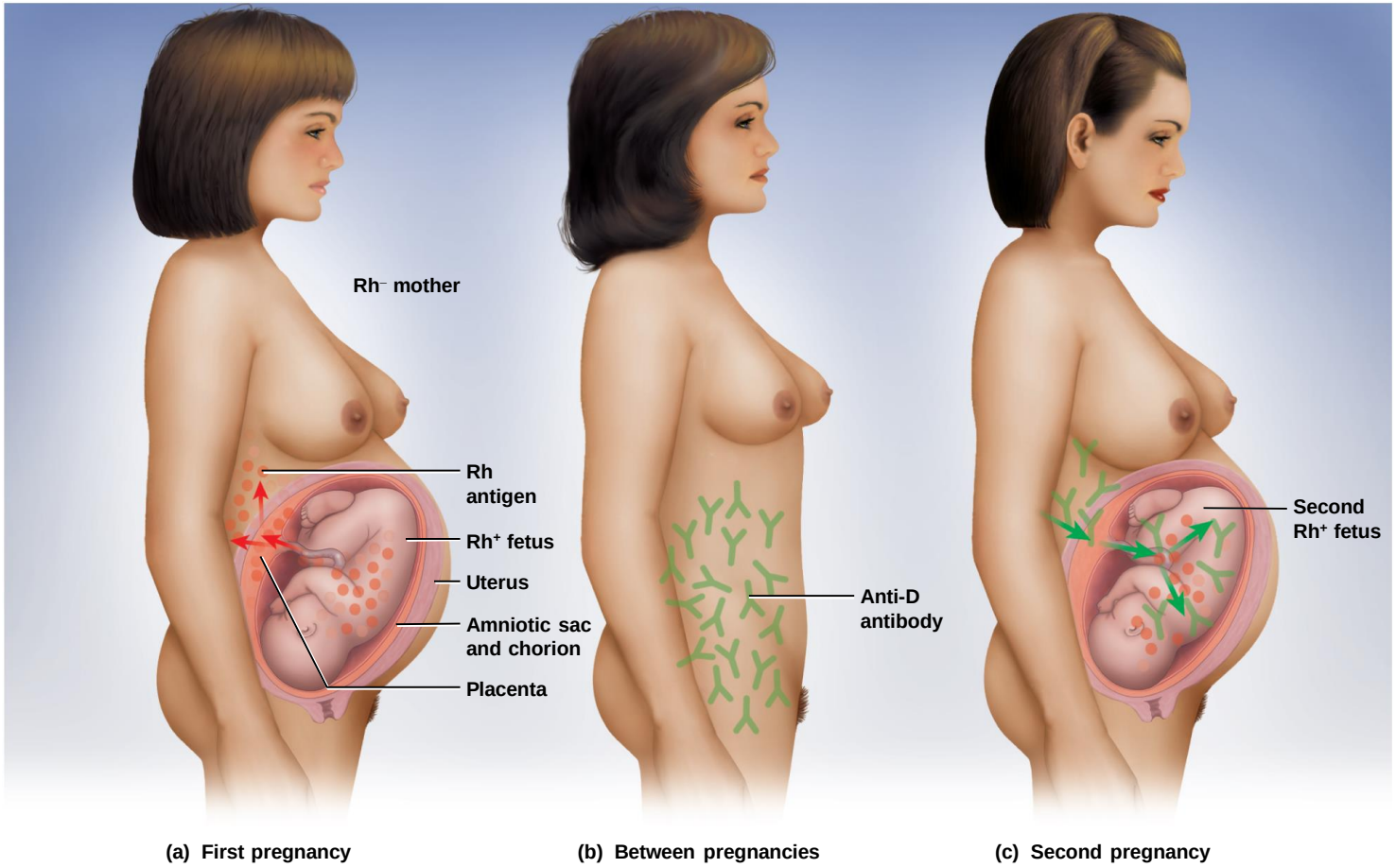
- Rh (C,D,E) agglutinogens discovered in rhesus monkey in 1940
  - Rh D is the most reactive and a patient is considered blood type Rh^+ if they have D antigen (agglutinogens) on RBCs
  - Rh frequencies vary among ethnic groups
- Anti-D agglutinins not normally present
  - form in Rh^- individuals exposed 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

Anatomy & Physiology: The Unity of Form and Function McGraw-Hill Education; 8th Edition



- Rh antibodies attack fetal blood

causing severe anemia and toxic brain syndrome

A baby with HDN typically has jaundice and an enlarged spleen. Explain these effects.

In hemolytic disease of the newborn, RBCs break down and release hemoglobin, and the hemoglobin is degraded to bilirubin at such a fast rate that the liver cannot dispose of the bilirubin. It accumulates in the blood and produces jaundice. Splenomegaly, enlargement of the spleen, occurs because the spleen is one of the sites of the accelerated erythropoiesis that occurs in HDN.

DEEPER INSIGHT 18.3

CLINICAL APPLICATION

Bone Marrow and Cord Blood Transplants

A **bone marrow transplant** is one treatment option for leukemia, sickle-cell disease, some forms of anemia, and other disorders. The principle is to replace cancerous or otherwise defective marrow with donor stem cells in hopes that they will rebuild a population of normal marrow and blood cells. The patient is first given chemotherapy or radiation to destroy the defective marrow and eliminate immune cells (T cells) that would attack the donated marrow. Bone marrow is drawn from the donor's sternum or hip bone and injected into the recipient's circulatory system. Donor stem cells colonize the patient's marrow cavities and, ideally, build healthy marrow.

DEEPER INSIGHT 18.3

CLINICAL APPLICATION

Bone Marrow and Cord Blood Transplants

There are, however, several **drawbacks to bone marrow transplant.** For one, it is difficult to find compatible donors. Surviving T cells in the patient may attack the donor marrow, and donor T cells may attack the patient's tissues (the *graft-versus-host response*). To inhibit graft rejection, the patient must take immunosuppressant drugs for life. These drugs leave a person vulnerable to infection and have many other adverse side effects. Infections are sometimes contracted from the donated marrow itself. In short, marrow transplant is a high-risk procedure; up to one-third of patients die from complications of treatment.

DEEPER INSIGHT 18.3

CLINICAL APPLICATION

Bone Marrow and Cord Blood Transplants

An alternative with several advantages is to use blood from placentas, which are normally discarded at every childbirth. **Placental blood** contains more stem cells than adult bone marrow, and is less likely to carry infectious microbes. With the parents' consent, it can be harvested from the umbilical cord with a syringe and stored almost indefinitely, frozen in liquid nitrogen at cord blood banks. The immature immune cells in cord blood have less tendency to attack the recipient's tissues; thus, cord blood transplants have lower rejection rates and do not require as close a match between donor and recipient, meaning that more donors are available to patients in need. Pioneered in the 1980s, cord blood transplants have successfully treated leukemia and a wide range of other blood diseases. Efforts are being made to further improve the procedure by stimulating fetal stem cells to multiply before the transplant, and by removing fetal T cells that may react against the recipient.

PART II

LEARNING OUTCOMES

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

- ***Discuss the structure of erythrocytes (RBCs)***
- ***Describe the structure of hemoglobin***
- ***Discuss the structure of leukocytes***

Learning outcomes:

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

- Microscopic and ultramicroscopic structure of erythrocytes, leucocytes, and thrombocytes.
- Embryonal development of blood
- Blood plasma, its functional significance
- Erythrocytes
- Classification of leukocytes
- Granulocytes
- Agranulocytes
- Blood platelets
- photomicrographs and diagrams of the cells of blood

Functions of the Blood

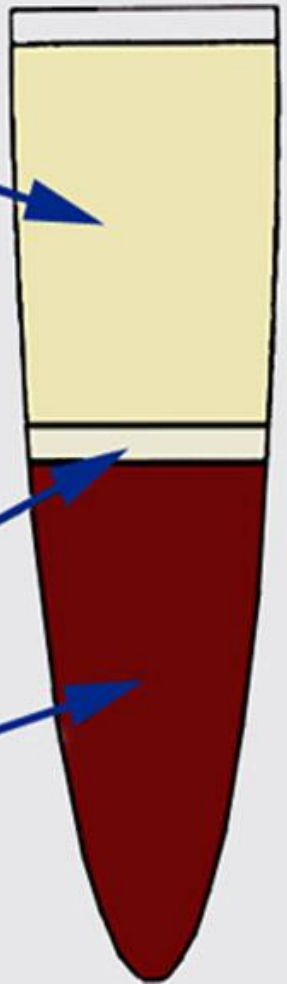
1. To transport nutrients, oxygen, wastes, and carbon dioxide to and from the tissues.

2. To convey hormones, cytokines, chemokines, and other soluble regulatory molecules.

3. To transport leukocytes and antibodies through the tissues.

4. To maintain homeostasis.

Contents of 1 μl of Peripheral Blood



Formed Elements (46%)

200,000-400,000 platelets
5,000-9,000 leukocytes

5,000,000-10,000,000 erythrocytes

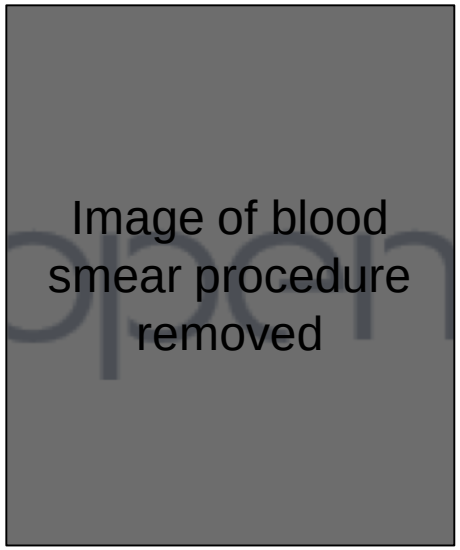
Major Plasma Proteins

Protein	Function
Albumin	Maintain colloid osmotic pressure; transport insoluble metabolites
Globulins	
α and β	Transport metal ions, protein-bound lipids, lipid-soluble vitamins
γ	Antibodies for host defense
Complement proteins	Destruction of microorganisms
Clotting factors	Formation of blood clots
Plasma lipoproteins	Transport of triglycerides and cholesterol to/from liver

Cells of the blood

- **Erythrocytes** (red blood cells, RBC)
- **Platelets** (thrombocytes)
- **Leukocytes** (white blood cells, WBC)
  - **Granulocytes** (with specific granules)
    - **Neutrophil (~60% of WBC)**
    - **Eosinophil (~4% of WBC)**
    - **Basophil (<1% of WBC)**
  - **Agranulocytes** (without specific granules)
    - **Lymphocyte (B-cell, T-cell) (~27% of WBC)**
    - **Monocyte (~8% of WBC)**

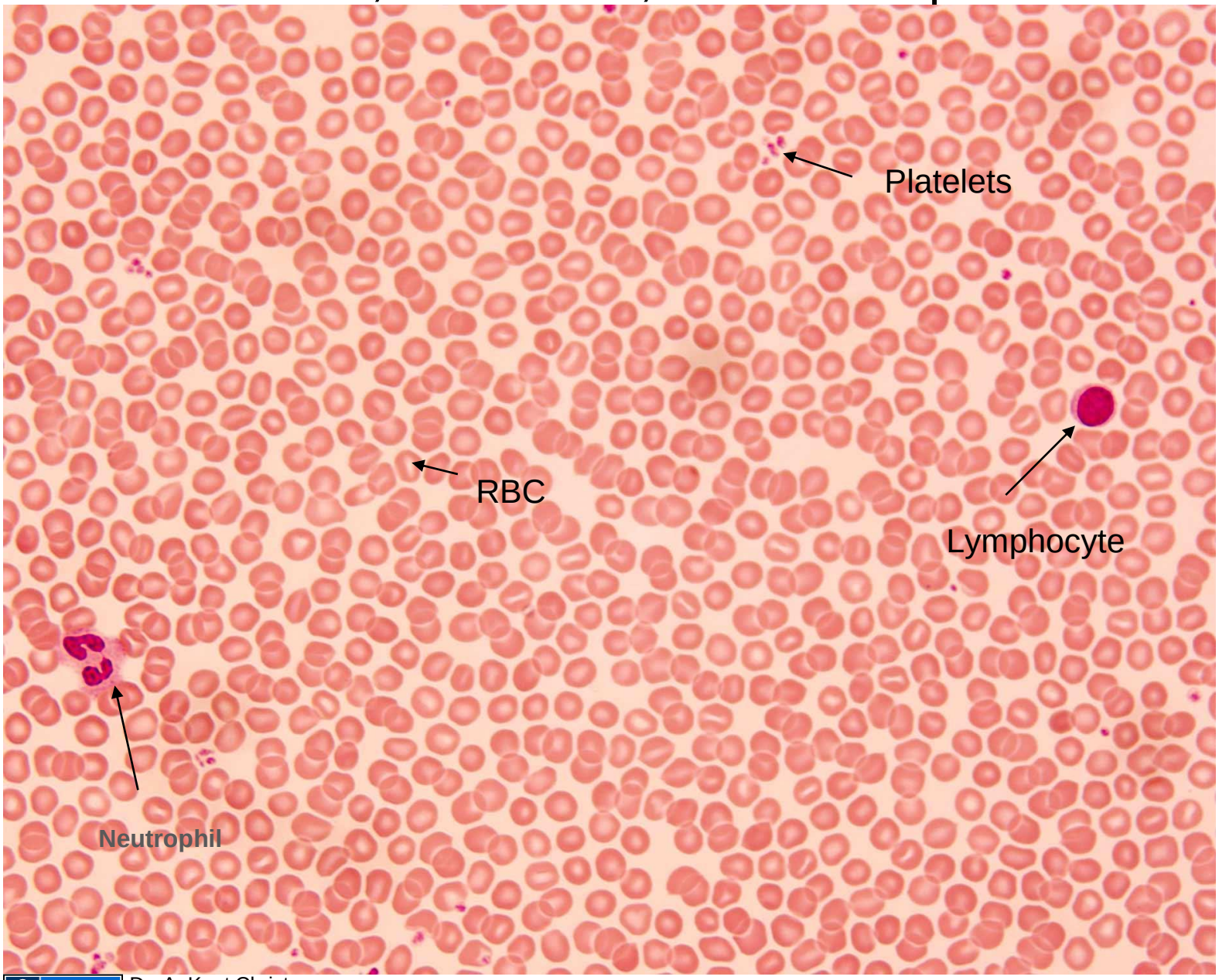
FYI, blood smear procedure



Original Source: Junqueira's histology text, 6th ed., page 231. BloodSmear-23J91(2).tif.

- The procedure for making a blood smear is shown at left.
- After the smear is made, it is air-dried and then stained. Common stains are Wright's stain and Giemsa stain. The stains generally include two or more dyes, one of them a basic dye (often methylene blue) and another an acidic dye (usually eosin). Reddish-blue azures are formed when methylene blue is oxidized (metachromasia). Cells usually stain pink/red with acidic dye and nuclei stain purple/black with basic dye, while specific granules stain characteristically.
- Remember that the cells you see in a blood smear have not been sectioned. Instead you are seeing whole cells dried down on the glass.

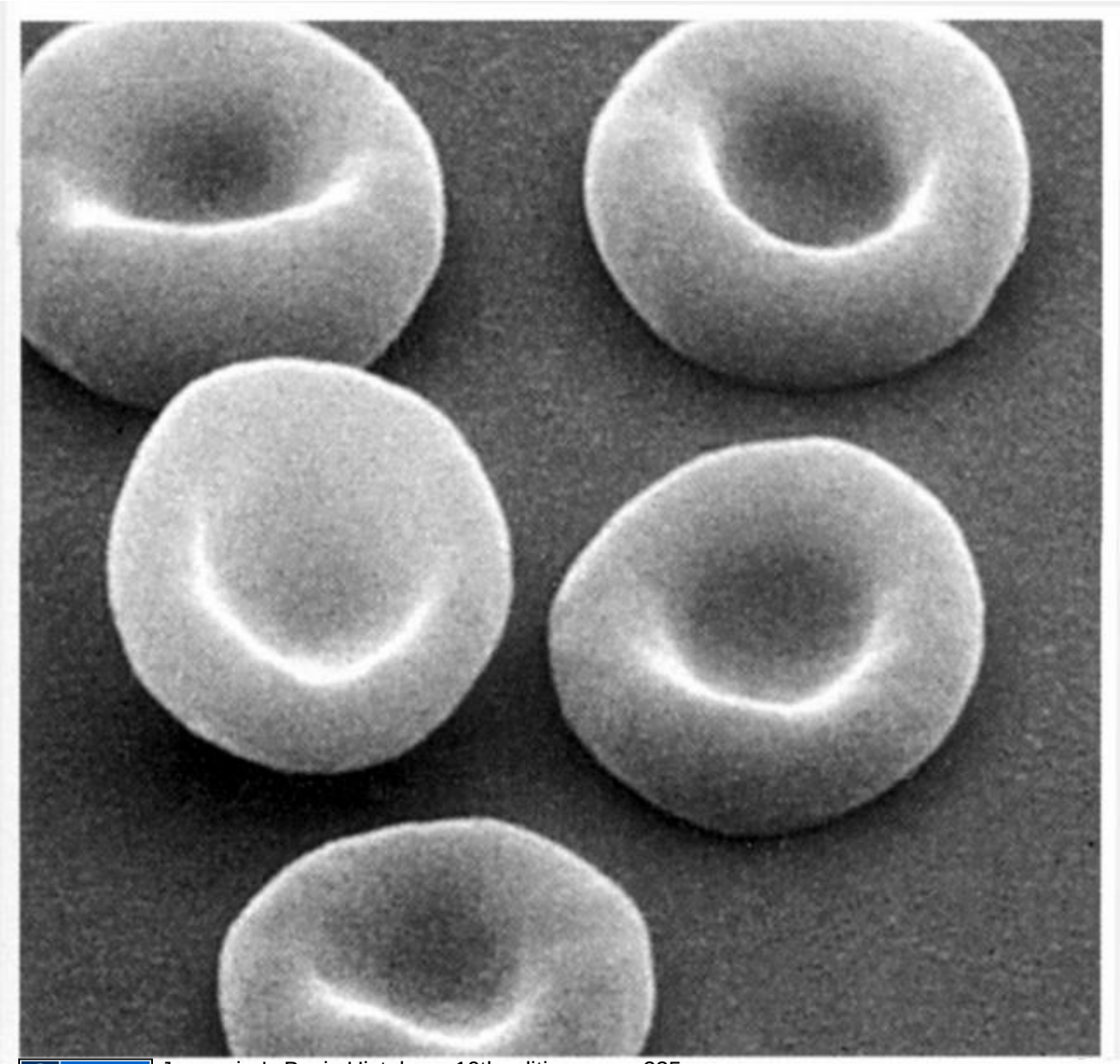
Human blood smear, with RBCs, WBCs and platelets



Erythrocyte (red blood cell, RBC)

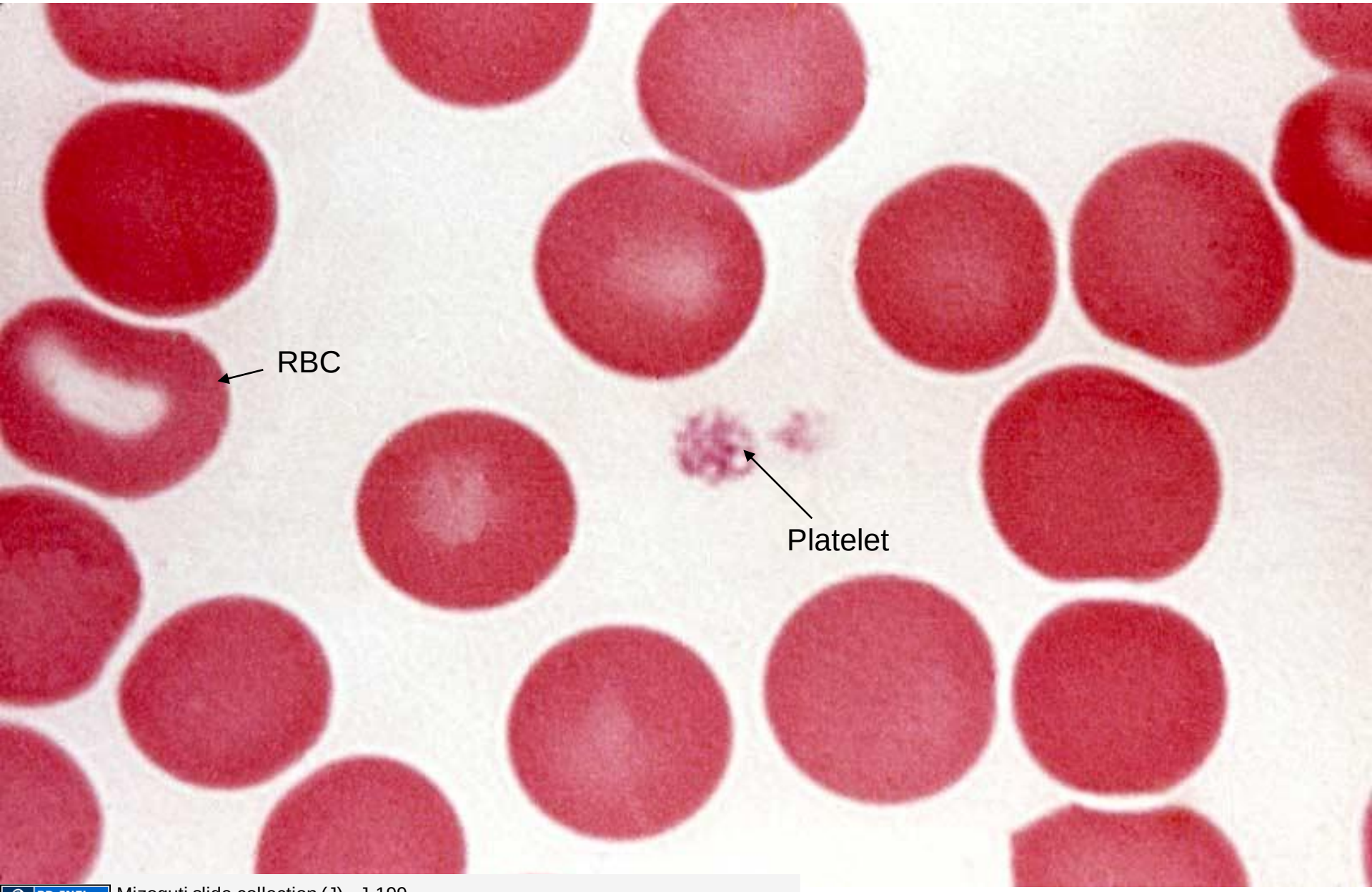
1. **Life span in blood:** About 120 days.
2. **Size and shape:**
   - biconcave disk, 8 μm diameter, 2μm at thickest point, 1 μm at thinnest
   - shape maintained by a cytoskeletal complex inside the plasma membrane (involving spectrin, actin and other components)
   - flexible: RBC's normally bend to pass through small capillaries
3. **LM appearance in smear:** Pink circle with light center (center is thinner because of the biconcave shape). No nucleus.
4. **TEM appearance:** Solid dark gray cytoplasm, because of highly concentrated hemoglobin.
5. **Function:**
   - Transport of oxygen and carbon dioxide
     - bound to hemoglobin (oxyhemoglobin and carboxyhemoglobin)
     - majority of CO_2 transported as HCO_3^-
   - pH homeostasis
     - carbonic anhydrase: $CO_2 + H_2O \rightarrow HCO_3^- + H^+$
     - band 3 membrane protein: exchanges HCO_3^- for extracellular Cl^-

RBCs, scanning electron microscopy

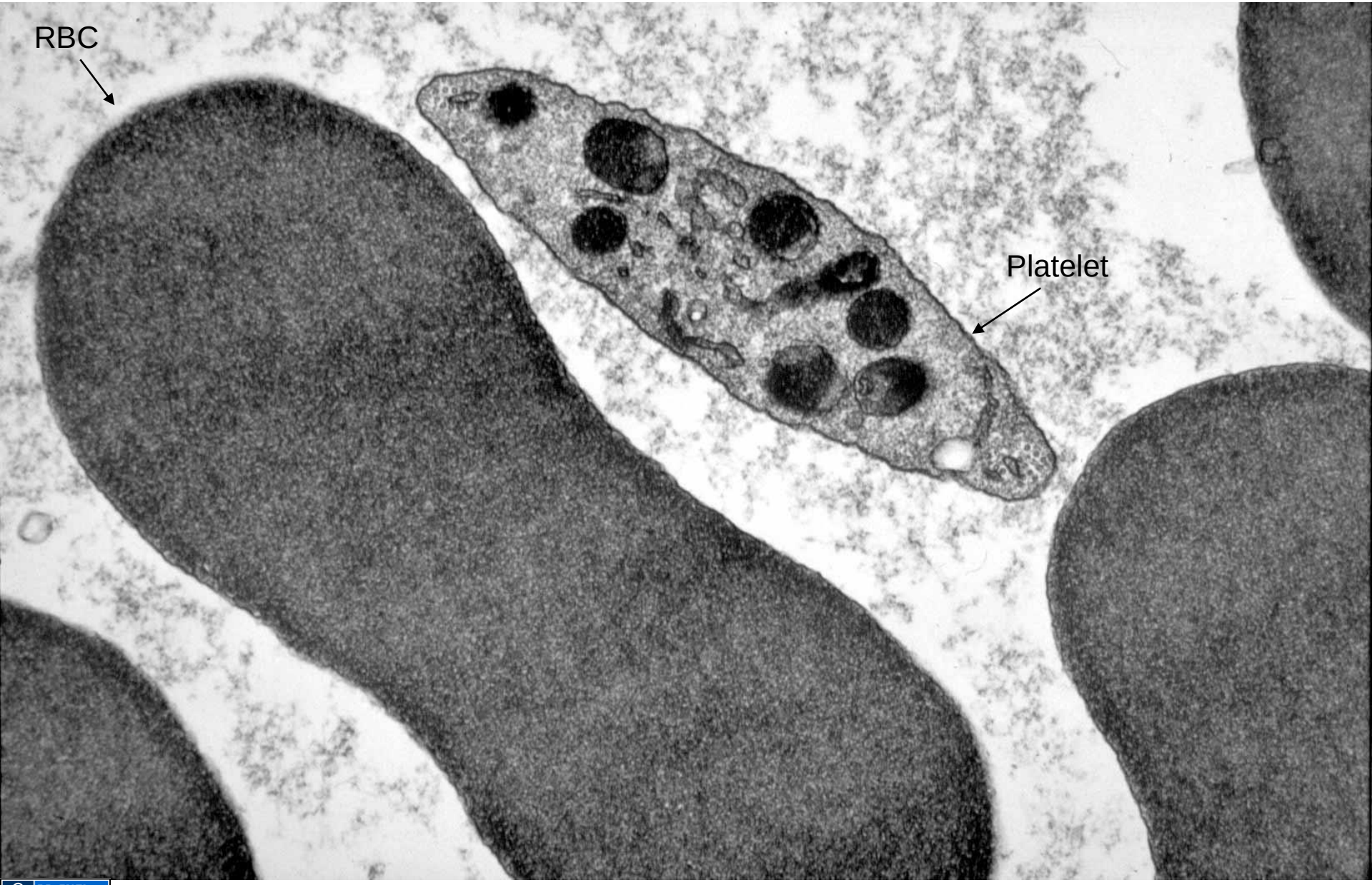


Junqueira's Basic Histology, 10th edition, page 235

Red blood cells in a blood smear



RBC, transmission electron microscopy



◆ PART II

LEARNING OUTCOMES

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

- ❑ ***Discuss the structure and function of erythrocytes (RBCs);***
- ❑ ***Describe the structure and function of hemoglobin;***
- ❑ ***State and define some clinical measurements of RBC and hemoglobin quantities;***
- ❑ ***Describe the life history of erythrocytes; and***
- ❑ ***Name and describe the types, causes, and effects of RBC excesses and deficiencies.***

Erythrocytes

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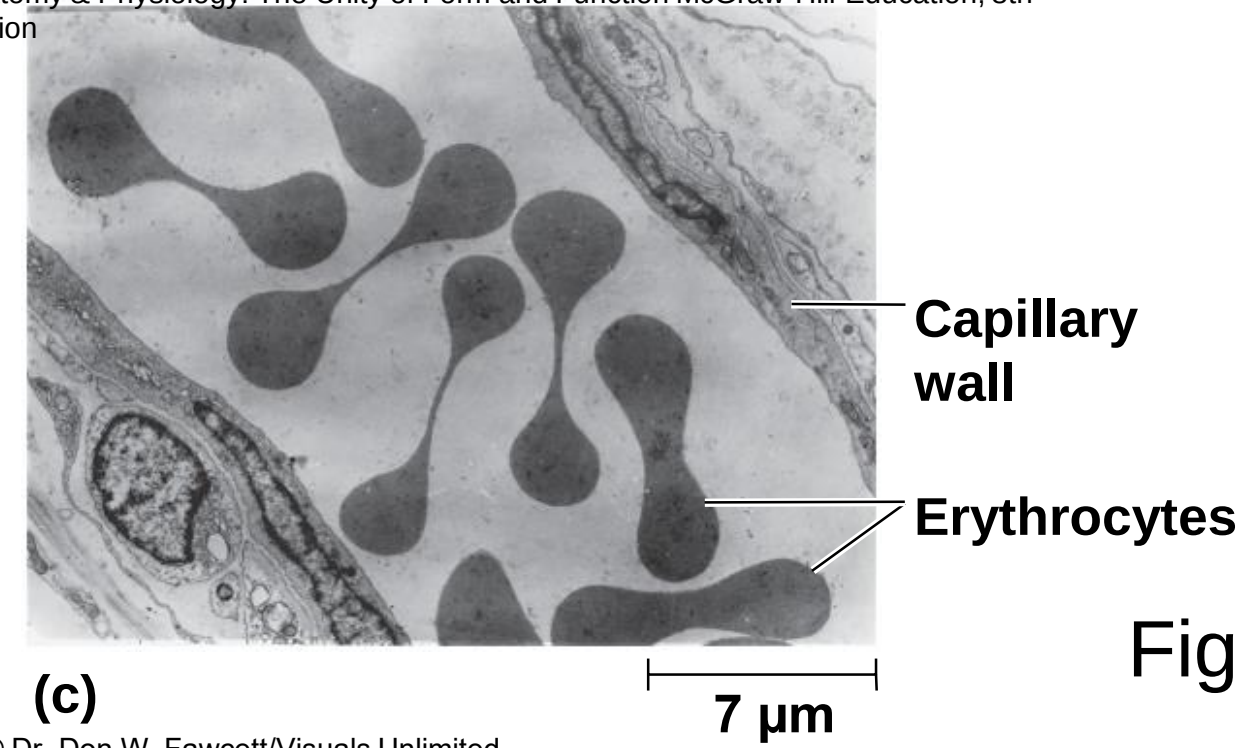


Figure 18.4c

- **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

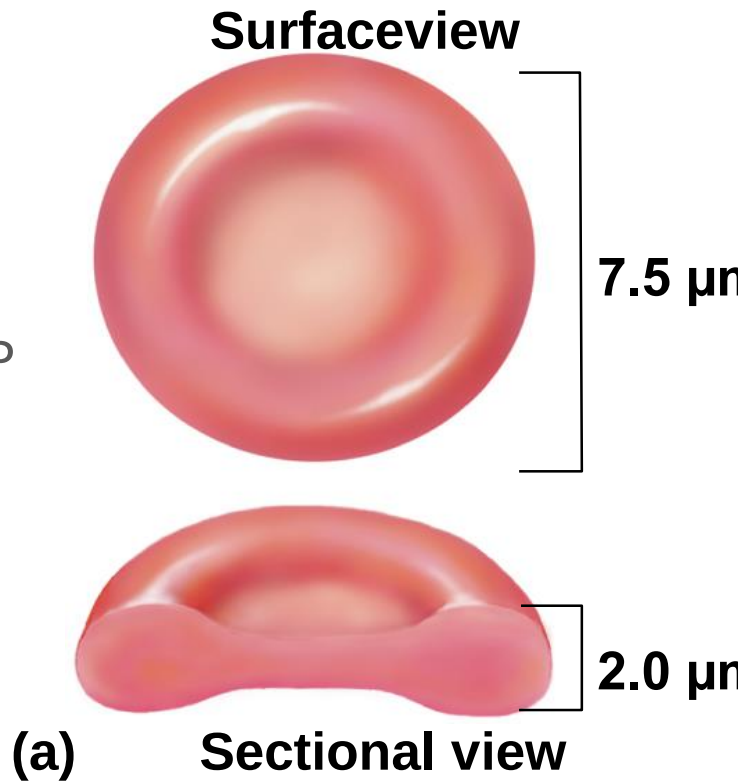
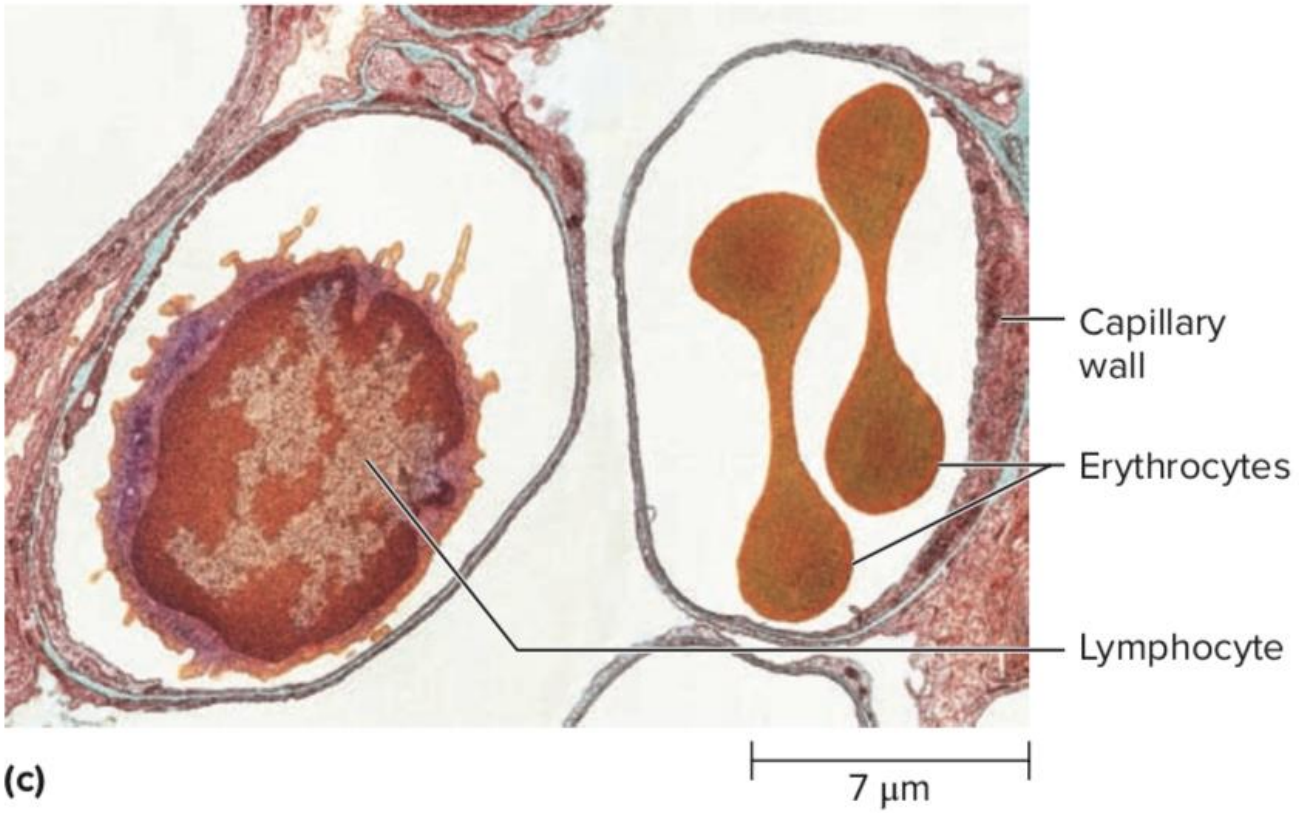


Figure 18.4a

Why are erythrocytes caved in at the center?



Erythrocyte Production (Erythropoiesis)

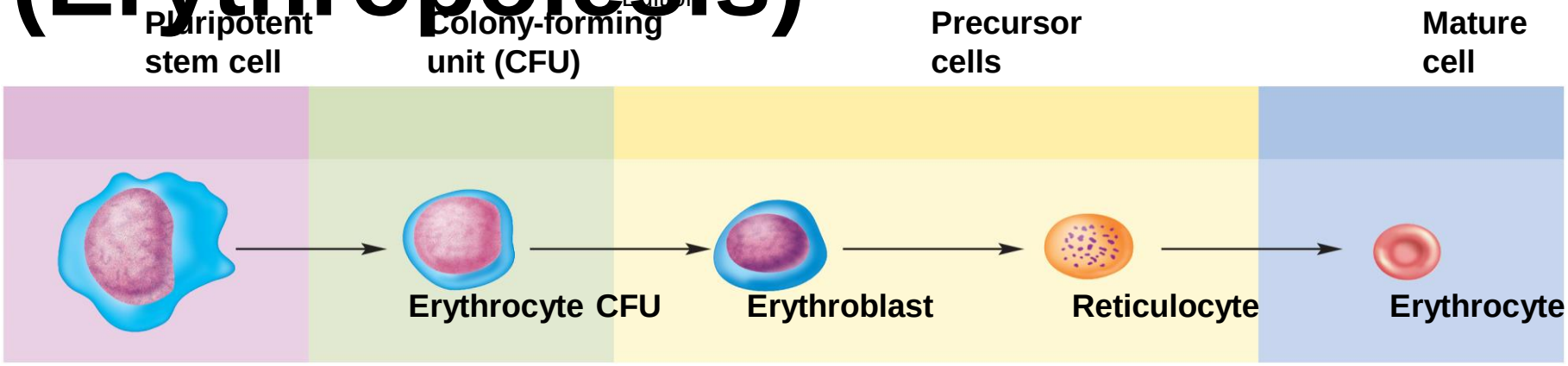


Figure 18.6

- 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

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

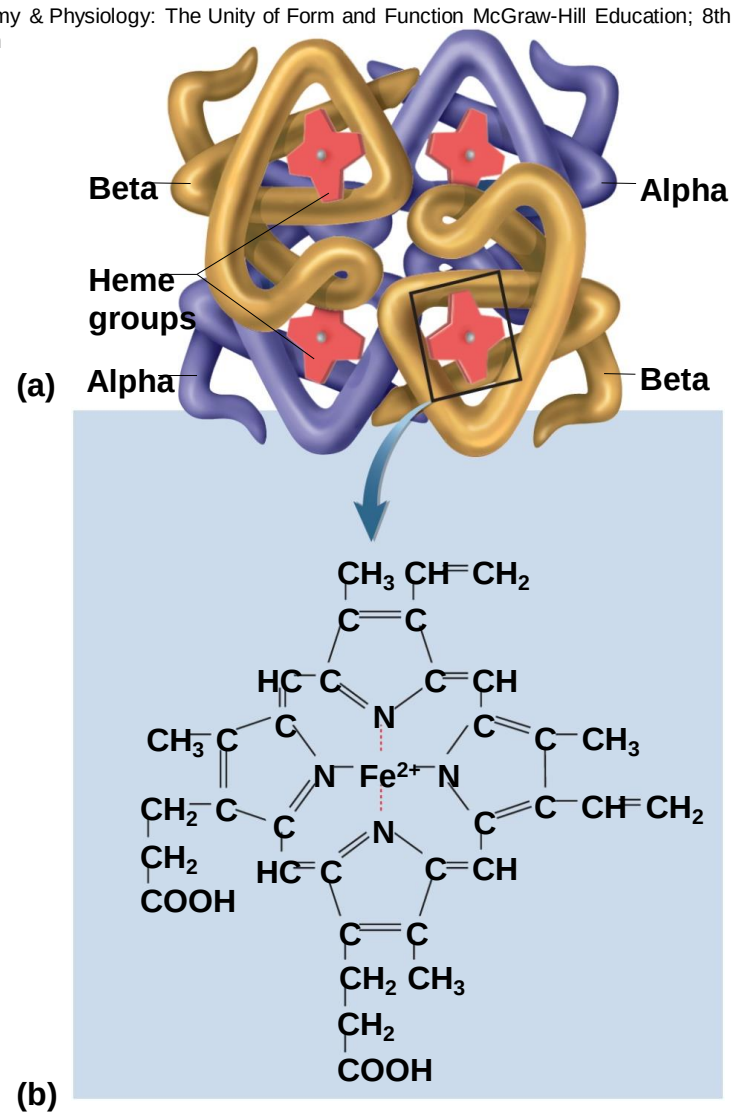
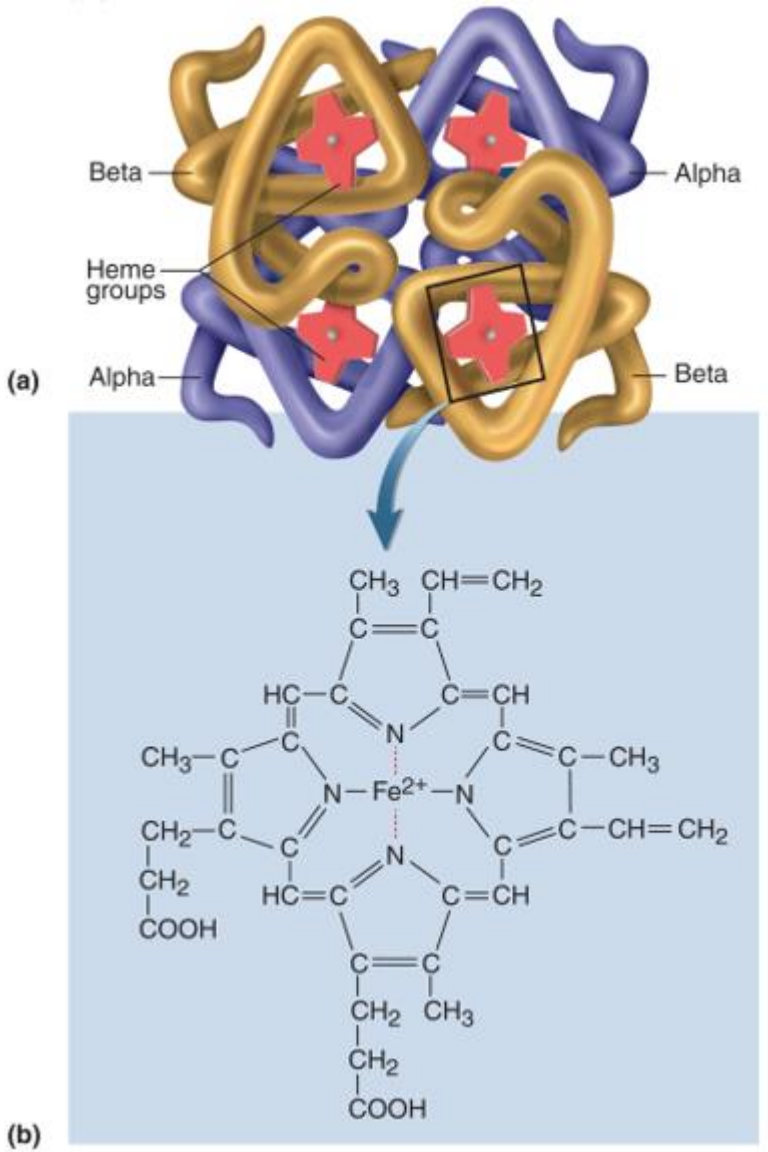


Figure 18.5 a-b

In what way does this exemplify a quaternary protein structure? What is the prosthetic group of hemoglobin? ?



Erythrocytes and Hemoglobin

- RBC count and hemoglobin concentration indicate amount of O_2 blood can carry
  - **hematocrit** [***hemato* = blood; *crit* = to separate**](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 Disorders

- **polycythemia** [*poly* = many; *cyt* = cell; *hem* = blood; *ia* = condition] - an excess of RBCs
- [The RBC count is normally 4.6 to 6.2 million RBCs/µL in men and 4.2 to 5.4 million/µL in women. The hematocrit (PCV) In men, it normally ranges between 42% and 52%; in women, between 37% and 48%.]
  - **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

▶▶▶APPLY WHAT YOU KNOW

Explain why the hemoglobin concentration could appear deceptively high in a patient who is dehydrated, when in fact the patient does not have a hemoglobin or RBC excess?

Anemia[*an* = without; *em* = blood; *ia* = condition]

- **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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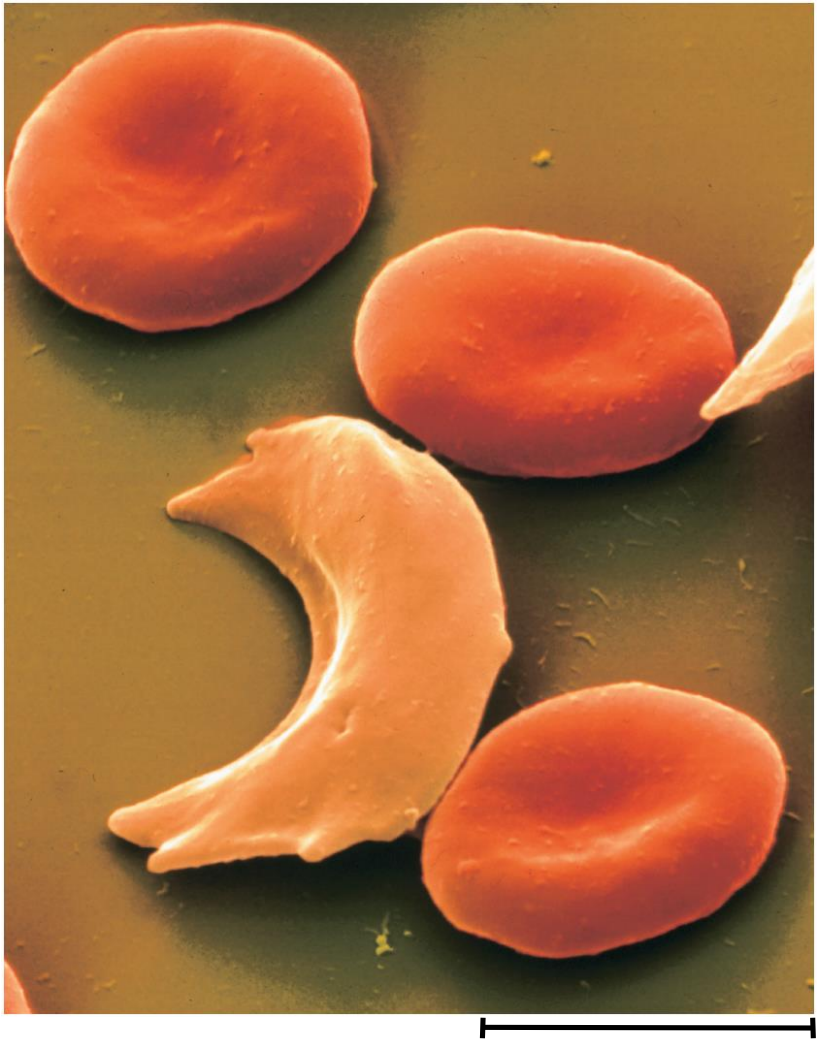

- hereditary hemoglobin defects that occur mostly among people of African descent

- 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

Figure 18.10

A Case of Iron Deficiency Anemia

by
David F. Dean, Department of Biology, Spring Hill College

Case Presentation

Dolores Welborn is a 28-year-old attorney living in Portland, Oregon. Dolores is in the second trimester of pregnancy with her first child, and though her pregnancy had been progressing normally, recently she has noticed that she tires very easily and is short of breath from even the slightest exertion. She also has experienced periods of light-headedness, though not to the point of fainting. Other changes she has noticed are cramping in her legs, a desire to crunch on ice, and the fact that her tongue is sore. She doubts that all of these symptoms are related to one another, but she is concerned, and she makes an appointment to see her physician.

A Case of Iron Deficiency Anemia

by
David F. Dean, Department of Biology, Spring Hill College

Case Presentation

Upon examining Dolores, her physician finds that she has tachycardia, pale gums and nail beds, and her tongue is swollen. Given her history and the findings on her physical exam, the physician suspects that Dolores is anemic and orders a sample of her blood for examination. The results are shown in Table.

Table 1. Blood Sample Results

Red Blood Cell Count	3.5 million/ mm^3
Hemoglobin (Hb)	7 g/dl
Hematocrit (Hct)	30%
Serum Iron	low
Mean Corpuscular Volume (MCV)	low
Mean Corpuscular Hb Concentration (MCHC)	low
Total Iron Binding Capacity in the Blood (TIBC)	high

A Case of Iron Deficiency Anemia

by
David F. Dean, Department of Biology, Spring Hill College

Case Presentation

A diagnosis of anemia due to iron deficiency is made and oral iron supplements prescribed. Dolores' symptoms are eliminated within a couple of weeks and the remainder of her pregnancy progresses without difficulty.

Describe the structure of a molecule of hemoglobin and explain the role played by iron in the transport of oxygen.

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

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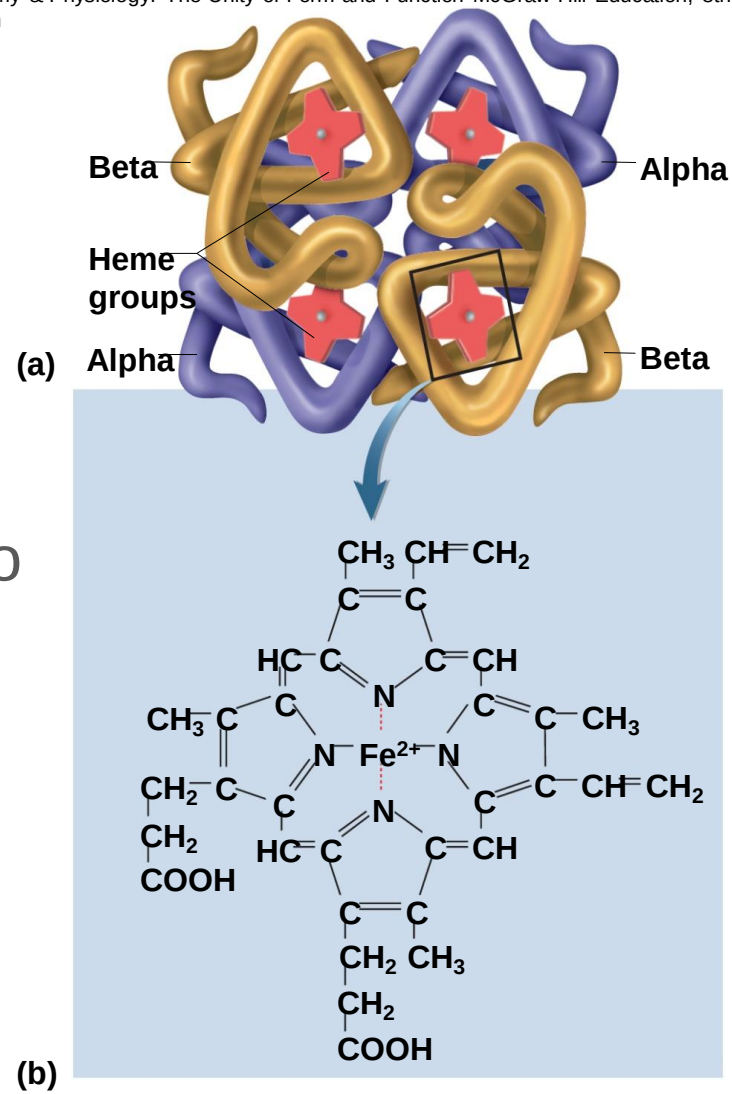

Figure 18.5 a-b

A Case of Iron Deficiency Anemia

by
David F. Dean, Department of Biology, Spring Hill College

How is iron stored and transported in the body?

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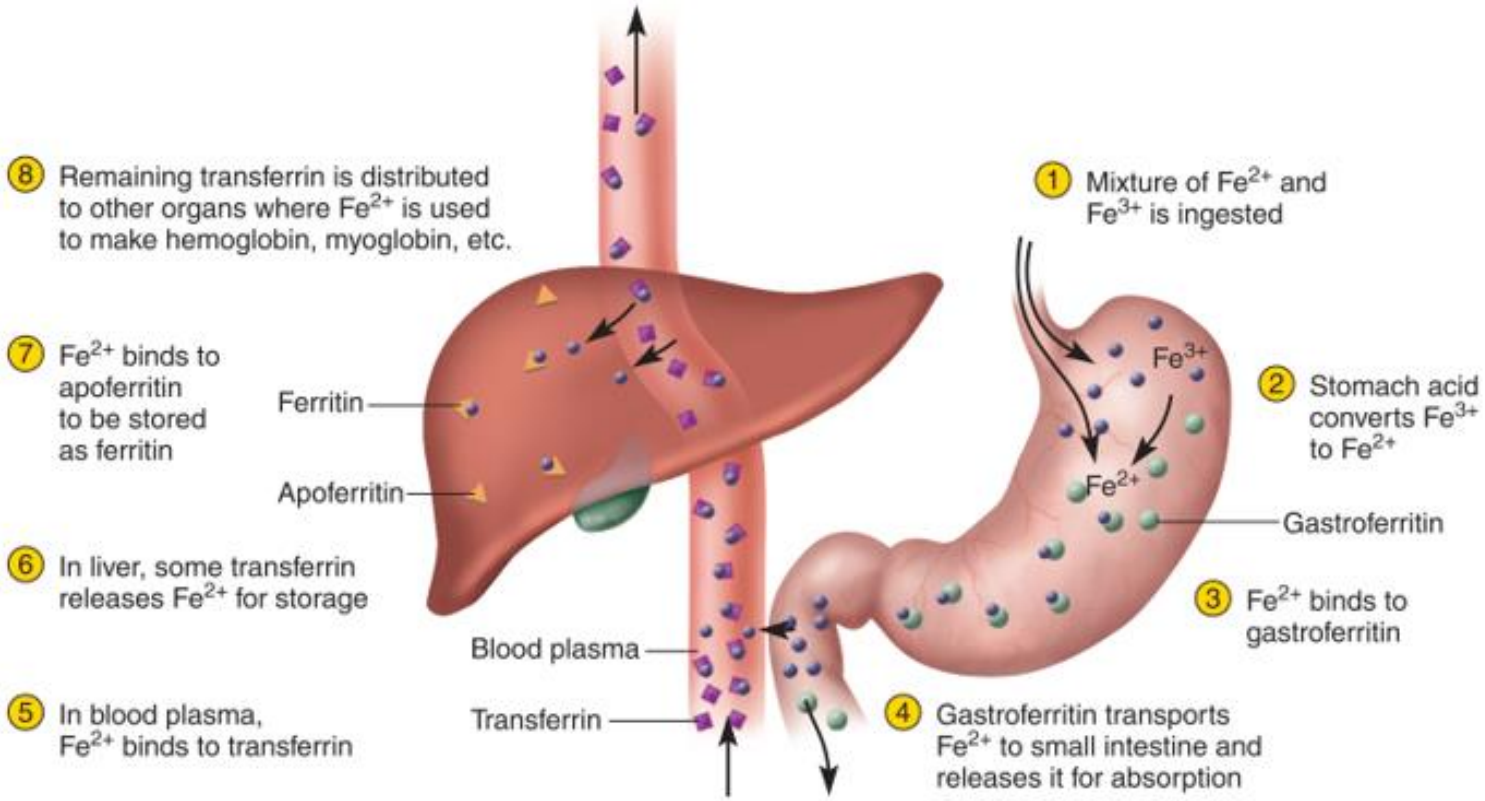

Nutritional Needs for Erythropoiesis

- **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[*gastro* = stomach; *ferrit* = iron; *in* = protein]** 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[*apo* = separated from; *ferrit* = iron; *in* = protein]** binds to create **ferritin** for storage

Iron Metabolism

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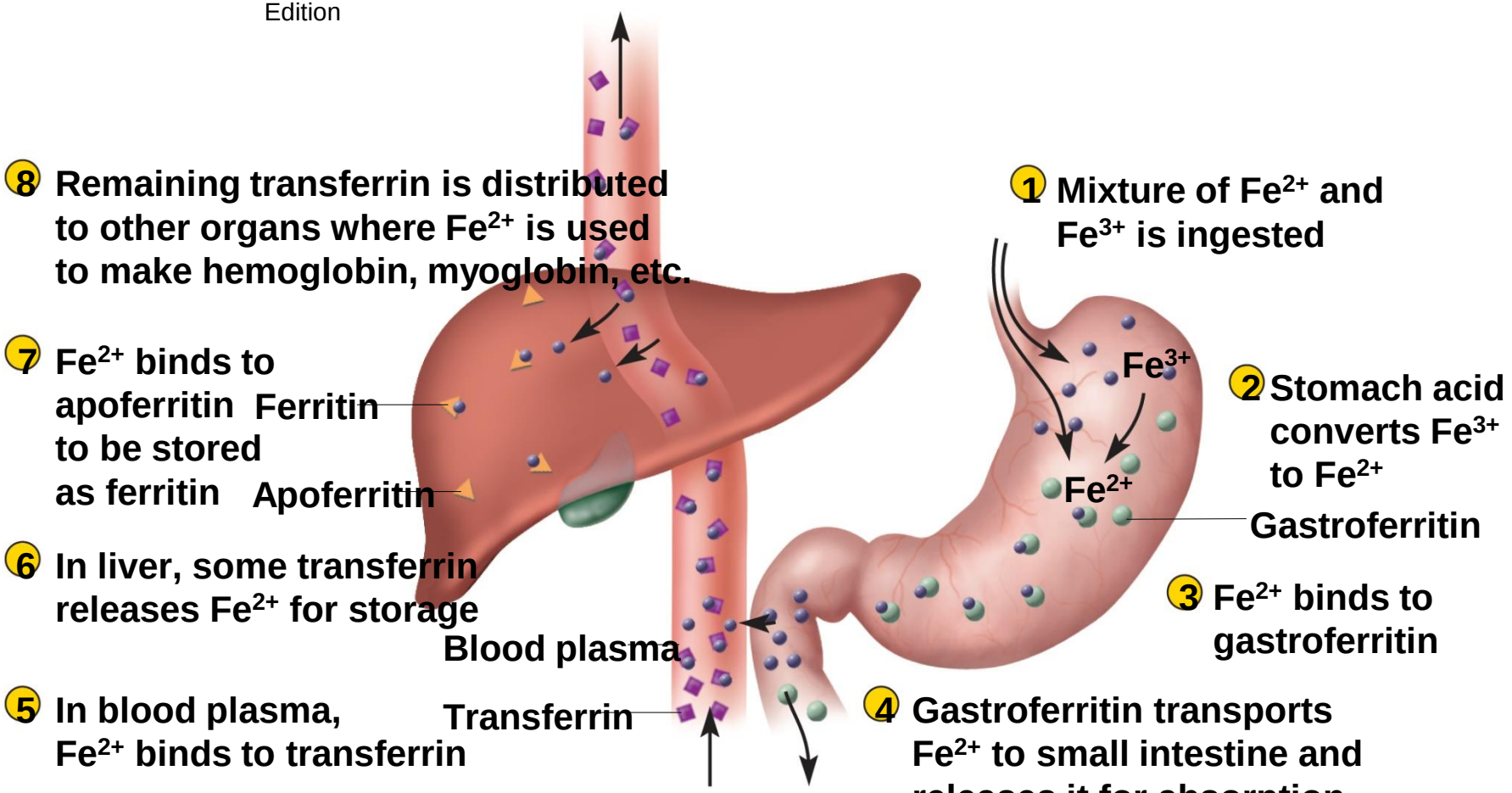

Figure 18.7

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[***cerulo*** **= blue-green, the color of oxidized copper;** ***plasm*** **= blood plasma;** ***in*** **= protein**]

A Case of Iron Deficiency Anemia

by
David F. Dean, Department of Biology, Spring Hill College

What is Iron Deficiency Anemia (ida) and how frequently does it occur?

A Case of Iron Deficiency Anemia

by
David F. Dean, Department of Biology, Spring Hill College

What What are the most common causes of ida? Why are women more prone to ida than men?

A Case of Iron Deficiency Anemia

by
David F. Dean, Department of Biology, Spring Hill College

What are the red blood cell indices, and what tests are diagnostic for ida? How is ida treated and prevented?

Erythrocyte Homeostasis

- **negative feedback** control
  - drop in RBC count causes kidney **hypoxemia [*hyp* = below normal; *ox* = oxygen; *emia* = blood condition]**
  - 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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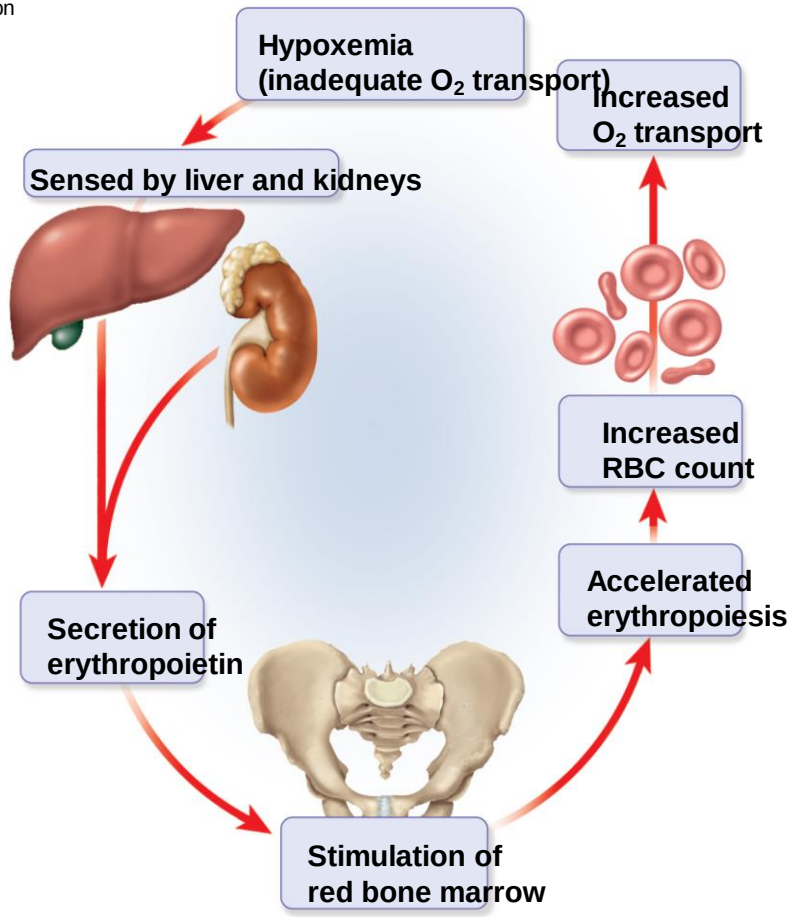


Figure 18.8

Erythrocytes Death and Disposal

- RBCs lyse in narrow channels in **spleen**
- **Hemolysis**(***hemo* = blood; *lysis* = splitting, breakdown**), the rupture of RBCs, releases hemoglobin and leaves empty plasma membranes
- macrophages in spleen
  - digest membrane bits
  - separate heme from globin
    - **globins** hydrolyzed into **amino acids**
    - **iron** removed from **heme**
      - heme pigment converted to **biliverdin [*bili* = bile; *verd* = green; *in* = substance]**(green)
      - biliverdin converted to **bilirubin[*bili* = bile; *rub* = red; *in* = substance]** (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 Recyc

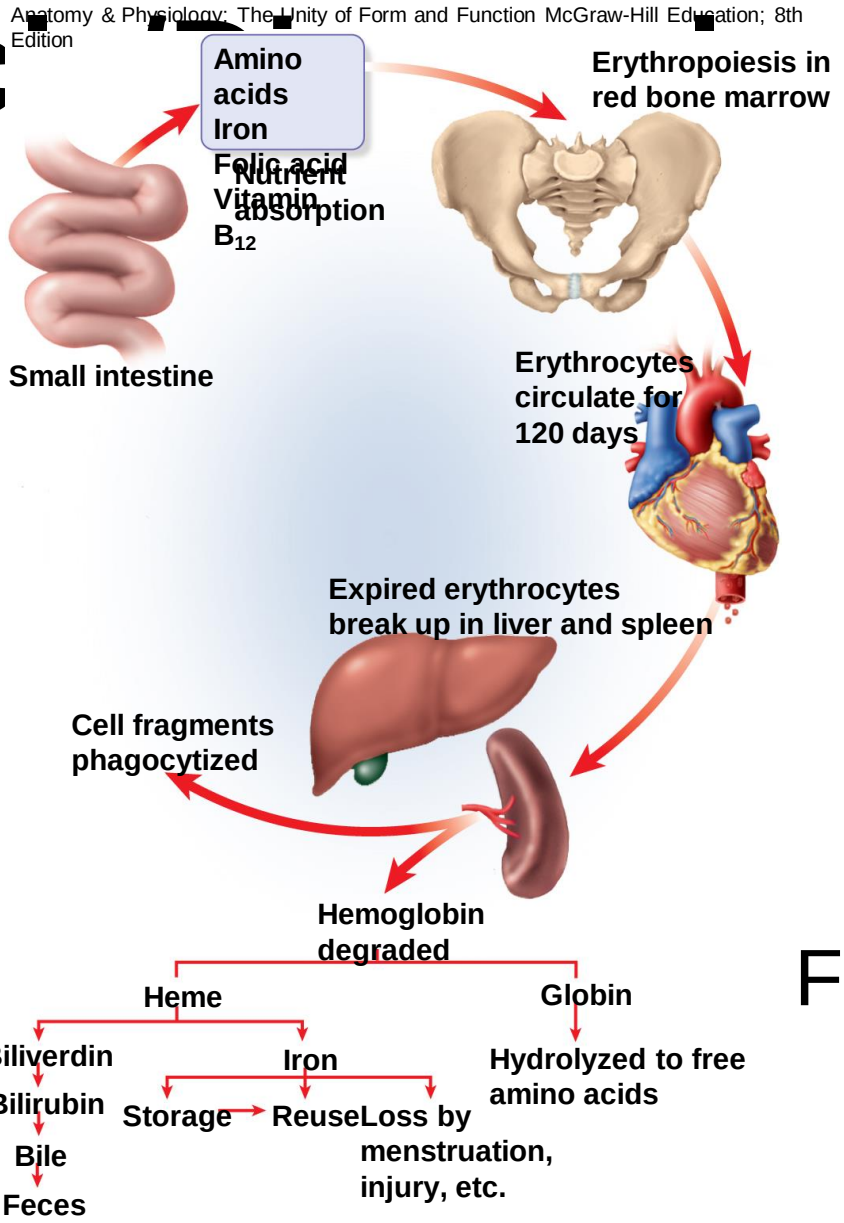


Figure 18.9

Al-Farabi Kazakh National University
Higher School of Medicine

Circulatory System

-Blood

PART III

LEARNING OUTCOMES

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

- ❑ ***Explain the function of leukocytes in general and the individual role of each leukocyte type;***
- ❑ ***describe the appearance and relative abundance of each type of leukocyte;***
- ❑ ***describe the formation and life history of leukocytes; and***
- ❑ ***discuss the types, causes, and effects of leukocyte excesses and deficiencies.***

Defenses Against Pathogens

- **pathogens [*patho* = disease, suffering; *gen* = producing]**– environmental agents capable of producing disease
  – infectious organisms, toxic chemicals, and radiation
- **three lines of defenses** against pathogens:

– **first line of defense** – external barriers, skin and mucous membranes

– **second line of defense** – several nonspecific defense mechanisms
  - **leukocytes** and macrophages, antimicrobial proteins, immune surveillance, inflammation, and fever
  - effective against a broad range of pathogens

– **third line of defense** – the immune system
  - defeats a pathogen, and leaves the body of a ‘memory’ of it so it can defeat it faster in the future

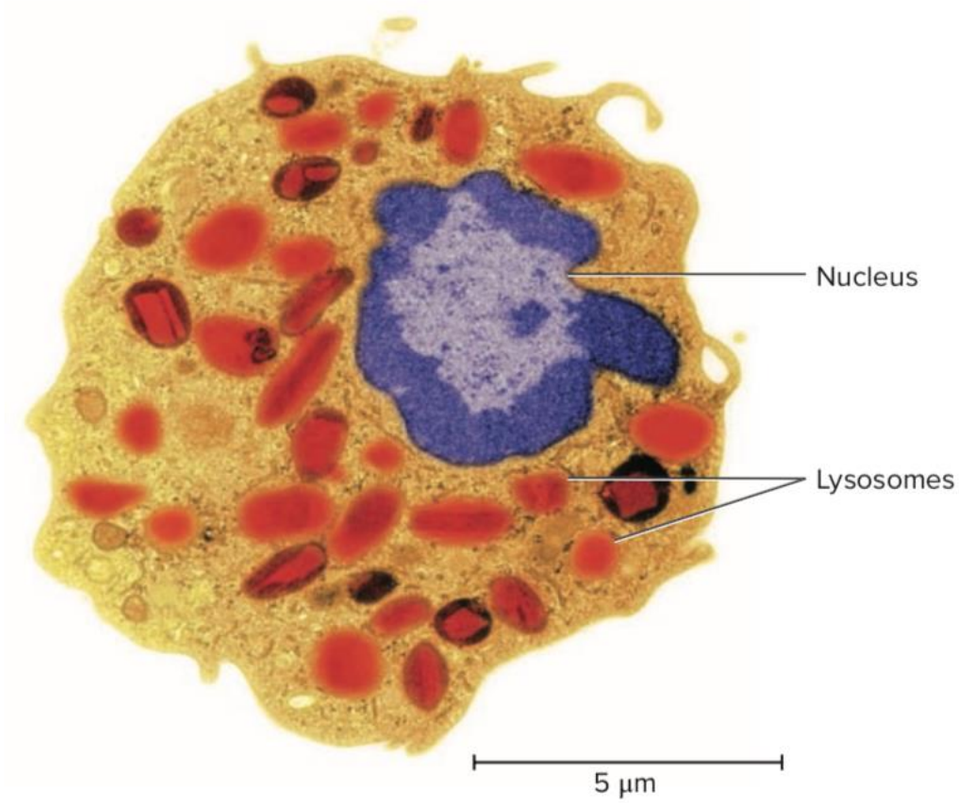
Leukocytes and Macrophages

- **phagocytes [phago- eating,cyt- cell]**– phagocytic cells with a voracious appetite for foreign matter

- five types of leukocytes
  - **neutrophils**
  - **eosinophils**
  - **basophils**
  - **monocytes**
  - **lymphocytes**

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—-*azuro* = blue; *philic* = loving**) granules
  – inconspicuous so cytoplasm looks clear
  – granulocytes have **specific granules** that contain enzymes and other chemicals employed in defense against pathogens



Granulocytes

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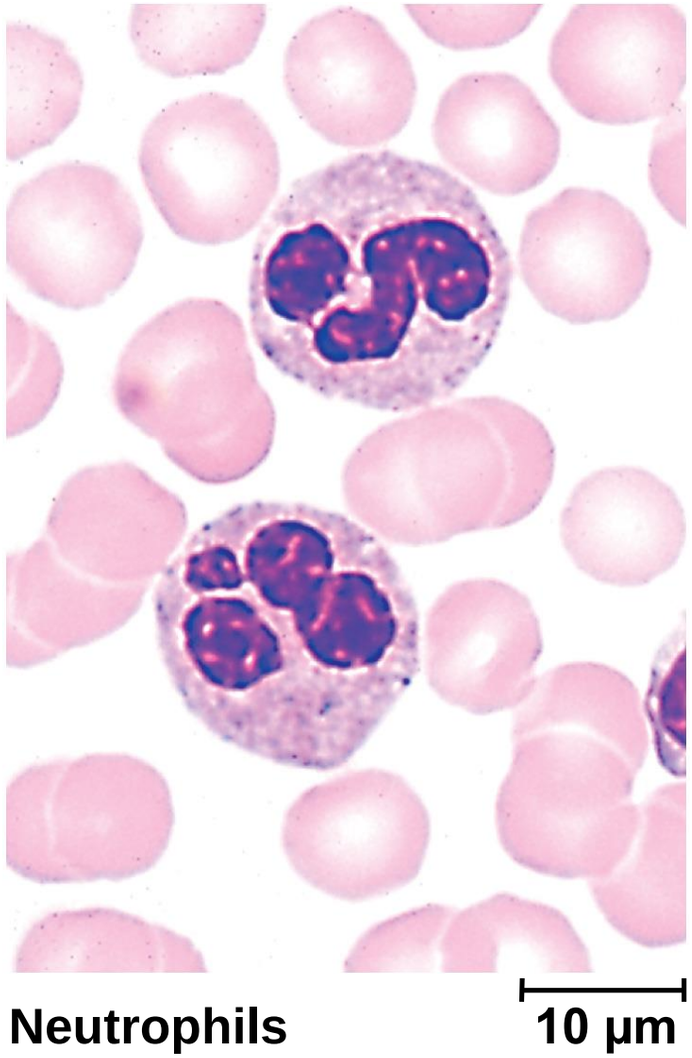

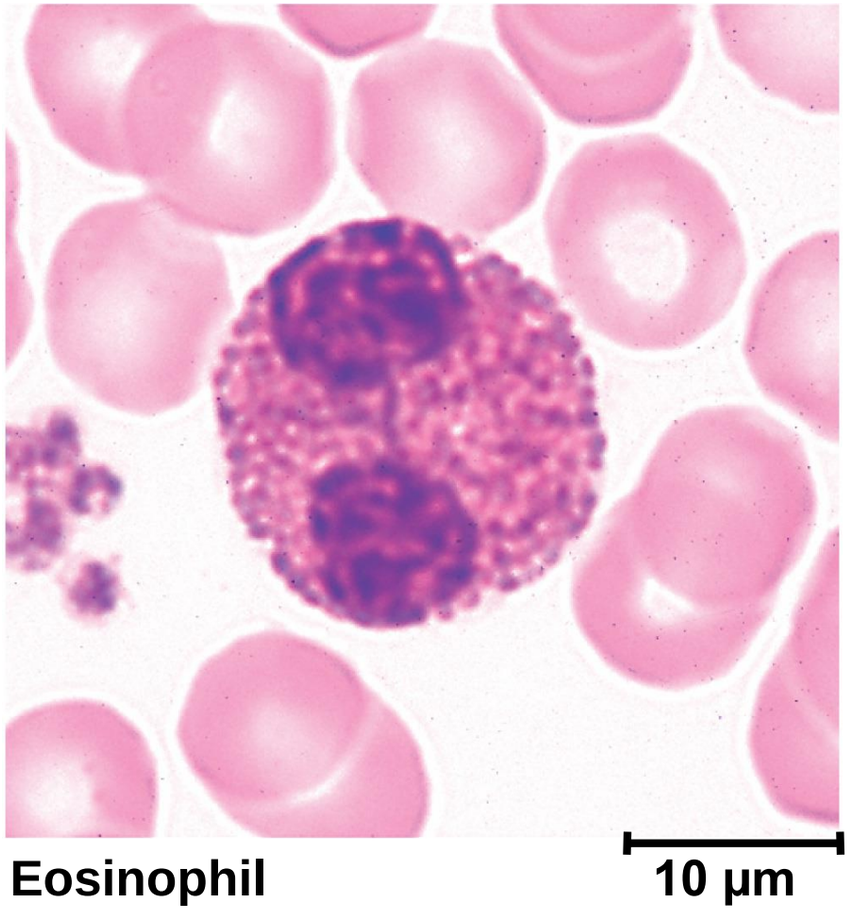

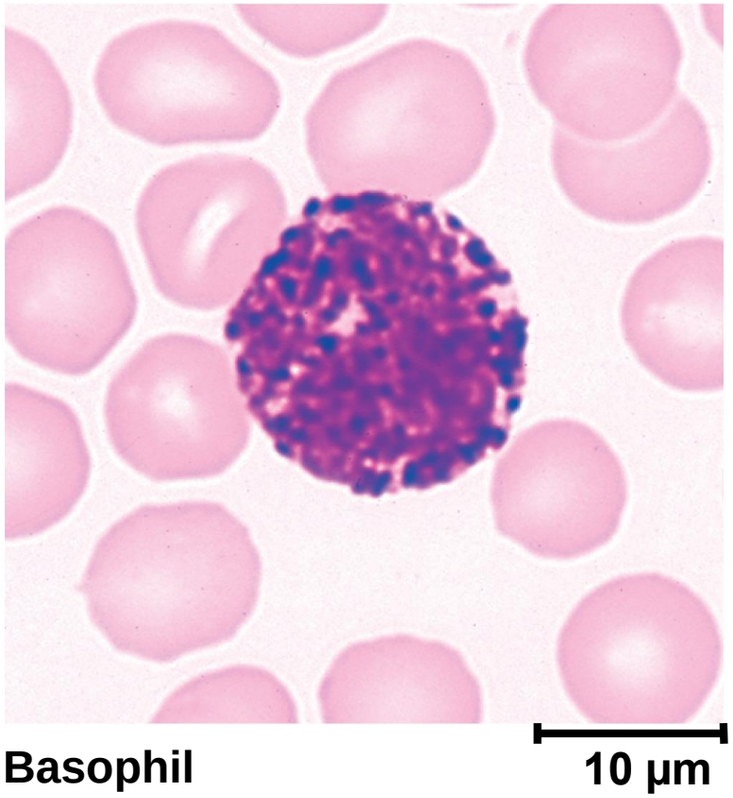

Figure TA 18.1

Figure TA 18.2

Figure TA 18.3

Agranulocytes

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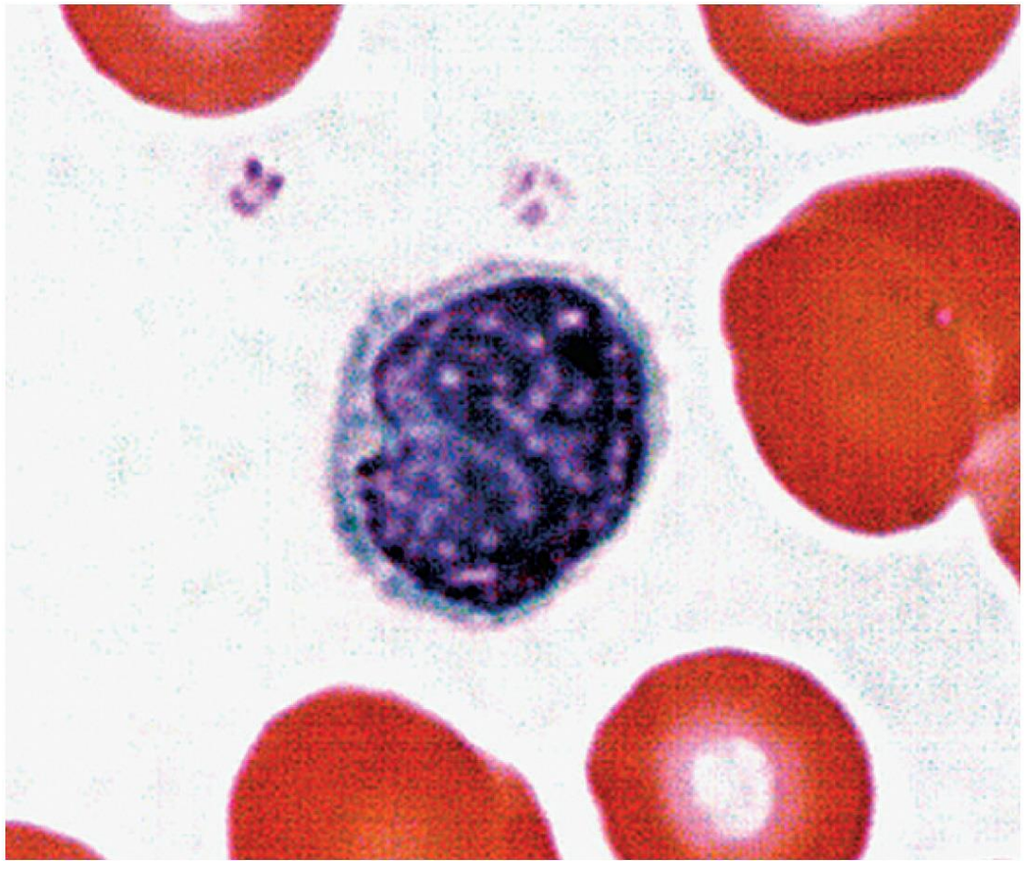
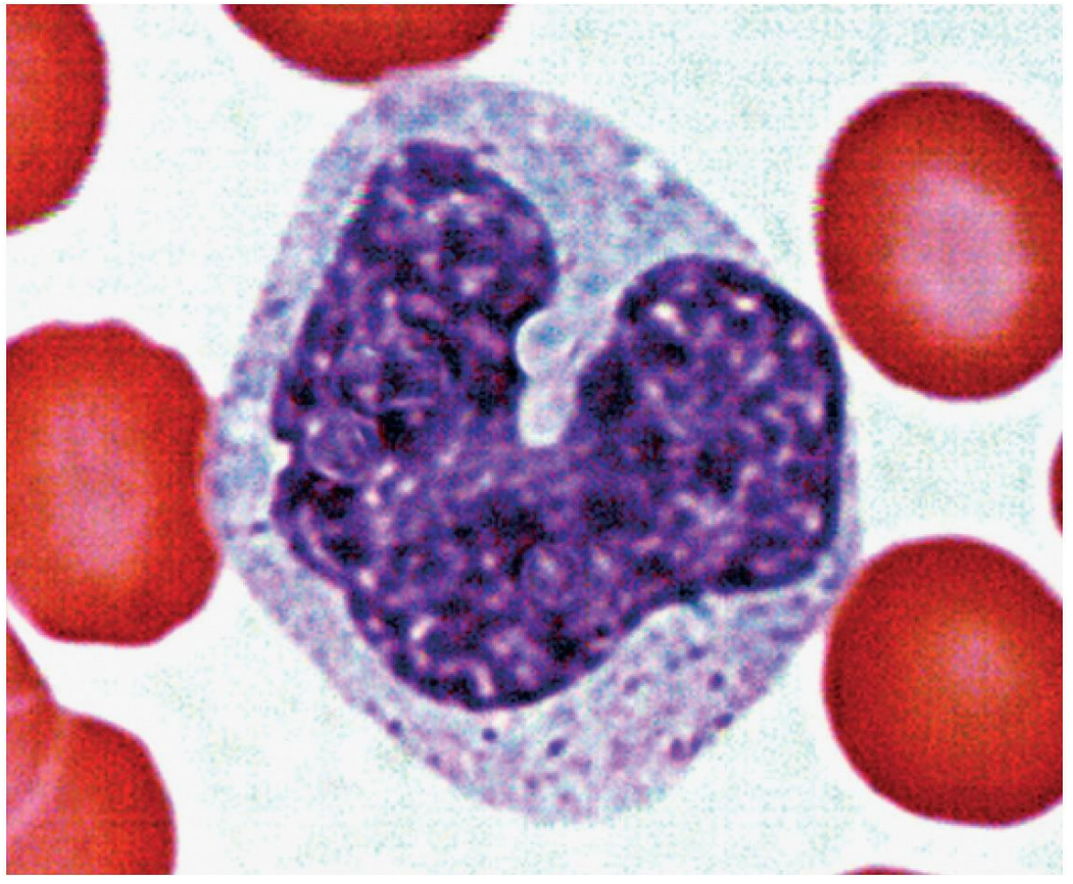


Lymphocyte



Monocyte

both: Michael Ross/Photo Researchers, Inc.

Figure TA 18.4

Figure TA 18.5

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

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

Neutrophils

- wander in connective tissue killing bacteria
  – phagocytosis and digestion
  – produces a cloud of bactericidal chemicals
- create a **killing zone**
  – degranulation
    - lysosomes discharge into tissue fluid
  – **respiratory burst** – neutrophils rapidly absorb oxygen
    - **toxic chemicals** are created ($O_2^{\bullet -}$, H_2O_2, HClO)
  – kill more bacteria with toxic chemicals than phagocytosis

Eosinophils

- found especially in the mucous membranes
- stand guard against **parasites**, **allergens** (allergy causing agents), and other pathogens
- kill tapeworms and roundworms by producing superoxide, hydrogen peroxide, and toxic proteins
- promote action of **basophils** and **mast cells**
- phagocytize **antigen-antibody complexes**
- limit action of **histamine** and other inflammatory chemicals

Basophils

- secrete chemicals that aid mobility and action of WBC other leukocytes
  - **leukotrienes** – activate and attract neutrophils and eosinophils
  - **histamine** – a vasodilator which increases blood flow
    - speeds delivery of leukocytes to the area
  - **heparin** – inhibits the formation of clots
    - would impede leukocyte mobility

- **mast cells** also secrete these substances
  - type of connective tissue cell very similar to basophils

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)**

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

Explain the meaning and relevance of the combining form* myelo-** ***seen in so many of these cell names.

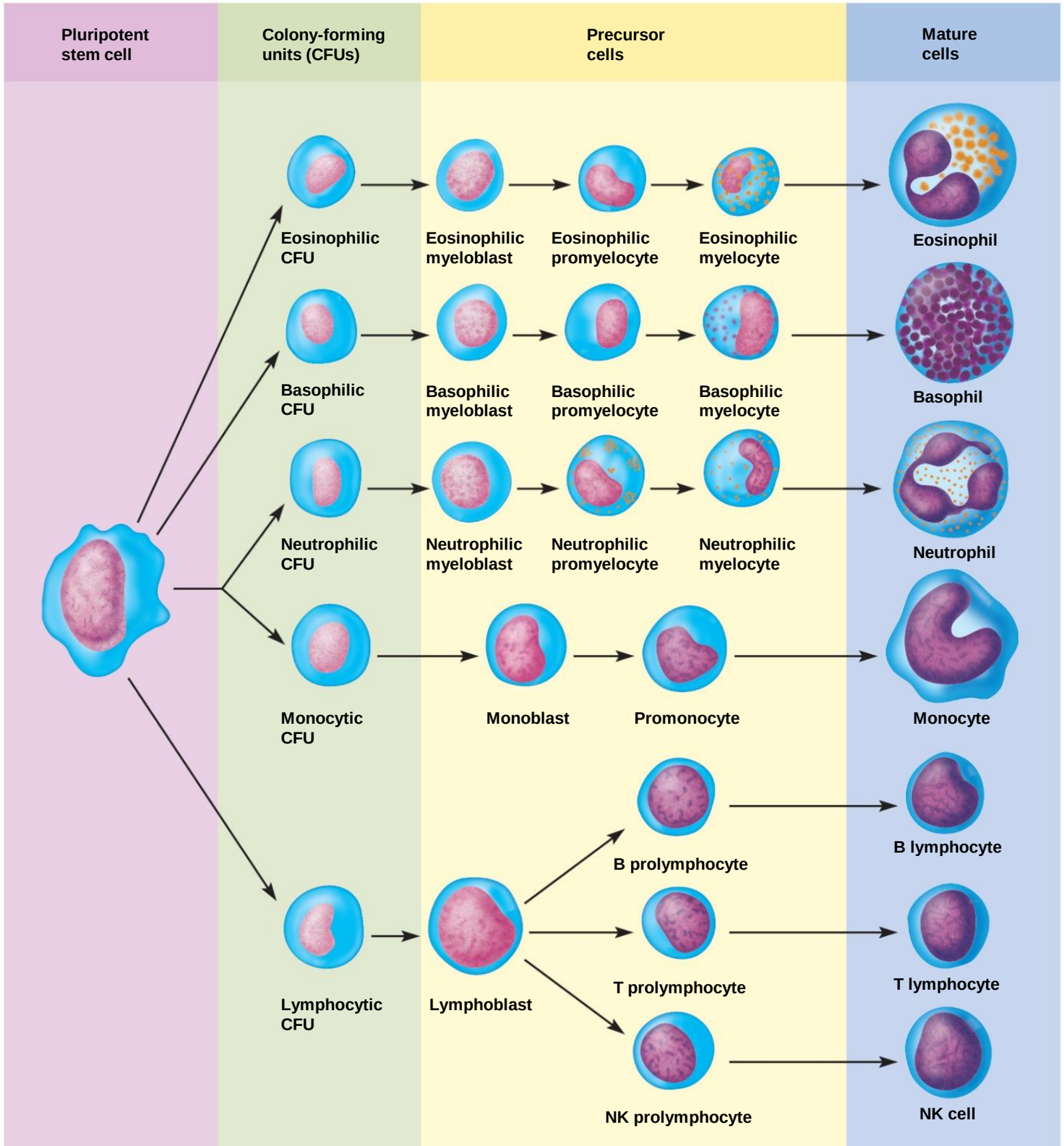


Figure 18.18

▶▶▶APPLY WHAT YOU KNOW

It is sometimes written that RBCs do not live as long as WBCs because RBCs do not have a nucleus and therefore cannot repair and maintain themselves. Explain the flaw in this argument.

DEEPER INSIGHT 18.4

CLINICAL APPLICATION

The Complete Blood Count

One of the most common clinical procedures in both routine physical examinations and the diagnosis of disease is a *complete blood count (CBC).* The CBC yields a highly informative profile of data on multiple blood values: the number of RBCs, WBCs, and platelets per microliter of blood; the relative numbers (percentages) of each WBC type, called a *differential WBC count;* hematocrit; hemoglobin concentration; and various *RBC indices* such as RBC size *(mean corpuscular volume, MCV)* and hemoglobin concentration per RBC *(mean corpuscular hemoglobin, MCH).*

DEEPER INSIGHT 18.4

CLINICAL APPLICATION

The Complete Blood Count

RBC and WBC counts used to require the microscopic examination of films of diluted blood on a calibrated slide, and a differential WBC count required examination of stained blood films. Today, most laboratories use *electronic cell counters.* These devices draw a blood sample through a very narrow tube with sensors that identify cell types and measure cell sizes and hemoglobin content. These counters give faster and more accurate results based on much larger numbers of cells than the old visual methods. However, cell counters still misidentify some cells, and a medical technologist must review the results for suspicious abnormalities and identify cells that the instrument cannot.

DEEPER INSIGHT 18.4

CLINICAL APPLICATION

The Complete Blood Count

The wealth of information gained from a CBC is too vast to give more than a few examples here. Various forms of anemia are indicated by low RBC counts or abnormalities of RBC size, shape, and hemoglobin content. A platelet deficiency can indicate an adverse drug reaction. A high neutrophil count suggests bacterial infection, and a high eosinophil count suggests an allergy or parasitic infection. Elevated numbers of specific WBC types or WBC stem cells can indicate various forms of leukemia. If a CBC does not provide enough information or if it suggests other disorders, additional tests may be done, such as coagulation time and bone marrow biopsy.

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 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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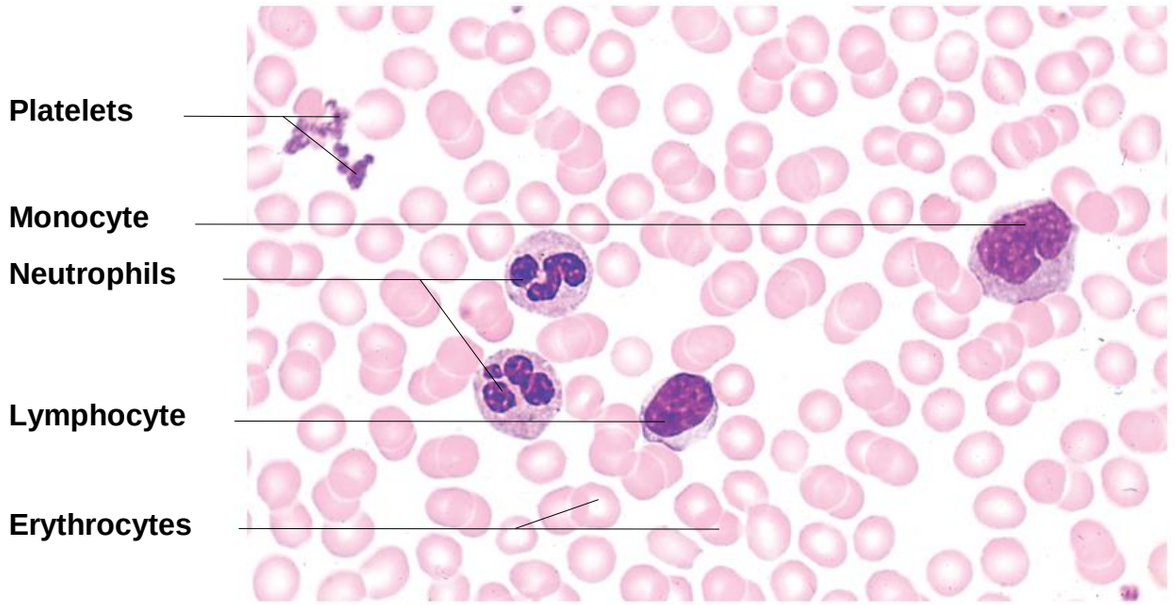
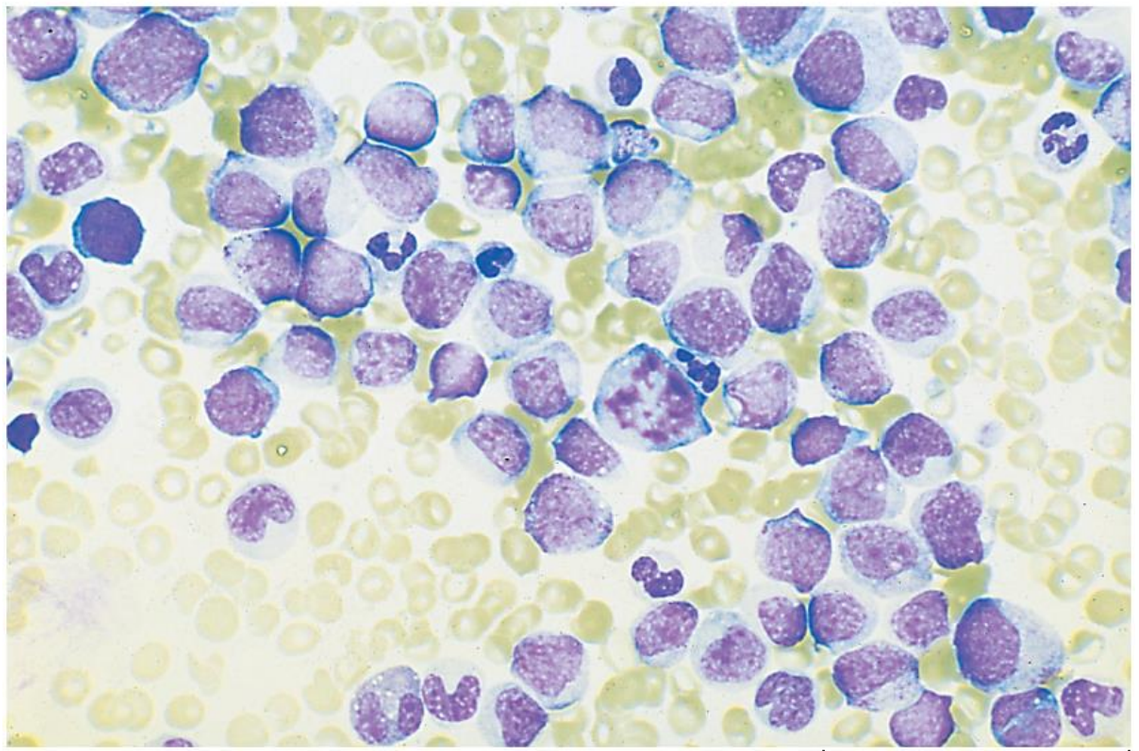


(a)



(b)

With all these extra white cells, why isn't the body's infection-fighting capability increased in leukemia?

A Case of Pharyngitis

by
David F. Dean, Department of Biology, Spring Hill College

Case Presentation

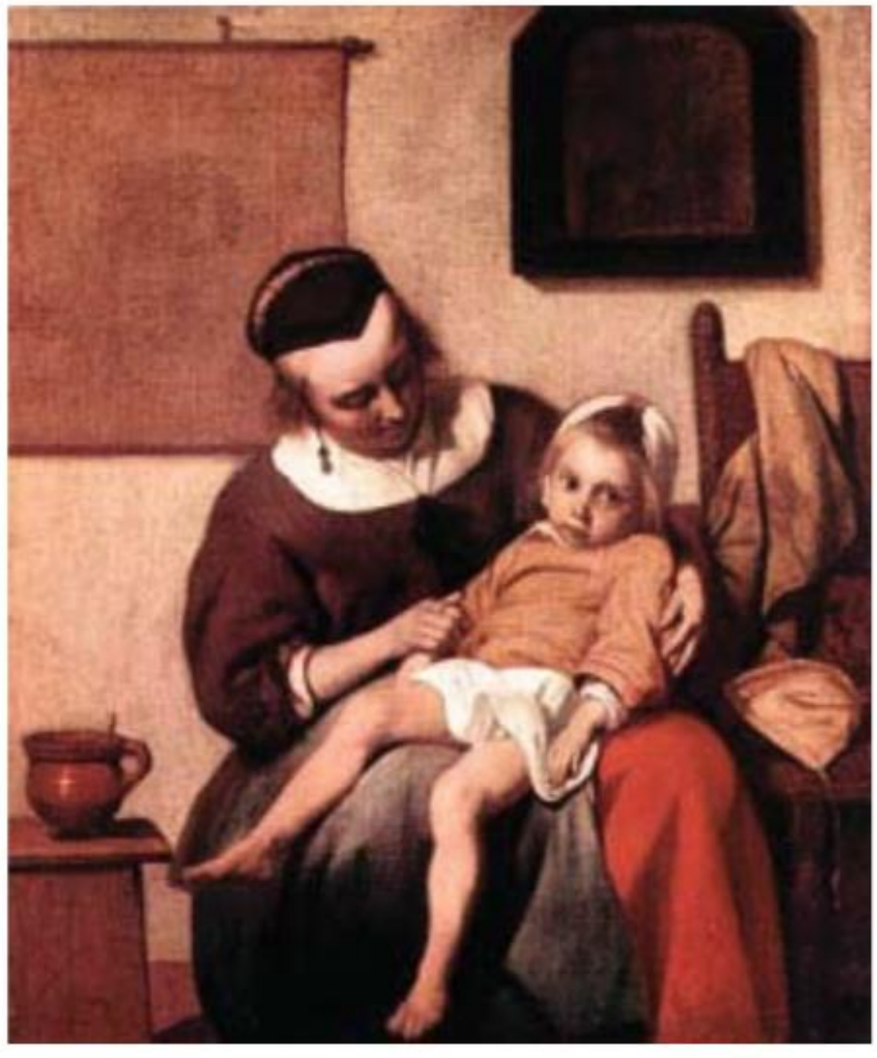
Jason Hornbuckle is not a happy little boy. For the past 12 hours he has complained of pain when he swallows, has a headache, and has vomited twice. His mother decides to take the seven-year-old to his pediatrician. Upon examining Jason, the doctor finds that Jason's pharynx, tonsils, and uvula are swollen and erythematous (red) and his tonsils are studded with white areas of exudate. He is febrile (temperature 40.3 degrees centigrade) with tender, bilateral, cervical lymphadenopathy (enlarged lymph nodes).

A Case of Pharyngitis

by
David F. Dean, Department of Biology, Spring Hill College

Case Presentation

A Complete Blood Count (cbc) performed on a sample of Jason's blood reveals that he has a leukocytosis (increased number of wbcs) due to a neutrophila (increased number of neutrophils).



A Case of Pharyngitis

by
David F. Dean, Department of Biology, Spring Hill College

Case Presentation

Jason is diagnosed as having acute bacterial pharyngitis and treated with phenoxymethyl penicillin for five days. A throat swab taken before starting antibiotics grows beta-hemolytic streptococci (Group A). After three days of treatment, Jason's temperature has returned to normal and he has made an uneventful recovery.

A Case of Pharyngitis

by
David F. Dean, Department of Biology, Spring Hill College

The pediatrician described Jason's pharynx, uvula, and tonsils as swollen and red. What are the four *cardinal signs of inflammation,* and how does each relate to changes in the blood vessels at a site of inflammation?

A Case of Pharyngitis

by
David F. Dean, Department of Biology, Spring Hill College

redness **heat**	**histamine and other vasoactive chemicals cause vascular smooth muscle to relax, producing vasodilation with increased blood flow to the site of injury.**
swelling	**the blood vessels become more permeable (leaky), resulting in the formation of edema (swelling).**
pain.	**the pressure applied by edema to pain receptors, and also the direct stimulation of those receptors by other chemicals released from the blood plasma.**

All four of these changes will be seen locally at sites of inflammation, and they occur in response to changes in the small blood vessels (arterioles, capillaries, and venules) at the site.

A Case of Pharyngitis

by

David F. Dean, Department of Biology, Spring Hill College

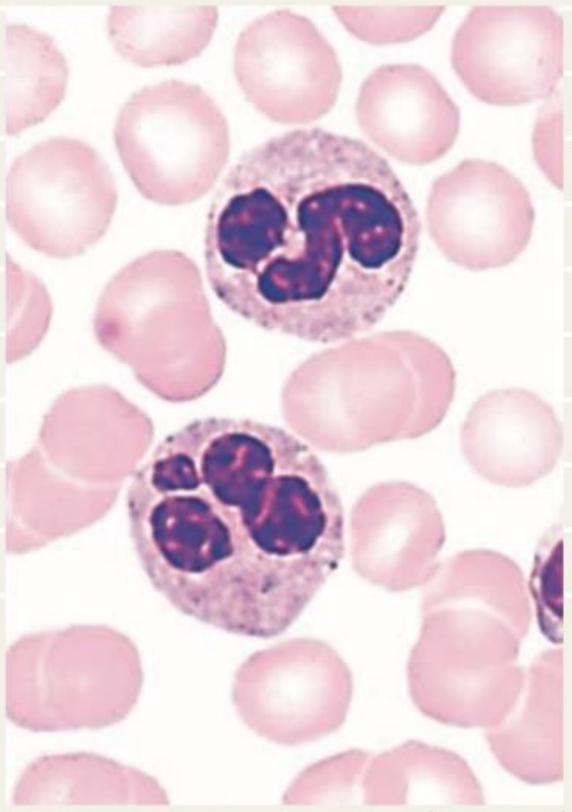
The exudate on Jason's tonsils consisted primarily of neutrophils, and the Complete Blood Count that was performed indicated that the number of neutrophils in his circulation was increased. What role do neutrophils play in the resolution of a bacterial infection?

A Case of Pharyngitis

by

David F. Dean, Department of Biology, Spring Hill College

Neutrophils	
Differential count (% of WBCs)	60% to 70%
Mean absolute count	4,150 cells/µL
Diameter	9–12 µm
Appearance*	
Nucleus usually with 3–5 lobes in S- or C-shaped array	
Fine reddish to violet specific granules in cytoplasm	
Variations in Number	
Increase in bacterial infections	
Functions	
Phagocytize bacteria	
Release antimicrobial chemicals	



Neutrophils 10 µm

A Case of Pharyngitis

by
David F. Dean, Department of Biology, Spring Hill College

What is the mechanism by which fever is induced and what are its benefits in terms of combating an infection?

Fever

- **fever** – an abnormally elevation of body temperature
  - results from trauma, infections, drug reactions, brain tumors, and other causes
- fever is an adaptive defense mechanism, in moderation, does more good than harm
  - promotes interferon activity
  - elevates metabolic rate and accelerates tissue repair
  - inhibits reproduction of bacteria and viruses
- initiation of fever by **exogenous pyrogens** – fever producing agents
  - glycolipids on bacterial and viral surfaces
  - attacking neutrophils and macrophages secrete chemicals, interleukins, interferons, and others that act as **endogenous pyrogens**
  - stimulate neurons in the anterior hypothalamus to secrete **prostaglandin E_2**
  - PGE_2 raises hypothalamic set point for body temperature
- stages of fever
  - **onset, stadium, defervescence**

Course of a Fever

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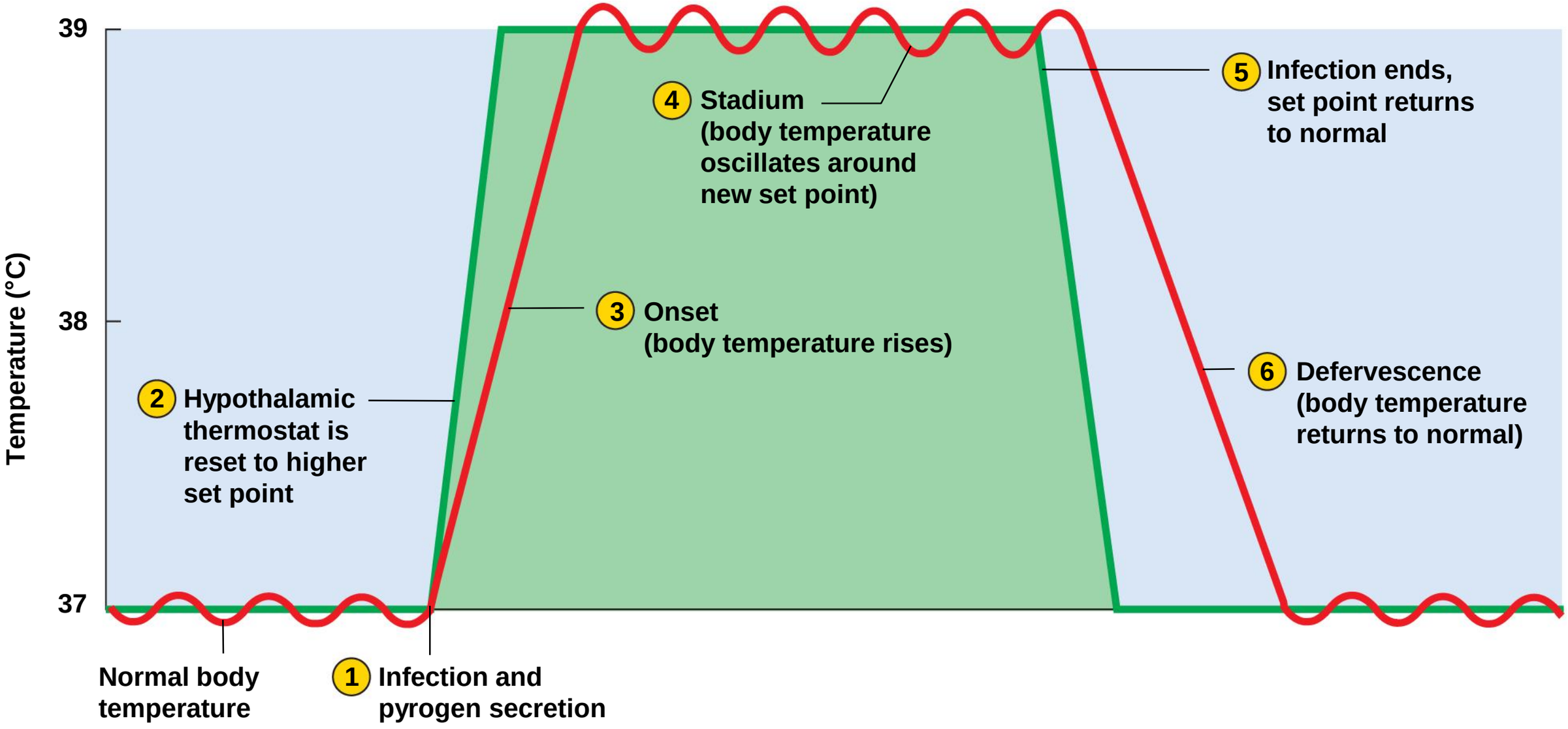

Figure 21.18

A Case of Pharyngitis

by

David F. Dean, Department of Biology, Spring Hill College

What is the mechanism by which the number of circulating white blood cells is increased?

A Case of Pharyngitis

by
David F. Dean, Department of Biology, Spring Hill College

The production of white blood cells in the red bone marrow is termed *leukopoiesis* and it is regulated in part by white blood cells already in the circulation. Active white blood cells engaged in fighting an infection stimulate the production of additional white blood cells by the release of chemicals called *leukopoietins*, thus providing a means by which leukopoiesis is matched to the body's need for white blood cells at a given point in time.

l-Farabi Kazakh National University
Higher School of Medicine

Circulatory System

-Blood

◆ PART IV

Platelets and Hemostasis — The Control of Bleeding

LEARNING OUTCOMES

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

- ❑ ***Describe the body's mechanisms for controlling bleeding;***
- ❑ ***list the functions of platelets;***
- ❑ ***describe two reaction pathways that produce blood clots;***
- ❑ ***explain what happens to blood clots when they are no longer needed;***
- ❑ ***explain what keeps blood from clotting in the absence of injury; and***
- ❑ ***describe some disorders of blood clotting.***

Hemostasis

- **hemostasis[*hemo* = blood; *stasis* = stability]**
- – 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

How is coagulation different from agglutination?

A Case of Thrombocytopenia

by
David F. Dean, Department of Biology, Spring Hill College

Case Presentation

Carolyn Jones is a 40-year-old professor of economics at a small private college in the Midwest. During the past week, Carolyn has felt fatigued and has experienced periods of general weakness. In the past day or so, she has noticed the appearance of small, red dots on her skin and gums, and when she cut herself preparing dinner, the wound bled for what seemed to be a prolonged period of time.

When examined by her physician, Carolyn's platelet count is found to be very low and her blood clotting profile indicates a prolonged clotting time. Carolyn does not have a history of taking any medications, nor does she have a recent history of viral infection. Her physician suspects that Carolyn has Idiopathic Thrombocytopenic Purpura (itp) and prescribes the appropriate course of therapy.

A Case of Thrombocytopenia

by
David F. Dean, Department of Biology, Spring Hill College

How and where are platelets produced in the body ?

Platelets

- **platelets** - small fragments of **megakaryocyte**
  - 2-4 μm diameter; contain "granules"
  - complex internal structure and open **canalicular system**

  They are anucleate and packed with granules, vesicles, microfilaments, microtubules, and occasionally mitochondria.
  - amoeboid[**change ,alternation**] movement and phagocytosis[**eat or ingest**]
- 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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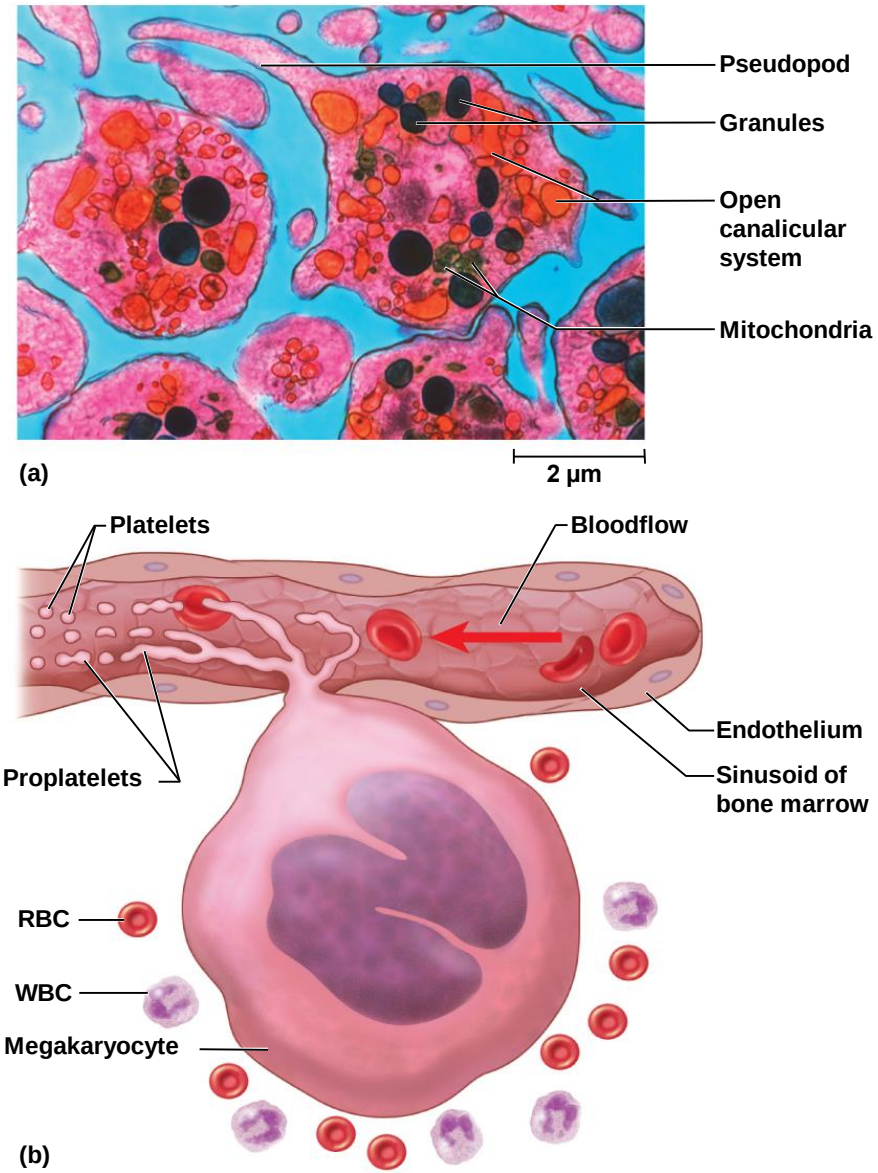

Figure 18.20 a-b

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

Platelet Production -Thrombopoiesis

- **stem cells** (***develop receptors for thrombopoietin, which is primarily produced by cells in liver, kidney, and red bone marrow.***) — 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

A Case of Thrombocytopenia

by
David F. Dean, Department of Biology, Spring Hill College

Describe the role played by platelets in hemostasis ?

Hemostasis

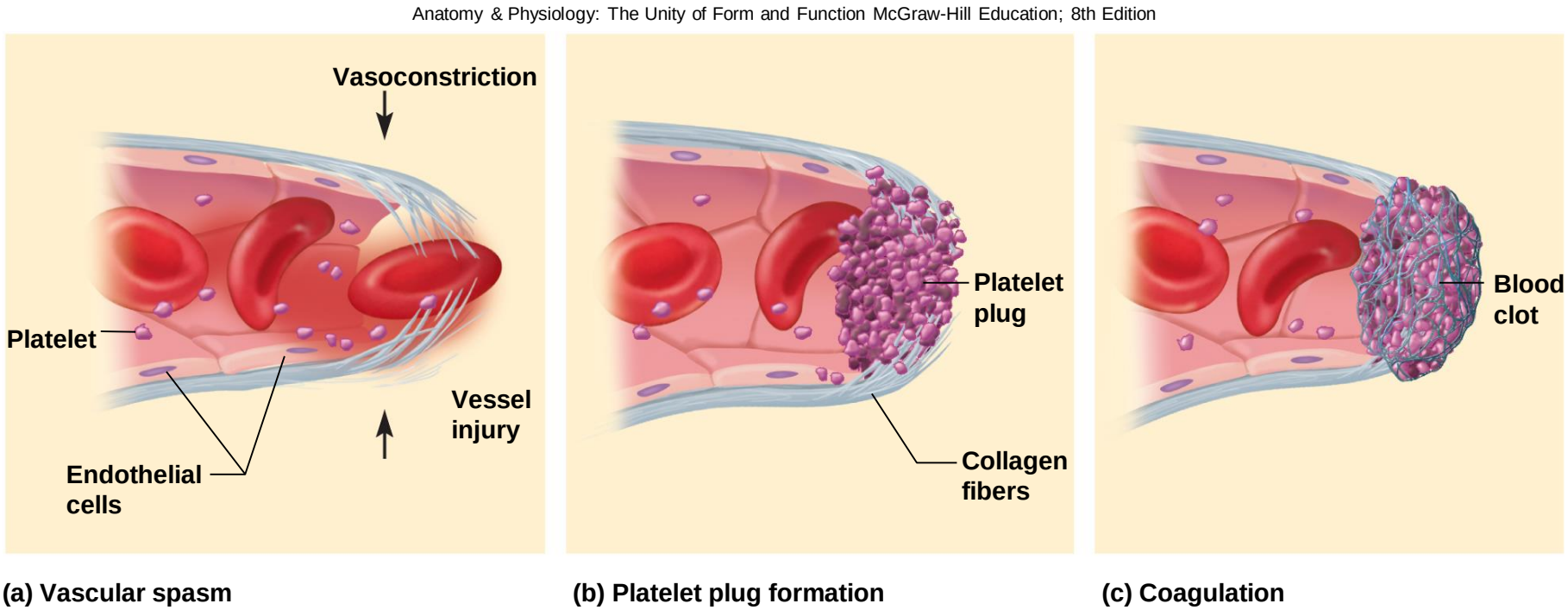

Figure 18.21 a-c

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)

Coagulation Pathways

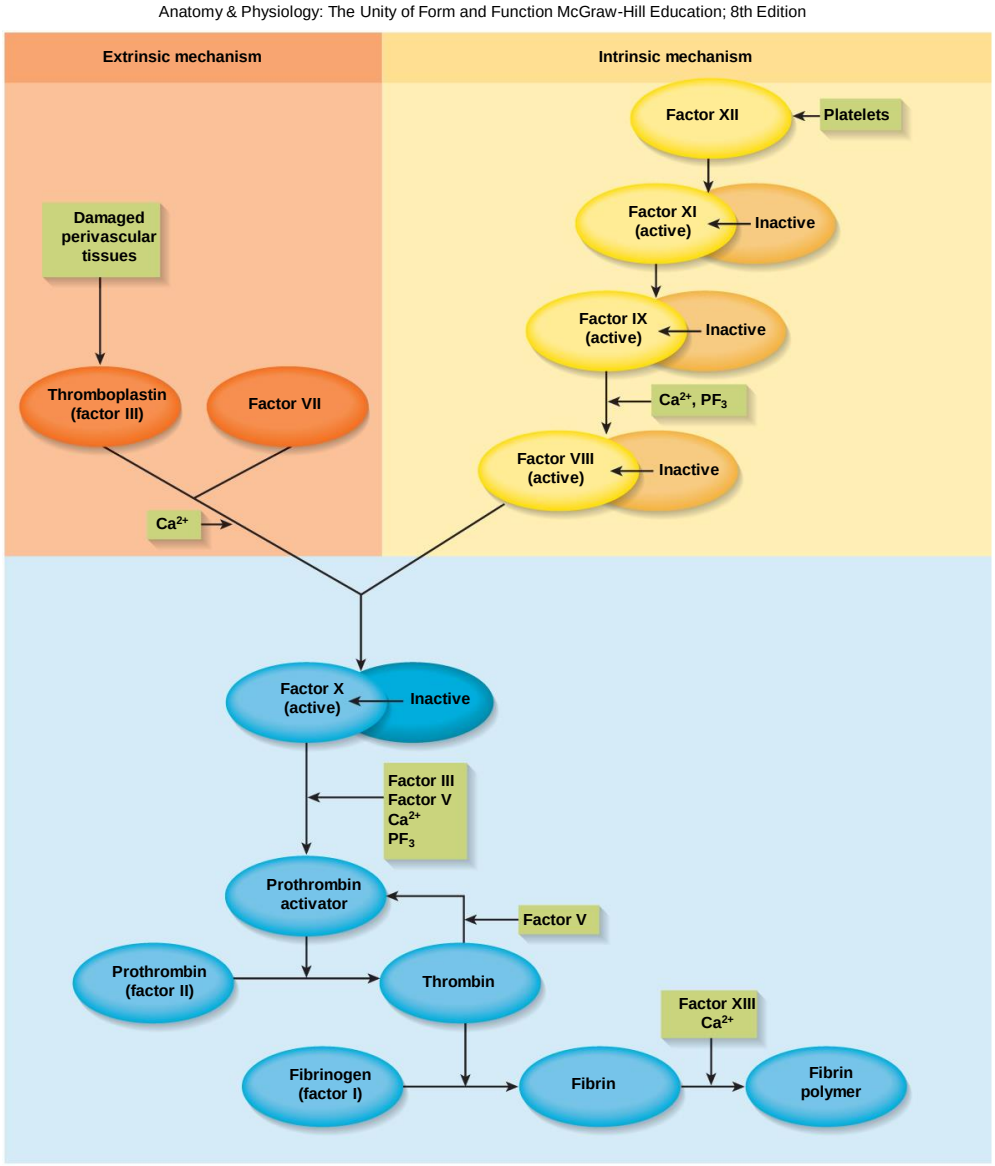

Figure 18.23

extrinsic pathway

- initiated by release of **tissue thromboplastin[*thrombo* = clot; *plast* = forming; *in* = substance]** (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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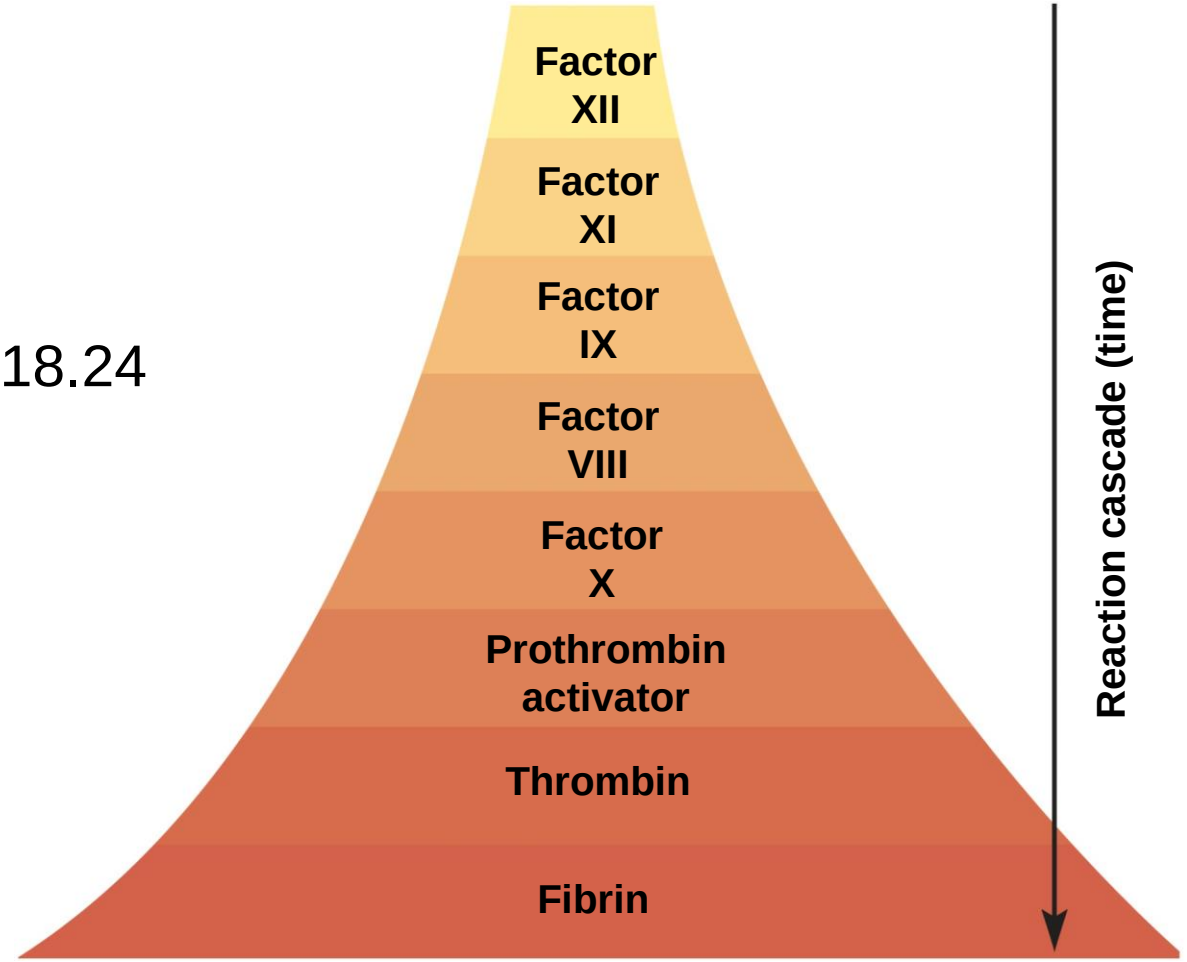
Figure 18.24



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

Hemostasis

How does a blood clot differ from a platelet plug?

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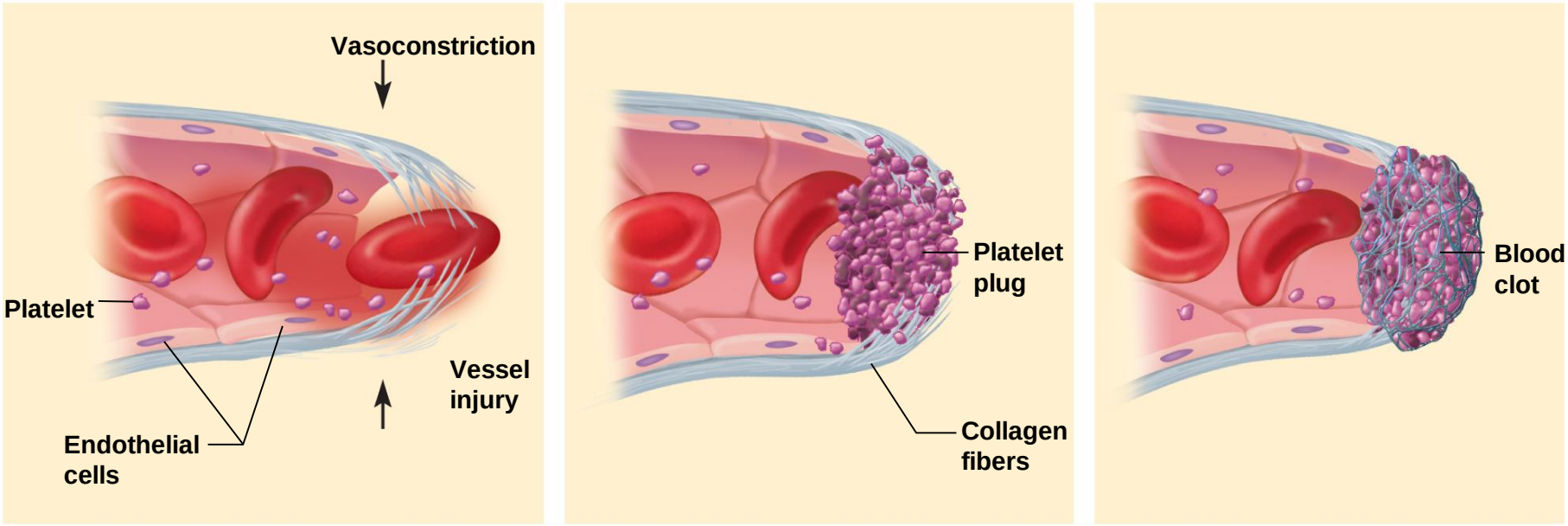

Figure 18.21 a-c

all 3 pathways involve platelets

A Case of Thrombocytopenia

by
David F. Dean, Department of Biology, Spring Hill College

Define thrombocytopenia and list the more common causes of this condition ?

Thrombocytopenia [*thrombo* = clotting; *cyto* = cell; *penia* = deficiency]

A condition in which the number of circulating platelets is less than the normal homeostatic range of 130,000 to 400,000 per cu/ml.

Decreased production of platelets in the red bone marrow due to such disease states as leukemia, aplastic anemia, and toxicity from certain drugs;

Increased destruction of platelets due to such conditions as hepatic cirrhosis, disseminated intravascular coagulation, and severe infection.

Thrombocytopenia can occur briefly following a viral infection, and as the result of an autoimmune disorder called idiopathic thrombocytopenic purpura (ITP).

A Case of Thrombocytopenia

by
David F. Dean, Department of Biology, Spring Hill College

What are the potential consequences of a low platelet count? ?

The principal consequence of a deficiency of circulating platelets is hemorrhage.

A Case of Thrombocytopenia

by
David F. Dean, Department of Biology, Spring Hill College

How might removal of the spleen (splenectomy) result in an increase in the number of circulating platelets ?

SEM of Blood Clot

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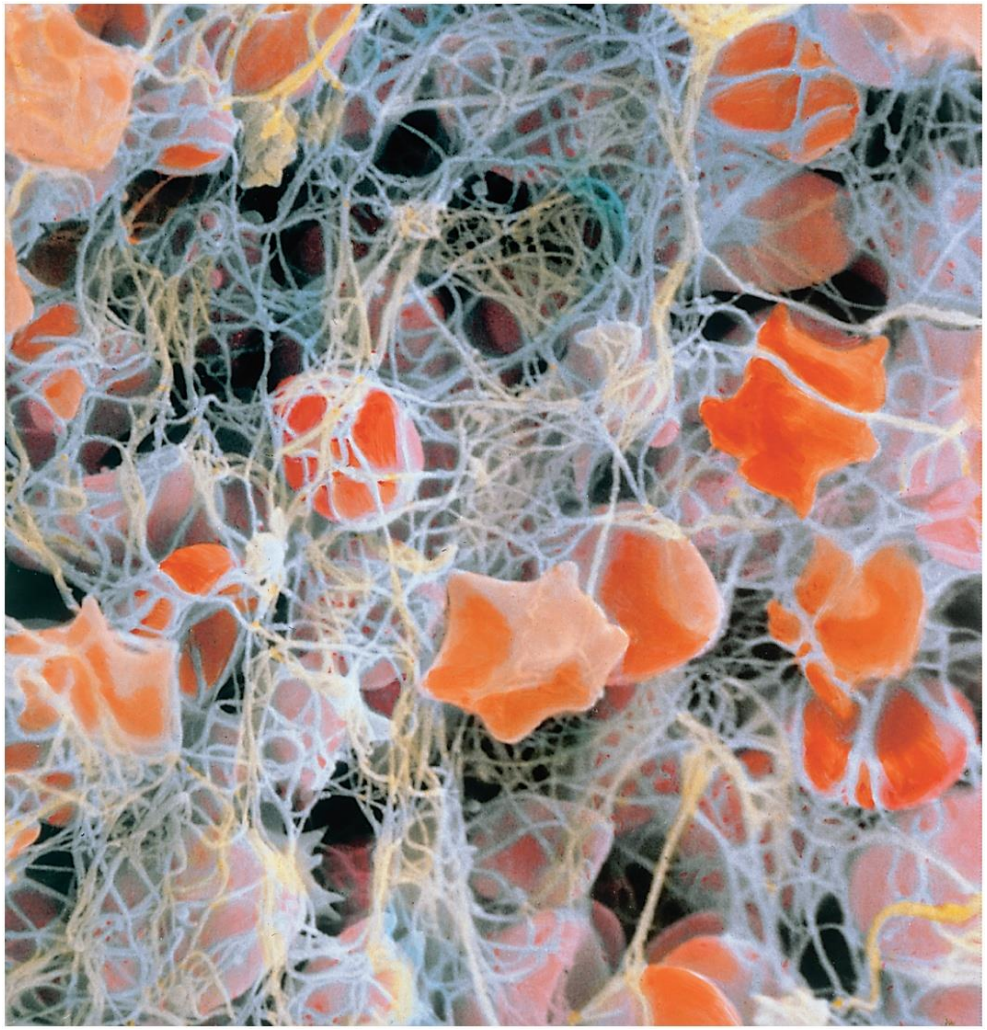
Figure 18.22



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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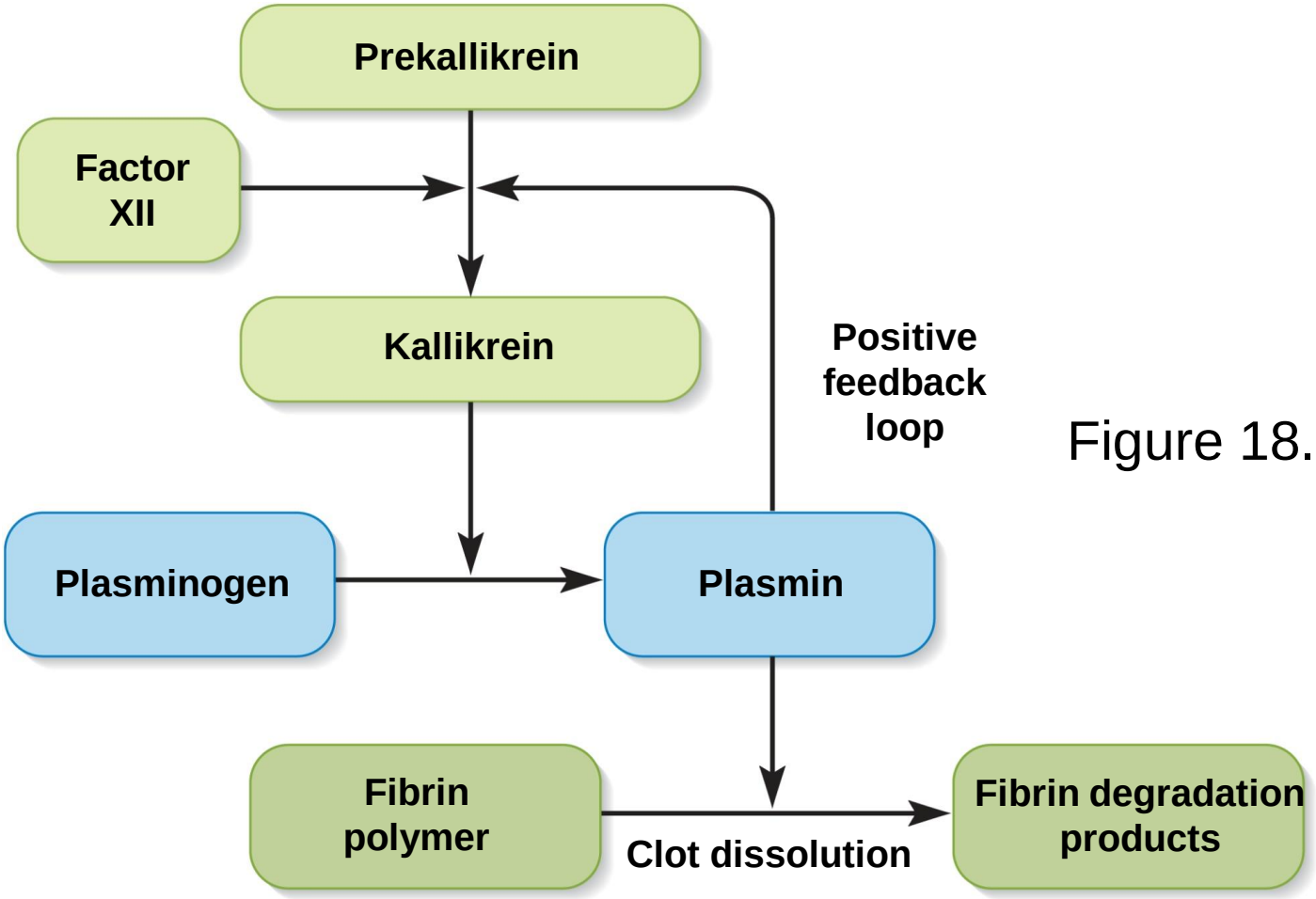

Figure 18.25

- 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
- **hematoma** – masses of clotted blood in the tissues

After you read about hemophilia C later in this chapter, explain whether it would affect the extrinsic mechanism, the intrinsic mechanism, or both.

Coagulation Pathways

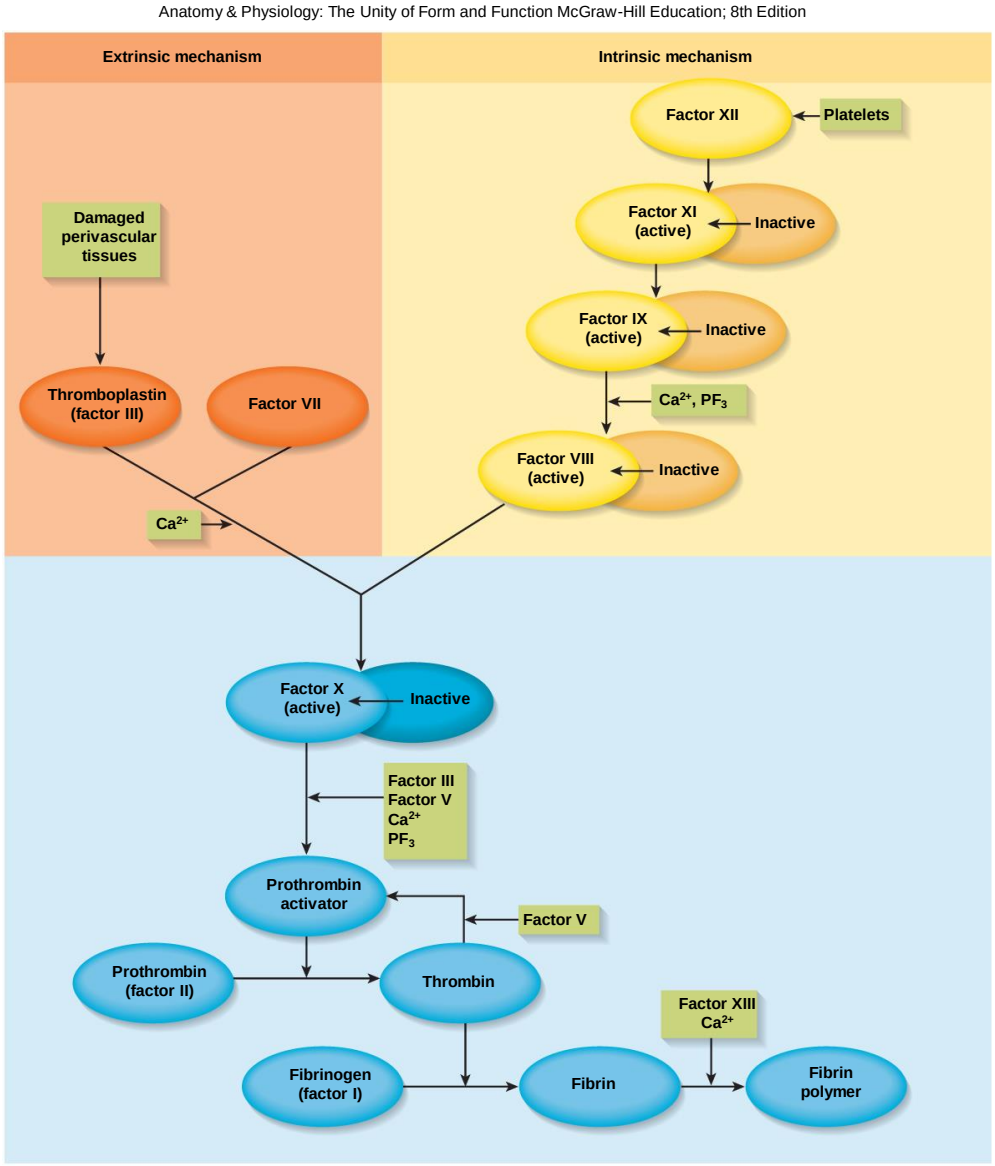

Figure 18.23

extrinsic pathway

- initiated by release of **tissue thromboplastin[*thrombo* = clot; *plast* = forming; *in* = substance]** (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

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