Chapter 17: Blood

Overview

• Blood functions
• Composition of whole blood
• Plasma
• RBCs – structure, function, and development
• Blood types
• WBCs
• Platelets
• Hemostasis

The Cardiovascular System

• A circulating transport system composed of:
  – a pump (the heart)
  – a conducting system (blood vessels)
  – a fluid medium (blood)
• Functions to transport:
  – oxygen and carbon dioxide
  – nutrients
  – hormones
  – immune system components
  – waste products

Blood – tissue type?

General Characteristics of Blood

• Blood is a sticky, opaque fluid with a metallic taste
• Color varies from scarlet to dark red
• High viscosity (due to cells)
• Temperature is 38°C
• Normal pH range = 7.35–7.45
• Blood volume (liters) = 7% of body weight (kilograms):
  – adult male: 5 to 6 liters
  – adult female: 4 to 5 liters

Blood - General Functions

• Transport of dissolved gases, nutrients, hormones, and metabolic wastes
• Regulation of pH, body temperature, ion composition of interstitial fluids
• Restriction of fluid loss at the injury site
• Defense against toxins and pathogens
Whole Blood

- **Plasma**: Fluid component
  - Water (90%)
  - Dissolved plasma proteins
  - Other solutes
- **Formed elements**: Cells and fragments
  - RBCs (carry Oxygen)
  - WBCs (immunity)
  - Platelets (cell fragments involved in clotting)

Plasma

- Makes up 50–60% of blood volume
- More than 90% of plasma is water
- Other constituents:
  - Plasma proteins
  - Lactic acid, urea, creatinine
  - Organic nutrients – glucose, carbohydrates, amino acids
  - Electrolytes – sodium, potassium, calcium, chloride, bicarbonate
  - Respiratory gases – oxygen and carbon dioxide

Body Fluids

- Extracellular Fluid (ECF) = Interstitial fluid (IF) and plasma plus a few other body fluids such as CSF
- Plasma and IF exchange water, ions, & small solutes across capillary walls
- Intracellular Fluid (ICF)=fluid inside cells
- ECF and ICF differ in their levels of:
  - $O_2$ and $CO_2$
  - Dissolved proteins: plasma proteins do not pass through capillary walls (too large)

Plasma proteins

- **Albumins** (60%): major component of osmotic pressure of plasma
  - Transport proteins for fatty acids, thyroid hormones, steroid hormones
- **Globulins** (35%): antibodies (immunoglobulins) and transport proteins:
  - hormone-binding proteins
  - metalloproteins
  - apolipoproteins (lipoproteins)
  - steroid-binding proteins
- **Fibrinogens** (4%)
  - functions in blood clotting (form fibrin)
- Others (1%) including hormones
Origins of Plasma Proteins

• 90% made in liver
• Others not made in the liver include:
  – Antibodies made by plasma cells (a special type of WBC)
  – Peptide hormones made by endocrine organs

Serum

• Liquid part of a blood sample in which dissolved fibrinogen has converted to solid fibrin
• Often, this term refers to plasma that has had the clotting proteins removed

Formed Elements

• These are the cells (and quasi-cellular) constituents of blood
• Red blood cells (RBCs) make up 99.9% of blood's formed elements
• White blood cells and platelets make up the rest

Components of Whole Blood

Measuring RBCs

• Red blood cell count: reports the number of RBCs in 1 microliter whole blood
  – Male: 4.5–6.3 million
  – Female: 4.2–5.5 million
• Hematocrit (packed cell volume, PCV): percentage of RBCs in centrifuged whole blood
  – Male: 40–54 (avg = 46)
  – Female: 37–47 (avg = 42)
RBCs make up about 1/3 of all cells in the body!
Why do RBCs look hollow?

No nucleus
Biconcave structure

Importance of RBC
Shape and Size
1. High surface-to-volume ratio:
   - Increase surface area for gas exchange
2. Discs form stacks:
   - Smooths flow through narrow blood vessels
3. Discs bend and flex entering small capillaries:
   - 7.8 µm RBC passes through 4 µm capillary

RBC Structure
- Small and highly specialized disc
- Thin in middle and thicker at edge

RBC characteristics
- Shaped like biconcave discs
- Function primarily to carry oxygen
  - Contain hemoglobin (95% of RBC protein)
- Lack a nucleus and contain few organelles
  (no mitochondria, ribosomes)
- Life span approx. 120 days
- Generate ATP anaerobically (no mitochondria) so they don’t consume any of the oxygen that they transport

Hemoglobin (Hb)
- Protein molecule inside RBCs that transports respiratory gases
- Composed of:
  - Four protein chains called globins
    - Adults: 2 alpha and 2 beta chains
  - Each of these four chains is bound to a pigment molecules called heme
    - Each of which contain one iron ion (red color) and bind one oxygen molecule
  - Each RBC ~280 million molecules

Hemoglobin Structure
- Complex quaternary structure
Fetal Hemoglobin (Hb F)
- Made up of 2 alpha and 2 gamma chains
- Has a higher affinity for oxygen than adult hemoglobin, "steals" oxygen from maternal hemoglobin in utero

RBC fate
After 100-120 days:
- 10% hemolyze in the blood
- 90% removed by macrophages in the spleen (especially), the liver and the bone marrow and heme is recycled:
  - heme degraded to biliverdin (green)
  - biliverdin converted to bilirubin (yellowish)
  - Bilirubin leaves Mphage, binds to albumin, tranported to liver for excretion in bile (high levels of bilirubin in jaundice)
- In colon, bacteria convert bilirubin to urobilinogens and stercobilinogens – colors feces
- Some is absorbed into circulation and eliminated by kidneys in urine – colors urine

Serum Bilirubin
- Red cells account for 85% of bilirubin formed = Unconjugated
- In liver it is conjugated and secreted into bile to large intestine
- Hemolytic jaundice: elevated levels of unconjugated bilirubin
- Obstructive jaundice: elevated levels of conjugated bilirubin because bile ducts are blocked (bile that can’t be secreted)

Recycling
- Iron
  - Heme iron is removed in spleen (or liver or bone marrow)
  - Binds to plasma protein called transferrin
  - Transferrin is taken up in bone marrow and used to make new heme in developing RBCs
  - Very efficient
- Globin protein
  - Amino acids travel through bloodstream to bone marrow and can be used in erythropoiesis

RBC recycling

Hematopoiesis
- Development of all the cells of the lymphoid/myeloid lineage
  - Includes: RBCs, all types of WBCs, and platelets
- All start out as hemocytoblasts, a pluripotent stem cell:
  - Myeloid stem cells give rise to RBCs, platelets and some WBCs
  - Lymphoid stem cells give rise to lymphocytes only
- Occurs in red bone marrow (axial and epiphyses)
Erythropoiesis

• Rate of RBC production controlled by erythropoietin - EPO (from where?)
• What is necessary for healthy RBCs?
  - amino acids
  - iron
  - vitamins B₁₂, B₆, and folic acid

RBC Maturation

• Hematocytoblast → myeloid stem cell → proerythroblast → erythroblast → reticulocyte → mature RBC
• Reticulocytes have no nucleus and enter bloodstream still containing ribosomes and mRNA. After a day or so of furious Hb production, lose their organelles and become mature RBCs

Regulation of Erythropoiesis

• Circulating erythrocytes – the number remains constant and reflects a balance between RBC production and destruction
  - Too few RBCs leads to tissue hypoxia
  - Too many RBCs causes undesirable blood viscosity

Blood Types

• Genetically determined cell surface markers (antigens) on RBCs, including
  - ABO group – glycolipids on RBC surface
  - Rh factor – membrane protein

4 Basic Blood Types

• A has surface antigen A
• B has surface antigen B
• AB has both antigens A and B
• O has neither A nor B

• A has type B antibodies
• B has type A antibodies
• O has both A and B antibodies
• AB has neither A nor B antibodies
4 Basic Blood Types

- Antigens also called agglutinogens
- Antibodies called agglutinins

ABO Antigens and Antibodies

<table>
<thead>
<tr>
<th>Surface Antigens</th>
<th>Antibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Anti-B</td>
</tr>
<tr>
<td>B</td>
<td>Anti-A</td>
</tr>
<tr>
<td>AB</td>
<td>A, B, none</td>
</tr>
<tr>
<td>O</td>
<td>Anti-A, Anti-B</td>
</tr>
</tbody>
</table>

The Rh Factor

- Also called D antigen
- Either Rh positive (Rh⁺) or Rh negative (Rh⁻)
- Only sensitized Rh⁻ blood has anti-Rh antibodies

<table>
<thead>
<tr>
<th>Surface Antigens</th>
<th>Antibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rh⁺</td>
<td>Rh factor</td>
</tr>
<tr>
<td>Rh⁻</td>
<td>none</td>
</tr>
<tr>
<td>Rh⁻⁰ Sens</td>
<td>Anti Rh</td>
</tr>
</tbody>
</table>

Cross-Reaction

- If donor and recipient blood types not compatible:
  - Plasma antibody meets its specific surface antigen and blood will agglutinate and hemolyze

Blood Type Test

- Determines blood type and compatibility
**Cross-Match Test**

- Performed on donor and recipient blood for compatibility to blood surface antigens other than ABO and Rh

**Blood type questions**

- Which blood type is the best in emergency settings (hint: which type can be given to anyone?)
- Which blood type is the lucky one that can receive blood from any donor?

**Hemolytic Disease of the Newborn (Erythroblastosis Fetalis)**

- Mother is Rh-
- Father and fetus are Rh+
- First pregnancy = sensitization at delivery due to hemorrhage
- Second pregnancy = Anti-Rh IgG antibodies can cross placenta to attack fetal RBCs → hemolysis and excess presence of erythroblasts

**Hemolytic Disease of the Newborn**

Rh⁺ Fetal cells enter mother's circulation at delivery

Second pregnancy is attacked by maternal antibodies

Treatment?
Transfusions

- Unit whole blood = 500ml
- About half of this is plasma which contains antibodies. There is a slight risk of graft versus host (GVH) reactions, but since the volume in one unit is only about 10% of total plasma volume, usually gets diluted out
- If RBCs are needed, can use packed RBCs instead of whole blood

White Blood Cells (WBCs)

- Leukocytes: the only blood components that are complete cells; have nuclei and other organelles, not involved in oxygen transport.
- Functions:
  - Defend against pathogens
  - Remove toxins and wastes
  - Attack abnormal cells

WBC in blood vs. tissue

- Very small numbers in blood:
  - 6000 to 9000 per microliter
  - Outnumbered 1000:1 by RBCs
  - But only 1% of WBC are in blood
- Most WBCs are not found in blood but instead in connective tissue proper and in lymphatic system organs
- Can leave capillaries via diapedesis

Circulating WBCs

- WBCs can migrate out of capillaries into tissues via diapedesis
- Have amoeboid movement (using actin)
- Attracted to chemical stimuli (positive chemotaxis)
- Some are phagocytic: neutrophils, eosinophils, and monocytes

5 Types of WBCs

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

“Never Let Monkeys Eat Bananas”
Neutrophils

- Also called polymorphonuclear leukocytes
- 50–70% of circulating WBCs
- Pale cytoplasm granules with lysosomal enzymes and bactericides (hydrogen peroxide and superoxide)
- Phagocytes that are the first to attack bacteria, engulf and digest pathogens with defensins
- Release prostaglandins and leukotrienes (inflammation and alarm call)
- Form pus

Eosinophils

- Also called acidophils
- 2–4% of circulating WBCs
- Attack large parasites by excreting toxic compounds
- Sensitive to allergens
- Control inflammation with enzymes that counteract inflammatory effects of neutrophils and mast cells

Basophils

- Less than 1% of circulating WBCs
- Small cells that accumulate in damaged tissue
- Release histamine to dilate blood vessels and heparin prevent blood clotting
- Similar to mast cells (found in the tissues)

Monocytes

- 2–8% of circulating WBCs
- Are large and spherical
- Enter peripheral tissues and become macrophages
- Engulf large particles and pathogens
- Secrete substances that attract immune system cells and fibroblasts to injured area

Lymphocytes

- T cells, B cells and NK cells
- 20–30% of circulating WBCs
- Note the little cytoplasm
- Migrate in and out of blood
- Most of them are in connective tissues and lymphatic organs (spleen, lymph nodes)
- Respond to specific antigens

The Differential Count of Circulating WBCs

- Detects changes in WBC populations during infections, inflammation, and allergic reactions
WBC Disorders

- **Leukopenia:**
  - abnormally low WBC count

- **Leukocytosis:**
  - high WBC count (normal response to infection)

- **Leukemia:**
  - extremely high WBC count

Blood disease nomenclature

- **-penia** (poverty): too little of a cell type in the blood
- **-cytosis:** too much of a cell type in the blood
- **-emia:** referring to the presence of something (anything) in the blood

WBC classes

- **Granulocytes** – neutrophils, eosinophils, and basophils
  - Contain cytoplasmic granules that stain specifically (acidic, basic, or both) with Wright’s stain
  - Are larger and usually shorter-lived than RBCs
  - Have lobed nuclei
  - Are all phagocytic cells

- **Agranulocytes** – lymphocytes and monocytes:
  - Lack visible cytoplasmic granules
  - Have spherical (lymphocytes) or kidney-shaped (monocytes) nuclei

WBC Production

- Like RBCs, WBCs originate from hemocytoblasts in the bone marrow
- Hemocytoblasts differentiate into **myeloid stem cells** and **lymphoid stem cells**
- Myeloid stem cells become **myeloblasts**, which give rise to neutrophils, basophils, and eosinophils (granulocytes), OR **monoblasts**, which become monocytes.
- Lymphoid stem cells become **lymphoblasts**, and give rise to lymphocytes (B, T, and NK cells)
- All complete their development in the bone marrow except T cells, which mature in the thymus

4 Colony-Stimulating Factors (CSFs)

- **Hormones that regulate blood cell populations:**
  - **M-CSF:**
    - stimulates monocyte production
  - **G-CSF:**
    - stimulates granulocyte production (neutrophils, eosinophils, and basophils)
  - **GM-CSF:**
    - stimulates granulocyte and monocyte production
  - **Multi-CSF:**
    - accelerates production of granulocytes, monocytes, platelets, and RBCs (all blood except lymphocytes)
Summary: Formed Elements of Blood

Table 19–3

Platelets
- Cell fragments involved in human clotting system (cf. thrombocytes)
- Functions:
  - Release important clotting chemicals
  - Temporarily patch damaged vessel walls
  - Actively contract tissue after clot formation
- Circulate for 9–12 days in blood
- Removed by spleen
- 1/3 are reserved in spleen for emergencies
- Have a central granule containing serotonin, Ca^{2+}, enzymes, ADP, and platelet-derived growth factor (PDGF)

Platelet Counts
- 150,000 to 500,000 per microliter
- **Thrombocytopenia:** abnormally low platelet count
- **Thrombocytosis:** abnormally high platelet count

Thrombocytopoiesis
- Like RBCs and WBCs (except lymphocytes), platelets come from myeloid stem cells in bone marrow
- Differentiate into giant cells called Megakaryocytes, which break off membrane bound packets of cytoplasm to form platelets
- Controlled by Thrombopoietin (TPO) from kidneys, Inteleukin-6 (IL-6), & Multi-CSF

Hemostasis
- Cessation of bleeding:
  - vascular phase
  - platelet phase
  - coagulation phase
- Provides framework for repairs

The Vascular Phase
- A cut triggers vascular spasm: smooth muscles in the vessel spasm to limit blood loss
- Immediate, 30-minute contraction
**The Platelet Phase**

- Begins within 15 seconds after injury

**Activated Platelets**

- Become spherical and extend cytoplasmic processes
- Granules break down and release several compounds
  - Serotonin enhances vascular spasm
  - Adenosine diphosphate (ADP) → aggregation
  - Thromboxane A₂ → spasms and aggregation
  - Clotting factors (see later)
- Positive f/b leads to plug formation in 1 min

**The Coagulation Phase**

- Begins 30 seconds – 1 min after the injury

**Platelet Plug Size is Restriction to Injury Site**

- **Prostacyclin:**
  - released by intact endothelial cells, inhibits platelet aggregation to the site of injury only
- **Inhibitory compounds:**
  - released by other white blood cells
- **Circulating plasma enzymes:**
  - break down ADP
- **Negative (inhibitory) feedback:**
  - at high concentration, serotonin blocks ADP action
- **Development of blood clot:**
  - isolates area by sealing it off

**The Platelet Phase**

- Platelets do not stick to each other or to blood vessel epithelium
- But when epithelium is damaged, platelets can bind to exposed collagen with help of Von Willebrand Factor (VWF)
- **Platelet adhesion** (attachment):
  - Platelets also become activated and aggregate (stick together) to form a platelet plug that closes small breaks

**Platelet Plug Size is Restriction to Injury Site**

- **Fibrinogen:**
  - circulating fibrinogen into insoluble fibrin and turns liquid blood into a gel
- **Blood clot:**
  - Covers platelet plug and cements it
  - Traps blood cells
  - Seals off area
Coagulation

Figure 17.13a

Clotting Factors

- Proteins or ions in plasma required for normal clotting
  - 11 major proteins
  - Calcium ions

3 Coagulation Pathways

- **Extrinsic pathway:**
  - begins in the vessel wall outside bloodstream
- **Intrinsic pathway:**
  - begins with circulating proenzymes within bloodstream

Normally, both are activated

- **Common pathway:**
  - where intrinsic and extrinsic pathways converge

The Extrinsic Pathway

- Damaged cells release **tissue factor (TF)** also called **factor III**
- TF + other compounds including Calcium = enzyme complex
- Activates **Factor X** (ten)

Shorter, faster pathway that bypasses several steps in the intrinsic pathway

The Intrinsic Pathway

- Activation of proenzymes by exposed **collagen**
- Combines with **PF–3** from platelets
- Series of reactions involving calcium result in factors **VIII** and **IX** combining to activate **Factor X**

Slower, more productive pathway

Happens in vitro (activated by glass surfaces)

The Common Pathway

- Activated **Factor X** leads to enzyme **prothrombinase (prothrombin activator)**
- This converts **prothrombin to thrombin**
- **Thrombin** converts **fibrinogen** (a ubiquitous plasma protein) to **fibrin**
- **Fibrin** polymer covers the platelet plug
Thrombin

• Stimulates formation of tissue factor, which stimulates release of PF-3 by platelets
• This positive feedback loop involves both intrinsic and extrinsic pathways and accelerates clotting

Clotting Area is Restricted

1. Anticoagulants (plasma proteins):
   – antithrombin-III
   – Fibrin itself binds thrombin and prevents it from exerting positive feedback
2. Heparin from endothelium
3. Prostacyclin from endothelium
4. Protein C (activated by thrombomodulin) activates plasmin

Other Factors

• Calcium ions (Ca²⁺) and vitamin K (from diet and colon bacteria) are both essential to the clotting process

Clot Retraction

• After clot has formed, platelets contract and pull torn area together, squeezing out serum
• Stabilizes injury site, facilitates repair
• Takes 30–60 minutes
• Repair
  – Platelet-derived growth factor (PDGF) stimulates rebuilding of blood vessel wall
  – Fibroblasts form a connective tissue patch
  – Stimulated by vascular endothelial growth factor (VEGF), endothelial cells multiply and restore the endothelial lining

Fibrinolysis

• Slow process of dissolving clot
• thrombin and tissue plasminogen activator (t-PA): activate plasminogen
  – Note that this is the same thrombin that helped activate the fibrin in the first place
• Plasminogen produces plasmin, which digests fibrin strands

Summary

• Blood functions
• Composition of whole blood
• Plasma
• RBCs – structure, function, and development
• Blood types
• WBCs
• Platelets
• Hemostasis
Blood disorders

Complete Blood Count (CBC)
- The CBC is used as a broad screening test to check for such disorders as anemia, infection, and others. It is actually a panel of tests that examines different parts of the blood and includes the following:
- **Red blood cell (RBC) count** is a count of the actual number of red blood cells per volume of blood. Both increases and decreases can point to abnormal conditions.
- **Hemoglobin** measures the amount of oxygen-carrying protein in the blood.
- **Hematocrit** measures the percentage of blood that is cells (red blood cells).

CBC tests: WBCs and Platelets
- **White blood cell (WBC) count** is a count of the actual number of white blood cells per volume of blood. Both increases and decreases can be significant.
- **White blood cell differential** looks at the numbers of the five types of white blood cells present.
- **Platelet count** is the number of platelets in a given volume of blood. Both increases and decreases can point to abnormal conditions of excess bleeding or clotting.

Blood Volume
- **Hypovolemia**
- **Hypervolemia**
- **Questions:**
  - What might cause each?
  - Symptoms?
  - Which is more common?
  - How does your body prevent these conditions (or correct them when they develop)?

Polycythemia
- Elevated hematocrit with normal blood volume
- **Erythrocytosis**: excess RBCs.
  - Happens when you travel to altitude (less oxygen can be carried per RBC, need more cells)
  - Occurs in heart failure or lung disease (inadequate tissue oxygenation), can make blood thick
  - Blood doping: Inject EPO or remove packed RBCs and reinfuse just before a race

Hemoglobin Disorders
- **Thalassemias**: result from inadequate production of either the alpha or beta chain of hemoglobin. Lowers number of mature RBCs in blood. Treatment includes transfusions.
- **Sickle-cell anemia**: mutation in beta globin gene that does not cause inadequate expression but causes another problem.
Thalassemias
• Alpha-thalassemia
  – We have four copies of alpha globin gene
  – 3 good/1bad: carrier
  – 2good/2bad: alpha-thalassemia trait
  – 1good/3bad: microcytic anemia
  – 4bad: die before birth
• Beta-thalassemia
  – We have only two copies of beta globin gene
  – No good copies: beta-thalassemia major:
    • Severe microcytic anemia
  – One good copy: beta-thalassemia trait
    • Few clinical symptoms

Anemias
• Hematocrit or hemoglobin levels are below normal, caused by several conditions
• Characterized by a decrease in the oxygen carrying capacity of the blood (due to the problems with RBCs or with hemoglobin)
• Can be macrocytic (big RBCs) or microcytic

Sickle-Cell Anemia
• Mutation in beta globin gene resulting in production of HbS
• At low oxygen, cells with HbS become rigid and adopt a “sickle” shape: makes them fragile and can become stuck in small capillaries (last 10 days in blood)
• One bad copy: sickling trait
• Two bad copies: SCA
• Treatments?
  Transfusions, hydroxyurea, butyrate

Pernicious Anemia
• Low RBC production due to lack of vitamin B₁₂
• Vitamin B₁₂ absorption requires Intrinsic factor (IF) from cells in the stomach. No IF, no B₁₂.

Iron Deficiency Anemia
• Caused by low dietary iron or blood loss
• RBCs made without enough functional hemoglobin: microcytic
• Low hematocrit
• 12% of menstruating women may have it
• Treatment?

Changes in blood parameters
• Macrocytic anemia caused by vitamin B₁₂ deficiency.
• Microcytic anemia is seen in iron deficiency anemia or thalassemias.
Iron Loading

- Excess iron intake, gets deposited in peripheral tissues notably heart valves
- Very dangerous, leads to heart failure
- Can develop as a result of repeated transfusions of whole blood given to severely anemic patients – they need the functional RBCs, but the RBCs keep getting broken down and the iron is retained

Leukemia

- Blood cancer – no solid tumor (cf. lymphoma)
- Myeloid or lymphoid
- Lymphoid more common in children
- Myeloid more common in adults
- Treatment?

Clotting Disorders: Excessive Clotting

- Embolus
- Thrombus
- Anticoagulant therapies:
  - Heparin: activates antithrombin III
  - Coumadin: blocks Vitamin K action
  - t-PA: activates plasmin
  - Streptokinase/urokinase: also activate plasmin
  - Aspirin: inactivates platelet enzymes and prostacyclin production
  - EDTA – Calcium chelator

Clotting Disorders: Inadequate Clotting

- Hemophilia A: Gene for factor VIII is on X chromosome (sex-linked) and so this type of hemophilia is almost exclusively in males
- DIC – disseminated intravascular coagulation: small fibrin clots form throughout the blood, leads to shortage of fibrin when it is needed