NOTE: Presentations extensively modified for use in MCB 244 & 246 at the University of Illinois by Drs. Kwast & Brown (2013-2014)

PowerPoint® Lecture Presentations prepared by Jason LaPres
Lone Star College—North Harris
Chapter 19 Learning Objectives

1. Describe the components and major functions of blood.
2. Describe the composition and function of plasma.
3. List the characteristics and functions of erythrocytes, including hemoglobin, and describe erythrocyte formation (erythropoiesis) and recycling.
4. Explain the basis of blood typing and histocompatibility.
5. Describe the structure/function of white blood cells and their formation.
6. Describe the structure/function of platelets.
7. Describe the mechanisms involved in blood clot formation.
Introduction to the Cardiovascular System

- **Cardiovascular System** = blood, heart & blood vessels
- **Circulatory System** = cardiovascular & lymphatic systems
- **Blood** – a fluid connective tissue with matrix (plasma) and formed elements (cells) involved in:

  1. Transport of dissolved substances (gases, nutrients, hormones, wastes)
  2. Regulation of pH and ion composition
  3. Restriction of fluid losses at injury sites (clotting)
  4. Defense against toxins and pathogens (leukocytes)
  5. Stabilization of body temperature
19-1 Physical Characteristics of Blood

Fig. 19-1
pH = 7.4
Temp. = 38°C
Vol. = 4-6 liters
(~7% body wt.)
High Viscosity

Hemopoiesis:
Hemocytoblasts →
myeloid & lymphoid stem cells
19-1 Physical Characteristics of Blood: Plasma

**Plasma Proteins**

Plasma proteins are in solution rather than forming insoluble fibers like those in other connective tissues, such as loose connective tissue or cartilage. On average, each 100 mL of plasma contains 7.6 g of protein, almost five times the concentration in interstitial fluid. The large size and globular shapes of most blood proteins prevent them from crossing capillary walls, so they remain trapped within the bloodstream. The liver synthesizes and releases more than 90% of the plasma proteins, including all albumins and fibrinogen, most globulins, and various prohormones.

**Albumins** (al-BØ-minz) constitute roughly 60% of the plasma proteins. As the most abundant plasma proteins, they are major contributors to the osmotic pressure of plasma.

**Globulins** (GLOB-øy-linz) account for approximately 35% of the proteins in plasma. Important plasma globulins include antibodies and transport globulins. Antibodies, also called immunoglobulins (i-mu-no-GLOB-øy-linz), attack foreign proteins and pathogen. Transport globulins bind small ions, hormones, and other compounds.

**Fibrinogen** (fi-BRIHN-øy-jen) functions in clotting, and normally accounts for roughly 4% of plasma proteins. Under certain conditions, fibrinogen molecules interact, forming large, insoluble strands of fibrin (Fi-brin) that form the basic framework for a blood clot.

**Other Solutes**

Other solutes are generally present in concentrations similar to those in the interstitial fluids. However, because blood is a transport medium there may be differences in nutrient and waste product concentrations between arterial blood and venous blood.

**Organic Nutrients:** Organic nutrients are used for ATP production, growth, and maintenance of cells. This category includes lipids (fatty acids, cholesterol, glycerides), carbohydrates (primarily glucose), and amino acids.

**Electrolytes:** Normal extracellular ion composition is essential for vital cellular activities. The major plasma electrolytes are Na⁺, K⁺, Ca²⁺, Mg²⁺, Cl⁻, HCO₃⁻, HPO₄²⁻, and SO₄²⁻.

**Organic Wastes:** Waste products are carried to sites of breakdown or excretion. Examples of organic wastes include urea, uric acid, creatinine, bilirubin, and ammonium ions.
### 19-1 Physical Characteristics of Blood: Formed Elements

#### Platelets
- **Platelets** are small, membrane-bound cell fragments that contain enzymes and other substances important to clotting.

#### White Blood Cells
- **White blood cells (WBCs), or leukocytes** (LOO-kō-sīts; leukos, white + -cyte, cell), participate in the body’s defense mechanisms. There are five classes of leukocytes, each with slightly different functions that will be explored later in the chapter.

#### Red Blood Cells
- **Red blood cells (RBCs), or erythrocytes** (e-RITH-ro-sīts; erythros, red + -cyte, cell), are the most abundant blood cells. These specialized cells are essential for the transport of oxygen in the blood.
19-2 Blood Fractions: **Plasma**

- Makes up 50–60% of blood volume
- More than 90% of plasma is water
- *Plasma* and *Interstitial Fluid* are both extracellular fluids: exchange H₂O, ions and small solutes (no protein) across the capillary wall
  - Composition of plasma and interstitial fluid differ in terms of
  - Levels of O₂ and CO₂
  - Concentrations and types of dissolved proteins
19-2 Blood Fractions: **Plasma Proteins**

- **Albumins** (60%)
  - Transport substances such as fatty acids, thyroid hormones, and steroid hormones; made by liver; major contributor to plasma osmotic pressure

- **Globulins** (35%)
  - Antibodies, also called immunoglobulins
  - Transport globulins (small molecules): hormone-binding proteins, metalloproteins, apolipoproteins (lipoproteins), & steroid-binding proteins

- **Fibrinogen** (4%)
  - Molecules that form clots and produce long, insoluble strands of fibrin
  - After soluble fibrinogen is turned into solid fibrin, remaining liquid = serum.

- **Other Plasma Proteins** (1%)
  - Enzymes, hormones, prohormones: Composition fluctuates

**Origin of Plasma Proteins:**
- 90% liver; Antibodies – plasma cells; Peptide hormones – endocrine
19-3 Blood Fractions: Red Blood Cells

• **Red blood cells (RBCs):** 99.9% of formed elements in blood

• **Hemoglobin**
  - The red pigment that gives whole blood its color
  - Binds and transports oxygen (and carbon dioxide)

• **Red blood cell count:** the number of RBCs in 1 microliter of whole blood
  - Male: 4.5 – 6.3 million; Female: 4.2 – 5.5 million

• **Hematocrit (HCT or Ht)** (packed cell volume [PCV] also used): percentage of RBCs in centrifuged whole blood
  - Male: 40 – 54; Female: 37 – 47
19-3 Blood Fractions: Red Blood Cells

- Erythrocyte Structure – biconcave disc
  - High surface-to-volume ratio
    - Quickly absorbs and releases oxygen
  - Discs form stacks called **rouleaux**
    - Smooth the flow through narrow vessels
  - Discs bend and flex to enter small capillaries:
    - 7.8 µm RBC passes through 4 µm capillary
19-3 Blood Fractions: **Red Blood Cells**

- Lack organelles including nuclei, mitochondria & ribosomes
- No cell division or repair possible
- *Anaerobic* metabolism only (no mitochondria) – *Why so??*
- Live ~ 120 days
- Cell is 97% **hemoglobin (Hb)**
  - ~280 million Hb/RBC, 4 O\(_2\) binding heme/Hb = >1 billion O\(_2\)/RBC x 25 trillion RBCs/indiv. = > 25 x 10\(^{21}\) O\(_2\)/indiv.!
  - 1/3 of all cells (25 trillion out of 75 trillion) are RBCs!
  - Normal hemoglobin 12 – 18 g/dL whole blood
19-3 Blood Fractions: Red Blood Cells

- Hemoglobin Structure/Function
  - Complex quaternary structure
  - 2 α chains & 2 β chains:
    - Each chain has 1 molecule of heme with O₂ binding iron
    - **Oxyhemoglobin** (O₂ bound, bright red)
    - **Deoxyhemoglobin** (no O₂, burgundy)
  - 98.5% of O₂ is carried by Hb compared to 20% of CO₂; the latter is bound to amino acids on α and β chains, NOT heme – called carbaminohemoglobin
  - At peripheral capillaries, low plasma O₂ leads to release of O₂ and binding of CO₂
  - At lungs, opposite occurs - O₂ loaded and CO₂ expelled
19-3 Blood Fractions: Red Blood Cells

Hemoglobin Oxygen Dissociation Curves
Comparison of Fetal vs. Adult Hb and Effects of pH, temp and di- (or bis-) phosphoglycerate (DPG or BPG)

Fig. 23–22
19-3 Blood Fractions: Red Blood Cells

Hemoglobin Disorders:

*Anemia* = O₂ starvation due to:
1. Insufficient numbers of erythrocytes
2. Low hemoglobin
3. Abnormal hemoglobin:

*Thalassemia*: an autosomal recessive mutation (Mediterranean origin) that results in the inability to produce sufficient α or β chains → slow RBC production and fragile & short-lived cells; periodic blood transfusions may be necessary; mutation thought to protect against malaria (same for *sickle-cell*).

*Sickle-Cell Anemia*: an autosomal recessive mutation in a single amino acid of β chain (sub-Saharan origin)

When Hb highly oxygenated, cells have normal shape
When Hb O₂ low, adjacent Hbs interact and RBCs deform into crescent shape: cells become fragile and block capillaries.
19-3 Blood Fractions: Red Blood Cell Turnover

- RBCs live for ca. 120 days (travel 700 miles!)
  - 1% of circulating RBCs “wear out” every day (lack repair mechanisms)
    - That’s about 3 million RBCs/second!
  - Macrophages of liver, spleen and bone marrow monitor RBCs and engulf before membranes rupture (hemolyze)
- Phagocytes break hemoglobin into constitutive components:
  - Globular proteins into amino acids; heme to biliverdin & iron
  - Transferrin, a plasma protein, transports iron back to bone marrow for new RBCs; excess transferrins removed by liver and spleen and iron stored as ferritin or hemosiderin
  - If excess hemoglobin breakdown, products can appear in urine; Hemoglobinuria
  - If whole red blood cells appear in urine, signals kidney or urinary tract damage; Hematuria
19-3 Blood Fractions: Red Blood Cell Turnover

- **Biliverdin** (green) is converted to **bilirubin** (yellow) and is released into blood, filtered by liver, and excreted in bile.

- **Jaundice** = failure of bilirubin to be excreted in bile, collects in peripheral tissues → yellow skin & eyes.

- In gut, **bilirubin** → **urobilins** (yellow) & **stercobilins** (brown) via intestinal bacteria.

- **Urobilins** absorbed or excreted in urine (hence yellow color to urine).

- **Stercobilins** remain in feces (hence brown color).
19-3 Blood Fractions: Red Blood Cell Turnover

Fig 19–5
Recycling of Red Blood Cell Components

Macrophages in liver, spleen, and bone marrow

Fe$^{2+}$ transported in circulation by transferrin

Amino acids

Fe$^{2+}$

Heme

Billiverdin

Bilirubin

Liver

Billirubin bound to albumin in bloodstream

Billirubin

Excreted in bile

Absorbed into the circulation

Urobilins, stercobilins

Kidney

Hb

Urobilins

Eliminated in urine

Eliminated in feces

Average life span of RBC is 120 days

90%

10%

Old and damaged RBCs

In the bloodstream, the rupture of RBCs is called hemolysis.

Hemoglobin that is not phagocytized breaks down, and the alpha and beta chains are eliminated in urine.
19-3 Blood Fractions: Red Blood Cell Formation

• **Erythropoiesis** (RBC Formation)

  • In adults, occurs only in **myeloid tissue** (red bone marrow):
    1. Hemocytoblasts differentiate into myeloid stem cells
    2. Myeloid stem cells undergo multiple stages of differentiation
    3. Cells fill with Hb, lose organelles (nucleus too)
    4. After ~ 5 days, reticulocytes are formed (Hb + some ribosomes); remain in bone marrow for 2 days and then released into blood, where they account for 0.8% of total blood RBCs
    5. After ~ 24h in circulation, reticulocytes lose ribosomes (lose protein synthesis capacity) and mature into erythrocytes

  • Vitamin B\textsubscript{12}, B\textsubscript{6} and folic acid necessary for stem cell division
  • Destruction of gastric parietal cells can lead to loss of intrinsic factor, which is required for B\textsubscript{12} absorption, and can lead to pernicious anemia
Stimulating Hormones

- **Erythropoietin (EPO):** hormone, released by kidney during hypoxia (low O$_2$, e.g., high altitude or disease), anemia, ischemia, etc.

- Stimulates RBC Production by:
  - ↑ cell division rates (10x; ~30 million cells/s)
  - ↑ Hb synthesis = ↓ maturation time

- “Blood Doping” = infusing additional RBCs to increase O$_2$ carrying capacity and, thus, enhance endurance performance; may also be produced by EPO injections:
  - ↑ O$_2$ to tissues, but also ↑ hematocrit/viscosity → clots, stroke, heart strain, kidney failure
### Evidence From the Investigation Into Alleged Doping by Lance Armstrong

<table>
<thead>
<tr>
<th>Year</th>
<th>ALLEGED DOPING METHOD</th>
<th>Human growth hormone</th>
<th>Testosterone</th>
<th>EPO</th>
<th>Administration or transportation of drugs</th>
<th>Evading positive tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>1998</td>
<td>Blood doping</td>
<td></td>
<td></td>
<td></td>
<td>The drugs were transported by team staff, administered by a team doctor</td>
<td>Armstrong receives saline to lower his red blood cell level in advance of a possible test</td>
</tr>
<tr>
<td>1999</td>
<td>An Armstrong assistant, nicknamed Motorman, followed the team on a motorcycle during Tour de France stages carrying EPO.</td>
<td></td>
<td></td>
<td></td>
<td>Armstrong tests positive for a corticosteroid. A doctor bookoates a prescription for it claiming Armstrong had saddle sore.</td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td>Team begins blood doping in part because a new test emerges for EPO. Smaller doses of EPO will now be used to help avoid positive tests.</td>
<td></td>
<td></td>
<td></td>
<td>No tests for blood transfusions are in place. Armstrong drops out of a race in Spain when warned of a test. He had just taken testosterone.</td>
<td></td>
</tr>
<tr>
<td>2001</td>
<td>Team members are supplied EPO by a team trainer.</td>
<td></td>
<td></td>
<td></td>
<td>Armstrong sleeps in a tent that simulates high-altitude conditions during competition to help mask EPO.</td>
<td></td>
</tr>
<tr>
<td>2002</td>
<td>Armstrong starts to personally enforce the team doping program. He supplies testosterone to teammates.</td>
<td></td>
<td></td>
<td></td>
<td>Still no testing for blood doping.</td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td>Transfusions continue, and Armstrong supplies teammates with EPO.</td>
<td></td>
<td></td>
<td></td>
<td>Armstrong receives small doses of EPO to help mask the effect of blood transfusions on his blood values.</td>
<td></td>
</tr>
<tr>
<td>2004</td>
<td>After a stage in the Tour de France, blood transfusions are given to the team members on the team bus ride back to the hotel.</td>
<td></td>
<td></td>
<td></td>
<td>Bought machinery to help monitor blood values to ensure they remained at acceptable levels.</td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td>Armstrong supplies EPO to teammates.</td>
<td></td>
<td></td>
<td></td>
<td>After his Tour victory, the team director sends a teammate to Armstrong's apartment to ensure there is no drug evidence there.</td>
<td></td>
</tr>
</tbody>
</table>

By JOE WARD and ALAN MOLGAN | textbook
### TABLE 19–1 RBC Tests and Related Terminology

<table>
<thead>
<tr>
<th>Test</th>
<th>Determines</th>
<th>Terms Associated with Abnormal Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit (Hct)</td>
<td>Percentage of formed elements in whole blood</td>
<td>Polycythemia (may reflect erythrocytosis or leukocytosis)</td>
</tr>
<tr>
<td></td>
<td>Normal = 37–54%</td>
<td></td>
</tr>
<tr>
<td>Reticulocyte count (Retic.)</td>
<td>Percentage of circulating reticulocytes</td>
<td>Reticulocytosis</td>
</tr>
<tr>
<td></td>
<td>Normal = 0.8%</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin concentration (Hb)</td>
<td>Concentration of hemoglobin in blood</td>
<td>Anemia</td>
</tr>
<tr>
<td></td>
<td>Normal = 12–18 g/dL</td>
<td></td>
</tr>
<tr>
<td>RBC count</td>
<td>Number of RBCs per μL of whole blood</td>
<td>Erythrocytosis/polycythemia</td>
</tr>
<tr>
<td></td>
<td>Normal = 4.2–6.3 million/μL</td>
<td></td>
</tr>
<tr>
<td>Mean corpuscular volume (MCV)</td>
<td>Average volume of single RBC</td>
<td>Macrocytic</td>
</tr>
<tr>
<td></td>
<td>Normal = 82–101 μm³ (normocytic)</td>
<td></td>
</tr>
<tr>
<td>Mean corpuscular hemoglobin</td>
<td>Average amount of Hb in one RBC</td>
<td>Hyperchromic</td>
</tr>
<tr>
<td>concentration (MCHC)</td>
<td>Normal = 27–34 pg/μL (normochromic)</td>
<td></td>
</tr>
</tbody>
</table>
### 19-4 Blood Typing

- All cell membranes have **surface antigens**: indicate “self” (antigen = substance that triggers immune response)
- RBCs have 50+ surface antigens (e.g., glycoproteins or glycolipids) of which 3 are very important for blood transfusion: 
  - *agglutinogens A, B, Rh (D)*
- Blood types: A, B, AB or O
  - genetically determined by presence or absence of surface antigens (A, B & Rh)
    - Rh\(^+\) = antigen Rh (85%); Rh\(^-\) = none (15%)
  - At birth, blood contains antibodies against A and/or B antigens; however, this is not true for Rh as only *sensitized* individuals have antibodies to Rh (D)
### Table 19–2 Differences in Blood Group Distribution

<table>
<thead>
<tr>
<th>Population</th>
<th>O</th>
<th>A</th>
<th>B</th>
<th>AB</th>
<th>Rh⁺</th>
</tr>
</thead>
<tbody>
<tr>
<td>U.S. (AVERAGE)</td>
<td>46</td>
<td>40</td>
<td>10</td>
<td>4</td>
<td>85</td>
</tr>
<tr>
<td>African American</td>
<td>49</td>
<td>27</td>
<td>20</td>
<td>4</td>
<td>95</td>
</tr>
<tr>
<td>Caucasian</td>
<td>45</td>
<td>40</td>
<td>11</td>
<td>4</td>
<td>85</td>
</tr>
<tr>
<td>Chinese American</td>
<td>42</td>
<td>27</td>
<td>25</td>
<td>6</td>
<td>100</td>
</tr>
<tr>
<td>Filipino American</td>
<td>44</td>
<td>22</td>
<td>29</td>
<td>6</td>
<td>100</td>
</tr>
<tr>
<td>Hawaiian</td>
<td>46</td>
<td>46</td>
<td>5</td>
<td>3</td>
<td>100</td>
</tr>
<tr>
<td>Japanese American</td>
<td>31</td>
<td>39</td>
<td>21</td>
<td>10</td>
<td>100</td>
</tr>
<tr>
<td>Korean American</td>
<td>32</td>
<td>28</td>
<td>30</td>
<td>10</td>
<td>100</td>
</tr>
<tr>
<td>NATIVE NORTH AMERICAN</td>
<td>79</td>
<td>16</td>
<td>4</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>NATIVE SOUTH AMERICAN</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>AUSTRALIAN ABORIGINE</td>
<td>44</td>
<td>56</td>
<td>0</td>
<td>0</td>
<td>100</td>
</tr>
</tbody>
</table>
19-4 Blood Typing

- Transfusion Cross-Reactions
  - Plasma antibody meets specific surface antigen
  - Blood will agglutinate and hemolyze
  - Occurs if donor and recipient blood are not compatible
    - O\(^-\) = “universal donor” (AB = “universal recipient”)

- Cross-Match Testing:
  - tests for other antigens by reacting donors RBCs to recipients plasma

Fig 19-7

Fig 19–8 Blood Type Test

<table>
<thead>
<tr>
<th>Anti-A</th>
<th>Anti-B</th>
<th>Anti-D</th>
<th>Blood type</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="19-4-Blood-Typing-Fig19-7.png" alt="Image" /></td>
<td><img src="19-4-Blood-Typing-Fig19-8.png" alt="Image" /></td>
<td><img src="19-4-Blood-Typing-Fig19-8.png" alt="Image" /></td>
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<td><img src="19-4-Blood-Typing-Fig19-8.png" alt="Image" /></td>
</tr>
</tbody>
</table>

Anti-D\(^+\) = Rh\(^+\)
Antibodies against Rh (D) antigen only form upon exposure and they are small enough to cross placenta (unlike anti-A and anti-B antibodies).

Hemolytic disease of newborn/Erythroblastosis fetalis: Rh⁻ mom pregnant with Rh⁺ baby, gets exposed to D antigen during birth, makes anti-D antibodies.

Pregnant with second Rh⁺ baby, her antibodies cross placenta, causing agglutination and lysis of fetal RBCs → anemia and death - fetal transfusion may be given and/or early delivery.

Easily prevented if known: Treat mom with RhoGam (anti-Rh antibodies) during last 3 months of her first Rh⁺ pregnancy: prevents antibody formation in the first place.
19-5 Blood Fractions: **White Blood Cells**

- **Leukocytes** (5 types)
  - Have nuclei & organelles but no hemoglobin (hence “white” or buff)
  - 5000 – 10,000 leukocytes/µl blood; < 1% total blood volume
  - Cells use the blood to travel; most are found in connective tissue & lymph

- **Functions:**
  - 1. Defend against pathogens
  - 2. Remove toxins and wastes
  - 3. Attack abnormal/damaged cells

- **Characteristics:**
  - 1. Amoeboid movement – cytoplasm flows into cellular processes
  - 2. Diapedesis (move out of blood):
    - a. Margination = adhere to vessel
    - b. Emigration = pass between endothelial cells
  - 3. Exhibit positive chemotaxis - pathogens, damaged tissue, other WBCs
  - 4. Phagocytosis (3 of 5) engulf pathogens and debris
19-5: 5 Types of Leukocytes

a-d: Nonspecific defense

e: Specific defense

Fig 19–10 a-e White Blood Cells
defensins that kill bacteria, fungi & enveloped viruses

- Very mobile: first at injury
- Life span < 10h

**Functions:**

1. Respiratory burst: $H_2O_2$ & $O_2^-$, acts as bactericide
2. Degranulation: defensins (peptide) lyse bacteria
3. Prostaglandins: induce inflammation to stop spread of injury
4. Leukotrienes: hormones that attract other phagocytes

**Nonspecific defense**

**Phagocytic**

- 50-70% of all WBCs
- 2-5 lobed nucleus
- 12 μm diameter
- Granules (lysosomes) contain digestive enzymes &
19-5 White Blood Cells: B. **Eosinophils** or Acidophils

- **Nonspecific defense**
- **Phagocytic** (secondary function)
- 2–4% of circulating WBCs
- Bilobed nucleus
- 12 µm diameter; 9-day life

**Functions:**

1. Attack antibody-coated objects (bacteria, protozoa, cell debris)
2. Defense against large parasites

- Excrete toxic compounds (primary function)
  - Nitric oxide (NO) & Cytotoxic enzymes
- Sensitive to allergens
- Control inflammation with enzymes that counteract inflammatory effects of neutrophils and mast cells
19-5 White Blood Cells: C. Basophils

- **Nonspecific defense**
- **NOT** phagocytic
- < 1% of WBCs
- “U” shaped nucleus
- 8 - 10µm diameter

- Granules contain
  - *histamine* – dilate blood vessels
  - *heparin* – prevent clotting (*book says this but actual function of heparin is likely defense against pathogenic infection*)

- Life span = 9 d

- Similar in function to mast cells in tissue; enhance their function

- **Functions:**
  1. Inflammation
  2. Allergic response  
     (via histamine)
19-5 White Blood Cells: D. Monocytes

- **Nonspecific defense**
- **Phagocytic**
- 2-8% of WBCs
- Kidney shaped nucleus
- 15 μm + diameter
- Circulate 24 h, then exit to tissues = *macrophage*
- Life span = several months

**Functions:**

1. Phagocytosis: viruses and bacteria
2. Attract phagocytes
3. Attract fibroblasts for scar formation
4. Activate lymphocytes: to mount immune response
19-5 White Blood Cells: E. Lymphocytes

- **Immune-Specific Response**
  - 20-30% of WBCs
  - Large round nucleus
  - 5-17µm diameter
  - Migratory between blood and tissues (bidirectional)
  - Most in lymphatic system

- Life span = days to lifetime

- **Function** (depends on type [3]):
  1. **T cells**: *cell-mediated immunity* (attack foreign cells directly or control the activity of other lymphocytes)
  2. **B cells**: *humoral immunity* (differentiate into plasma cells, which synthesize and secrete antibodies)
  3. **Natural Killer (NK) cells**: immune surveillance or innate immunity (detect and destroy abnormal tissue; e.g., cancer)
19-5 Leukocyte Disorders & Diagnostics

- Changes in differential count and WBC profiles can signal infections, inflammation, and allergic reactions.

- **Leukopenia**: low WBC count (*penia* = poverty)

- **Leukocytosis**: high WBC count (*cytosis* = more cells)

  - Normal infection: WBCs from 7,500 - 11,000/µl
    - >100,000/µl → *leukemia*, cancerous stem cells, WBCs produced are immature and abnormal.

- Infectious Mononucleosis (mononuclear leukocytosis):
  Epstein Bar virus infection causes production of excess agranulocytes (monocytes and lymphocytes) that are abnormal.
19-5 White Blood Cell Production: Leukopoiesis & Lymphopoiesis

- All blood cells originate from hemocytoblasts, which produce:

1. **Myeloid Stem Cells**
   - Differentiate into **progenitor cells**, which produce all WBCs except lymphocytes

2. **Lymphoid Stem Cells**
   - **Lymphopoiesis**: the production of lymphocytes
   - All WBCs except monocytes (and lymphocytes—see below) develop fully in bone marrow
     - Monocytes develop into macrophages in peripheral tissues
19-5 Leukopoiesis

- Myeloid stem cells → Basophils, Eosinophils, Neutrophils and Monocytes as directed by specific colony stimulating factors (CSFs) produced by Macrophages and T cells
- Different CSFs (hormones) result in different cell types:
  1. **M-CSF** stimulates monocyte production
  2. **G-CSF** stimulates production of granulocytes (neutrophils, eosinophils, and basophils)
  3. **GM-CSF** stimulates granulocyte and monocyte production
  4. **Multi-CSF** accelerates production of granulocytes, monocytes, platelets, and RBCs
19-5 Lymphopoiesis

- Hemocytoblasts differentiates into Lymphoid Stem Cells → Lymphoblast → Prolymphocytes → Lymphocytes
- Some lymphocytes are derived from lymphoid stem cells that remain in bone marrow → B cells and NK cells
- Many lymphoid stem cells migrate to peripheral lymphoid tissues (e.g., thymus, spleen & lymph nodes) and then differentiate into mature lymphocytes
- Lymphoid stem cells in the thymus give rise to T cells

*(Discussed in much greater detail in Chapter 22 – Adaptive Immune Response)*
19-5 Origins & Differentiation of Blood Formed Elements

Fig 19-11
19-6 Blood Fractions: **Platelets**

- Flattened *cell fragments* involved in human clotting systems
- No nucleus (non-mammalian vertebrates have whole cells involved in clotting called thrombocytes) (*thrombo-* = clot)
- 2-4 µm diameter, 1 µm thick
- Constantly replaced, removed by spleen (phagocytized)
- 9–12 days in circulation
- 150,000 - 500,000 / µl of blood
  - *Thrombocytopenia* – abnormally low platelet count
  - *Thrombocytosis* – high platelet count (infection, inflammation, cancer)
- 1/3 are reserved (in spleen and other organs) for emergencies
19-6 Blood Fractions: **Platelets**

- **Three Functions of Platelets:**
  1. Transport & release important clotting chemicals
  2. Temporarily patch damaged vessel walls (plug)
  3. Actively contract tissue after clot formation (contain actin & myosin)

- **Platelet Production (Thrombocytopoiesis)**
  - Megakaryocytes in bone marrow breaks off membrane-enclosed cytoplasm (each megakaryocyte can produce ~4000 platelets)
  - Induced by
    1. *Thrombopoietin* (TPO) from kidney
    2. *Interleukin-6* (IL-6) – stimulates platelet formation
    3. Multi-CSF (promotes growth of megakaryocytes)
19-7 Hemostasis

- Hemostasis = cessation of bleeding
- Consists of three complex (and not necessarily sequential or independent) phases:
  1. Vascular phase
  2. Platelet phase
  3. Coagulation phase
19-7 Hemostasis: 1. Vascular Phase

- A cut triggers vascular spasm that lasts some 30 minutes
- Three steps of the vascular phase
  1. **Endothelial cells contract:**
     - expose basal lamina to bloodstream
  2. **Endothelial cells release:**
     - chemical factors: ADP, tissue factor, and prostacyclin
     - local hormones: endothelins, which stimulate smooth muscle contraction and cell division
  3. **Endothelial plasma membranes become “sticky”:**
     - seal off blood flow
2. Platelet Phase

- **Platelet adhesion** (attachment) – begins within 15 s of injury
  - Adhere to sticky endothelial surfaces, basal lamina & exposed collagen

- **Platelet aggregation** (stick together)
  - Forms platelet plug (closes small breaks)

- **Activated platelets** release clotting cmpds:
  - \( ADP \rightarrow \) platelet aggregation
  - \( \text{Thromboxane A}_2 \) & serotonin \( \rightarrow \) vascular spasm
  - **Clotting factors**
  - **Platelet-derived growth factor**
    \( \rightarrow \) blood vessel repair
  - Calcium ions \( \rightarrow \) aggregation
Platelet aggregation must be controlled and the area restricted. Several factors limit the growth of the platelet plug:

- **Prostacyclin**: released by endothelial cells, inhibits platelet aggregation

- **Inhibitory compounds** released by WBCs entering area

- **Circulating plasma enzymes** - break down ADP at plug

- **Negative (inhibitory) feedback**: e.g., serotonin blocks ADP

- **Development of blood clot** - isolates and restricts the area
19-7 Hemostasis: 3. Coagulation Phase

- Begins 30 seconds or more after the injury
- Blood clotting (coagulation)
  - Cascade reactions:
    - chain reactions of enzymes and proenzymes
    - form three pathways (extrinsic, intrinsic & common)
    - convert circulating fibrinogen into insoluble fibrin
- Clotting Factors
  - Also called procoagulants (Ca\(^{2+}\) & 11 different proteins)
  - Many of the proteins are proenzymes
  - Required for normal clotting
# 19-7 Hemostasis: 3. Coagulation Phase

<table>
<thead>
<tr>
<th>Table 19-4</th>
<th>Clotting Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Factor</strong></td>
<td><strong>Structure</strong></td>
</tr>
<tr>
<td>I</td>
<td>Protein</td>
</tr>
<tr>
<td>II</td>
<td>Protein</td>
</tr>
<tr>
<td>III</td>
<td>Lipoprotein</td>
</tr>
<tr>
<td>IV</td>
<td>Ion</td>
</tr>
<tr>
<td>V</td>
<td>Protein</td>
</tr>
<tr>
<td>VI</td>
<td>(No longer used)</td>
</tr>
<tr>
<td>VII</td>
<td>Protein</td>
</tr>
<tr>
<td>VIII</td>
<td>Protein factor (AHF)</td>
</tr>
<tr>
<td>IX</td>
<td>Protein factor</td>
</tr>
<tr>
<td>X</td>
<td>Protein</td>
</tr>
<tr>
<td>XI</td>
<td>Protein antecedent (PTA)</td>
</tr>
<tr>
<td>XII</td>
<td>Protein</td>
</tr>
<tr>
<td>XIII</td>
<td>Protein factor (FSF)</td>
</tr>
</tbody>
</table>

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19-7 Hemostasis: 3. Coagulation Pathways

1. **Extrinsic pathway**
   - Begins in the vessel wall (endothelial cells), outside of bloodstream
   - Damaged cells release **Factor III or tissue factor (TF)**
   - TF + Ca$^{2+}$ + clotting factor VII = enzyme complex that activates Factor X

2. **Intrinsic pathway**
   - Begins with circulating proenzymes, within bloodstream
   - Activation of enzymes (usually Factor XII) by collagen
   - Platelets release factors (e.g., PF–3)
   - Series of reactions then activates Factor X

3. **Common pathway**
   - Where intrinsic and extrinsic pathways converge
   - Forms enzyme prothrombinase
   - Converts prothrombin to thrombin
   - Thrombin converts fibrinogen to fibrin
Figure 19–12
The Coagulation Phase of Hemostasis

NOTE: Both the extrinsic and intrinsic pathways produce thrombin, but the extrinsic is shorter and faster; thus, it results in the rapid production of a small amount of thrombin that is later reinforced by additional thrombin from the intrinsic pathway.
19-7 Hemostasis: Other Considerations

- **Positive Feedback:** Production of thrombin by common pathway stimulates formation of tissue factor (TF-*extrinsic*) and PF-3 from platelets (*intrinsic*), thus forming a positive feedback loop with both the intrinsic and extrinsic pathways, respectively.

- **Clotting: Area Restriction** – affected by factors that either deactivate or remove factors/agents:
  - **Anticoagulants** (plasma proteins)
    - Antithrombin-III
    - Alpha-2-macroglobulin
  - **Heparin** (produced by basophils and mast cells)
  - **Protein C** (activated by thrombomodulin)
  - **Prostacyclin** – inhibits platelet aggregation
Dietary: Calcium Ions and Vitamin K affect almost all aspects of clotting

- Calcium ions (Ca\(^{2+}\)) needed for all 3 pathways (intrinsic, extrinsic and common)
- Vitamin K required by liver for synthesis of 4 of the clotting factors, including prothrombin

Clot Retraction (occurs after clot formation)

- Platelets contract, pull torn area together and reduce size of damaged area (takes 30–60 min)

Fibrinolysis = slow process of clot dissolving

- Thrombin and tissue plasminogen activator (t-PA):
  - activate plasminogen
- Plasminogen produces plasmin, which digests fibrin strands
19-7 Bleeding Disorders

- **Thrombosis** = clotting in undamaged vessels → prevents or slows flow (intrinsic pathway)
- **Embolus** = free floating thrombosis, blocks small vessels → tissue damage, heart attack, stroke
- **Disseminated Intravascular Coagulation** = widespread clotting followed by systemic bleeding, *rare*: complication of pregnancy, septicemia or mismatched transfusion
- **Hemophilia** = inadequate production of clotting factors
  - Type A → Factor VIII (X linked-recessive)
  - Type B → Factor IX
  - Type C → Factor XI
# Chapter 19 Summary: Formed Elements in Blood

<table>
<thead>
<tr>
<th>Table 19–3</th>
<th>Formed Elements of the Blood</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cell</strong></td>
<td><strong>Abundance</strong> (average number per μL)</td>
</tr>
<tr>
<td>RED BLOOD CELLS</td>
<td>5.2 million (range: 4.4–6.0 million)</td>
</tr>
</tbody>
</table>

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Chapter 19 Summary: Formed Elements in Blood

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<th>Table 19–3</th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Cell</strong></td>
<td><strong>Abundance (average number per μL)</strong></td>
</tr>
<tr>
<td><strong>WHITE BLOOD CELLS</strong></td>
<td>7000 (range: 5000–10,000)</td>
</tr>
<tr>
<td><strong>Neutrophils</strong></td>
<td>4150 (range: 1800–7300) Differential count: 50–70%</td>
</tr>
<tr>
<td><strong>Eosinophils</strong></td>
<td>165 (range: 0–700) Differential count: 2–4%</td>
</tr>
<tr>
<td><strong>Basophils</strong></td>
<td>44 (range: 0–150) Differential count: &lt;1%</td>
</tr>
</tbody>
</table>
### Table 19-3: Formed Elements of the Blood

<table>
<thead>
<tr>
<th>Cell</th>
<th>Abundance (average number per μL)</th>
<th>Appearance in a Stained Blood Smear</th>
<th>Functions</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WHITE BLOOD CELLS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monocytes</td>
<td>456 (range: 200–950)</td>
<td>Very large cell; kidney bean-shaped nucleus; abundant pale cytoplasm</td>
<td>Enter tissues to become macrophages; engulf pathogens or debris</td>
<td>Move into tissues after 1–2 days; survive for months or longer; produced primarily in red bone marrow</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>2185 (range: 1500–4000)</td>
<td>Generally round cell, slightly larger than RBC; round nucleus; very little cytoplasm</td>
<td>Cells of lymphatic system, providing defense against specific pathogens or toxins</td>
<td>Survive for months to decades; circulate from blood to tissues and back; produced in red bone marrow and lymphatic tissues</td>
</tr>
</tbody>
</table>

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<thead>
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<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PLATELETS</strong></td>
<td>350,000 (range: 150,000–500,000)</td>
<td>Round to spindle-shaped cytoplasmic fragment; contain enzymes, proenzymes, actin, and myosin; no nucleus</td>
<td>Hemostasis: Clump together and stick to vessel wall (platelet phase); activate intrinsic pathway of coagulation phase</td>
<td>Remain in bloodstream or in vascular organs; remain intact for 7–12 days; produced by megakaryocytes in red bone marrow</td>
</tr>
</tbody>
</table>
Chapter 19 Knowledge Checklist

1. Describe the components and major functions of blood.
2. Describe the composition and function of plasma.
3. List the characteristics and functions of erythrocytes, including hemoglobin, erythrocyte formation (erythropoiesis) and recycling.
4. Explain the basis of blood typing and histocompatibility.
5. Describe the structure function of white blood cells and their formation.
6. Describe the structure function of platelets.
7. Describe the mechanisms involved in blood clot formation.