Chapter 19: Blood

The Cardiovascular System

• A circulating transport system:
  – a pump (the heart)
  – a conducting system (blood vessels)
  – a fluid medium (blood)
Functions of the Blood

- **Transport functions:**
  - oxygen and carbon dioxide
  - nutrients
  - hormones
  - waste products

- **Regulatory functions:**
  - Maintaining appropriate body temperature
  - Maintaining normal pH of body tissues
  - Maintaining adequate fluid volume in the circulatory system
    - Salt content of blood
    - Protein content of blood

- **Protective functions:**
  - Houses and distributes the immune system components
    - Prevents infection
  - Contains clotting agents to prevent fluid loss

Characteristics of blood

- **Viscous liquid**
  - 5X more viscous than water
  - 5-6 liters in male
  - 4-5 liters in female
    - Difference mainly due to larger size of male but testosterone also stimulates blood cell formation
    - normovolemic
    - hypovolemic
    - hypervolemic

- **Slightly alkaline**
  - pH 7.35 to 7.45
    - Venous blood of the systemic circulation is more acidic
    - Slightly alkaline
What are the components of blood?

Blood

• Is specialized type of connective tissue
  – Made of:
    • Plasma
      – Is a fluid matrix
    • Formed elements
      – Red blood cells
      – White blood cells
      – Platelets
What is the composition and function of plasma?

Plasma

- Makes up 50–60% of blood volume
  - Contains
    - Water
    - Dissolved plasma proteins
    - Other solutes
      - Ions
      - Gases
      - Wastes
      - nutrients
Plasma

3 Classes of Plasma Proteins

- Albumins (60%)
- Globulins (35%)
- Fibrinogen (4%)

- Other types (less than 1%)
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**Albumins**

- Holds water in the circulatory system:
  - Contribute to osmotic pressure of blood
- Are pH buffers:
- Are transport proteins:
  - fatty acids
  - thyroid hormones
  - steroid hormones

*albumins are made by the liver

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**Globulins**

1. **immunoglobulins**, also called **Antibodies**
   *are made by white bloods cells called plasma cells*
2. **Transport globulins** (small molecules):
   - hormone-binding proteins
   - Metalloproteins
     - (transferrin-iron, ceruloplasmsin-copper)
   - apolipoproteins (fatty acids, cholesterol)
   - steroid-binding proteins

* transport globulins are made by the liver
Fibrinogen

- Most numerous of the clotting proteins
- Produce long, sticky, insoluble strands of fibrin

*made by the liver

Serum

- Liquid part of a blood sample:
  - Plasma in which dissolved fibrinogen has converted to solid fibrin and removed
Other Plasma Proteins

- Less than 1% of plasma proteins:
  - Constantly changing quantities of specialized plasma proteins
  - enzymes, hormones, and prohormones

Origins of Plasma Proteins

- 90% made in liver
- Antibodies made by plasma cells
- Peptide hormones made by endocrine organs
Formation of Formed Elements (Hemopoiesis)

- Hemocytoblasts form in the blood islands of the yolk sac
  - Main function is to produce RBC to support early embryo
  - First appears at third week of development
- A second population of cells form called hemanigioblast
  - Located in the embryo at the forming aorta and heart
  - Gives rise to
    - Endothelium stem cells
      - Involved in blood vessel formation
    - Hemocytoblast
      - Migrates to the liver, spleen, thymus, and red bone marrow
      - Produces RBC, WBC, and platelets

Sites of Hemopoiesis
Cell arising from the Hemocytoblast

- Lymphoid stem cell
  - Lymphoblast
  - Prolymphocyte
  - Lymphocytes
- Myeloid stem cell
  - Proerythroblast
  - Erythrocytes
  - Granulocyte-macrophage colony-forming unit
  - Myeloblast
    - Bands cells
      - Neutrophils
      - Eosinophils
      - Basophils
  - Monoblast
    - Monocytes
      - Macrophages
  - Megakaryoblast
    - Platelets

Blood Cell Production
Types of Formed Elements

- 1. Red blood cells
  - Erythrocytes
- 2. White blood cells
  - Leucocytes
- 3. Platelets

1. Erythrocytes (RBC)
What are the characteristics red blood cells?

Red Blood Cells

- Red blood cells (RBCs) make up 99.9% of blood's formed elements
Measuring RBCs

- **Red blood cell count:**
  - reports the number of RBCs in 1 microliter whole blood
- **Hematocrit (packed cell volume or PCV):**
  - percentage of RBCs in centrifuged whole blood

Normal Blood Counts

- **RBC:**
  - male: 4.5–6.3 million/microliter
  - female: 4.2–5.5 million/microliter

Single drop of blood will have 260 million RBC
25 trillion RBC in an adult

- **Hematocrit:**
  - male: 46%
  - female: 42%
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**RBC Structure**

- Small and highly specialized biconcave disc
  - Bags of hemoglobin (97% dry weight)
- Thin in middle and thicker at edge

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**Importance of RBC Shape and Size**

1. High surface-to-volume ratio:
   - quickly absorbs and releases oxygen
2. Discs form stacks (rouleaux)
   - smoothes flow through narrow blood vessels
3. Discs bend and flex entering small capillaries:
   - 7.8 \( \mu m \) RBC passes through 4 \( \mu m \) capillary
Functions of Red Blood Cells

1. Transportation of respiratory gases
   - Role of hemoglobin

2. pH regulation
   - Also a role of hemoglobin
What is the structure and function of hemoglobin?

Hemoglobin (Hb)

- Protein molecule, transports respiratory gases
- Normal hemoglobin (adult male):
  - 14–18 g/dl whole blood
Hemoglobin Structure

• Complex quaternary structure

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Hemoglobin Structure

• 4 globular protein subunits:
  – each with 1 molecule of heme
    • Made from four pyrrole rings
  – each heme contains 1 iron ion
    • Located between the pyrrole rings

• Iron ions easily:
  – associate with oxygen (oxyhemoglobin)
  – or dissociate from oxygen (deoxyhemoglobin)
Hemoglobin Structure

- Complex quaternary structure

Forms of Hemoglobin

- Oxyhemoglobin
  - Found with high oxygen levels (lungs)
  - Hb bound to oxygen
  - Almost 100% of Hb in this form as it leaves the lungs

- Deoxyhemoglobin
  - Found with low oxygen levels (peripheral capillaries)
  - Hb releases oxygen
    - Binds to acid (H) and carries it to lungs
    - Functioning to buffer pH

- Carbaminohemoglobin
  - Found with low oxygen and high CO2 (peripheral capillaries):
    - Hemoglobin releases oxygen (forms deoxyhemoglobin)
    - Binds carbon dioxide and carries it to lungs
    - 23% of Hb in this form as it leaves the tissues

*All three forms can be present in a single RBC*
Fetal Hemoglobin

- Form of hemoglobin found in embryos
  - Two beta chains are replace with gamma chains
  - Fetal Hb Has higher binding affinity for oxygen
    - Takes oxygen from mother’s hemoglobin
    - Treat sickle cell anemia with butyrate (a food additive) to promote synthesis of fetal Hb

Anemia

- Hematocrit or hemoglobin levels per cell are below normal
  - Results in low blood oxygen levels
- Is caused by several conditions
  - Low dietary iron
  - Blood loss
  - Low B12 (pernicious anemia)
  - Low protein intake
  - Blood diseases (sickle cell, malaria)
  - Chemotherapy
**Erythropoiesis**

*Red blood cell formation*

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**Lifespan of RBCs**

- Lack nuclei, mitochondria, and ribosomes
  - Unable to make repairs
  - Make a complete round trip in one minute
    - 700 miles in its lifespan
- Live about 120 days
  - Must replace about 3 million RBCs per second
Erythropoiesis

- Red blood cell formation
- Occurs only in red bone marrow
- Located in the spongy bone in adults
  - Also located in the marrow cavity in the long bones of children
- A process whereby a stem cell matures to become RBCs

Stages of Erythropoiesis

- Myeloid stem cell
  - Embryonic stem cell that is present but not active in the adult
  - Migrates to the bone marrow
- Proerythroblast
  - Located in the bone marrow
  - Constantly undergoing mitosis forming replacement proerythroblasts and erythroblasts
- Erythroblast
  - Located in the bone marrow
  - Contains large numbers of ribosomes
  - Actively synthesizing proteins (heme)
- Normoblast
  - Located in the bone marrow
  - Is a erythroblast that has stopped transcription and is preparing to eject the nucleus
- Reticulocyte
  - Located in the bone marrow but later is released into the blood
  - Forms from the normoblast following the ejection of the nucleus and most other organelles
  - Continues to produce Hb using remaining ribosomes and stored mRNA
- Mature RBC
  - Located in the blood
  - After the reticulocyte stops producing more Hb the remaining cell is termed a erythrocyte
Regulation of Erythropoiesis

- **Erythropoietin (EPO)**
- Also called *erythropoiesis-stimulating hormone*:
  - secreted from kidneys and liver when oxygen in peripheral tissues is low (hypoxia)
    - Move to high altitude
    - Blood loss
    - Athletic training
    - Reduced lung function
      - Emphysema triggers polycythemia
  - secreted from kidneys when BP drops

Can increase rbc production to 30 million/sec
Effects of erythropoietin

- Stimulates cell division in proerythroblast
- Stimulates hemoglobin synthesis in erythroblasts, normoblasts, and reticulocytes

Requirements for Erythropoiesis

- Erythropoietin
- Amino acids
- Iron
- Vitamins $B_{12}$
  - Required for purine synthesis
- Vitamin $B_6$
  - Coenzyme in amino acid and lipid metabolism
- Folic acid
  - Coenzyme in nucleic acid metabolism
Recycling RBCs

- 1% of circulating RBCs wear out per day:
  - about 3 million RBCs per second
  - 90% are engulfed by macrophages
  - 10% undergo hemolysis in the blood

- Macrophages are located in the liver, spleen, and bone marrow:
  - monitor spectrin levels of RBCs
    - As spectrin levels drop they lose flexibility and are trapped in reticular connective tissue
  - engulf RBCs before membranes rupture (hemolysis)
Hemoglobin Recycling

- Phagocytes break hemoglobin into components:
  - globular proteins to amino acids
  - heme to biliverdin
- Release iron
Iron Recycling

- Carried in the blood on transport proteins (transferrin)
- Stored in cells bound to storage proteins (feritin and hemosiderin)

Recycling RBCs
**Breakdown of Biliverdin**

- **Biliverdin** (green) while in the macrophage is converted to **bilirubin** (yellow)
  - Bilirubin is excreted from the macrophage into the blood
    - Binds to albumin (is lipid soluble)
    - Removed from the blood by the liver
    - Excreted by the liver as part of the bile into the small intestine
    - Converted by intestinal bacteria to urobilins and stercobilins
    - Eliminated in feces
  - Small amounts of bilirubin and break-down products are eliminated by the kidneys

**Recycling RBCs**
Jaundice

- The accumulation of bilirubin in fatty tissues
  - Typically the hypodermis and sclera
  - Results from exceeding the capacity of albumin to carry bilirubin in the blood
    - Blockage of bile ducts
    - Liver disease
      - Low blood albumin
      - Hepatocytes can't remove bilirubin from blood
    - Blood disease
      - Rapid removal of damaged rbc
      - Hemolytic diseases

2. white blood cells
White Blood Cells (WBCs)

- Also called leukocytes
- Do not have hemoglobin
- Have nuclei and other organelles

WBC Functions

- Defend against pathogens
- Remove toxins and wastes
- Attack abnormal cells
WBC Movement

- Most WBCs in:
  - connective tissue proper
  - lymphatic system organs
- Small numbers in blood:
  - 6000 to 9000 per microliter

Circulating WBCs

1. Migrate out of bloodstream
2. Have amoeboid movement
3. Attracted to chemical stimuli (positive chemotaxis)
4. Some are phagocytic:
   - neutrophils, eosinophils, and monocytes
5 Types of WBCs

1. Neutrophils
2. Eosinophils
3. Basophils
4. Monocytes
5. Lymphocytes
Neutrophils

- Also called polymorphonuclear leukocytes
- 50–70% of circulating WBCs

Neutrophil Action

- Very active and highly mobile, first to attack bacteria
- Engulf pathogens
  - phagosome
- Digest pathogens
  - Phagosome fusses with lysosome
- Release prostaglandins and leukotrienes
  - Stimulate inflammation
  - Restrict spread of pathogens
  - Attract other WBCs
Neutrophil Action (cont.)

- **Degranulation**
  - Granules from cytoplasm fuse with the phagosome
  - granules contain:
    - bactericides
      - hydrogen peroxide and superoxide
    - Defensins:
      - peptides that attack pathogen membranes
      - Form large channels in the pathogen

Eosinophils

- Also called **acidophils**
- 2–4% of circulating WBCs
- Attack large parasites
Eosinophil Actions

• Are phagocytic
  – Not the primary mode of attach
• Excrete toxic compounds:
  – nitric oxide
  – cytotoxic enzymes
• Are attracted to site of injury
  – Control inflammation with enzymes that counteract inflammatory effects of neutrophils and mast cells

Basophils

• Are less than 1% of circulating WBCs
• Are small
• Accumulate in damaged tissue
Basophil Actions

- **Release histamine:**
  - dilates blood vessels
  - Mediator of inflammation
  - Histamine also released by mast cells

- **Release heparin:**
  - prevents blood clotting
  - Also released by mast cells

Monocytes

- 2–8% of circulating WBCs
- Are large and spherical
- Enter peripheral tissues and become macrophages
Macrophage Actions

- Engulf large particles and pathogens
- Secrete substances that attract immune system cells and fibroblasts to injured area

Lymphocytes

- 20–30% of circulating WBCs
- Migrate in and out of blood
- Mostly in connective tissues and lymphatic organs
Lymphocyte Actions

- Are part of the body’s specific defense system

3 Classes of Lymphocytes

1. T cells
2. B cells
3. Natural killer (NK) cells
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**T cells**
- Cell-mediated immunity
- Attack foreign cells directly

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**B cells**
- Humoral immunity
- Differentiate into plasma cells
- Synthesize antibodies
Natural Killer Cells (NK)

- Detect and destroy abnormal tissue cells (cancers)

WBC Disorders

- Leukopenia:
  - abnormally low WBC count
- Leukocytosis:
  - abnormally high WBC count
- Leukemia:
  - extremely high WBC count
3. Platelets

Platelets

- Cell fragments involved in human clotting system
- Nonmammalian vertebrates have thrombocytes (nucleated cells)
Platelet Circulation

- Circulates for 9–12 days
- Are removed by spleen
- 2/3 are reserved for emergencies

Platelet Counts

- 150,000 to 500,000 per microliter
- **Thrombocytopenia:**
  - abnormally low platelet count
- **Thrombocytosis:**
  - abnormally high platelet count
3 Functions of Platelets

1. Release important clotting chemicals
2. Temporarily patch damaged vessel walls
3. Actively contract tissue after clot formation

Platelet Production

• Also called thrombocytopoiesis:
  – occurs in bone marrow
Megakaryocytes

- Giant cells
- Located in bone marrow
- Shed cytoplasm in small membrane-enclosed packets (platelets)
- Will produce about 4000 platelets before engulfed by phagocytes

Hormonal Controls

- Thrombopoietin (TPO)
  - Produced by kidneys
    - Stimulates formation of new megakaryocytes
    - Stimulates platelet formation
- Inteleukin-6 (IL-6)
  - Stimulates platelet formation
- Multi-CSF
  - Stimulates formation of new magakaryocytes
Platelet function

Hemostasis

- The cessation of bleeding
- Consists of three phases
  - vascular phase
  - platelet phase
  - coagulation phase
The Vascular Phase

- A cut triggers *vascular spasm*
- 30-minute contraction

3 Steps of the Vascular Phase

1. Endothelial cells contract:
   - exposes basal lamina (collagen) to bloodstream
3 Steps of the Vascular Phase

2. Endothelial cells release:
   - chemical factors:
     • ADP, tissue factor, and prostacyclin
   - local hormones:
     • endothelins
       - stimulate smooth muscle contraction (spasm)
       - Stimulates cell division of endothelial cells, smooth muscle cells, and fibroblasts

3. Endothelial cell membranes become “sticky”:
   - seal off blood flow
     • Vessel ends may stick together
     • Facilitates attachment of platelets
The Platelet Phase

- Begins within 15 seconds after injury

**Figure 19–11b**

The Platelet Phase

- **Platelet adhesion** (attachment):
  - to sticky endothelial surfaces
  - to basal lamina
  - to exposed collagen fibers

  - During this process platelets become activated
The Platelet Phase (cont.)

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

Activated Platelets
Release Clotting Compounds

- Adenosine diphosphate (ADP)
  - Stimulates platelet aggregation and secretion
- Thromboxane A₂ and serotonin
  - Stimulate vascular spasm
- Tissue factor (III)
- PF-3
- Platelet-derived growth factor (PDGF)
  - Stimulates vessel repair
- Calcium ions
  - Required for platelet aggregation and blood clotting
The Platelet Phase

Platelet Plug: Size Restriction

- **Prostacyclin:**
  - released by endothelial cells
  - inhibits platelet aggregation
- **Circulating enzymes:**
  - break down ADP
- **Development of blood clot:**
  - isolates area
- **Inhibitory compounds:**
  - released by other white blood cells
The Coagulation Phase

• Begins 30 seconds or more after the injury

The Coagulation Phase

• Blood clotting (coagulation):
  – Involves a series of steps
  – converts circulating fibrinogen into insoluble fibrin
Blood Clot

- Fibrin network
  - Covers platelet plug
  - Traps blood cells
  - Seals off area

Clotting Factors

- Also called procoagulants
  - Calcium and 11 different Proteins
- Required for normal clotting
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**Plasma Clotting Factors**

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<thead>
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<td><strong>Factor</strong></td>
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<td>I</td>
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<tr>
<td>II</td>
<td>Thrombin</td>
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<td>III</td>
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*Note: The concentration values are in milligrams per milliliter (mg/mL) and are typical for healthy individuals.

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**Cascade Reactions**

- During coagulation phase
- Chain reactions of enzymes and proenzymes
- Form 3 pathways
3 Coagulation Pathways

• **Extrinsic pathway:**
  – begins in the vessel wall
  – outside blood stream
• **Intrinsic pathway:**
  – begins with circulating proenzymes
  – within bloodstream

3 Coagulation Pathways

• **Common pathway:**
  – where intrinsic and extrinsic pathways converge
The **Extrinsic Pathway**

- Damaged endothelial cells and paravascular tissue release tissue factor (TF) (III)
- TF combines with calcium and proconvertin (VII)
- This complex Activates Stuart factor (X)
  - Activated factor X (called prothrombinase) is first step in common pathway

The **Intrinsic Pathway**

- Starts by the activation of Hageman factor (XII) in the blood by exposure to collagen at the injury
  - Also activated by glass and plastic
  - Activation of Hageman factor is assisted by PF-3 released from aggregating platelets
- Activated Hageman factor (XII) combines with plasma thromboplastin (IX) to form a complex
- complex activates Stuart Factor (X)
  - This is called prothrombinase
The Common Pathway

- Activate Stuart Factor X (prothrombinase)
- Converts prothrombin to thrombin
- Thrombin converts fibrinogen to fibrin

Functions of Thrombin

- Stimulates formation of tissue factor
  - stimulates release of PF-3:
  - forms positive feedback loop (intrinsic and extrinsic):
    - accelerates clotting
Bleeding Time

- Normally, a small puncture wound stops bleeding in 1–4 minutes

Clotting: Area Restriction

1. Anticoagulants (plasma proteins):
   - antithrombin
   - alpha-2-macroglobulin
     • Inhibits thrombin
2. Heparin
   - from mast cells and basophils
   - activates antithrombin-III
3. Thrombomodulin
   - activates Protein C
   - stimulates the formation of plasmin
   - breaks down fibrin strands
4. Prostacyclin
   - inhibits platelet aggregation
Other Factors

- Calcium ions (Ca^{2+}) and vitamin K are both essential to the clotting process

Clot Retraction

- After clot has formed:
  - Platelets contract and pull torn area together
    - Accomplished by actomyosin
  - Takes 30–60 minutes
Fibrinolysis

- Slow process of dissolving clot:
  - Requires
    - thrombin from common pathway
    - tissue plasminogen activator
      - released from damaged tissue
    - They Convert Plasminogen to plasmin:
      - digests fibrin strands