Chapter 17

Blood
17.2 Composition of Blood

- Blood is the only fluid tissue in body
- Type of connective tissue
  - Matrix is nonliving fluid called plasma
  - Cells are living blood cells called formed elements
    - Cells are suspended in plasma
    - Formed elements
      - Erythrocytes (red blood cells, or RBCs)
      - Leukocytes (white blood cells, or WBCs)
      - Platelets
Blood
Figure 17.1 The major components of whole blood.

1. Withdraw blood and place in tube.
2. Centrifuge the blood sample.

- **Plasma**
  - 55% of whole blood
  - Least dense component

- **Buffy coat**
  - Leukocytes and platelets
  - <1% of whole blood

- **Erythrocytes**
  - 45% of whole blood (hematocrit)
  - Most dense component

- **Formed elements**
Physical Characteristics and Volume

• Blood is a sticky, opaque fluid with metallic taste
• Color varies with O₂ content -
• pH -
• Makes up ~8% of body weight
• Average volume:
  – Males:
  – Females:
17.1 Functions of Blood

• Functions include
  – Transport
    • What?

  – Regulation
    • Which substances?

  – Protection from what?
(b) Photomicrograph of a human blood smear, Wright’s stain (610×)
17.3 Erythrocytes
Structural Characteristics

• Erythrocytes are small-diameter (7.5 μm) cells that contribute to gas transport
• Cell has biconcave disc shape, is anucleate, and essentially has no organelles
• Filled with hemoglobin (Hb) for gas transport
• RBC diameters are larger than some capillaries
• Contain plasma membrane protein spectrin and other proteins
  – Spectrin provides flexibility to change shape
Figure 17.3 Structure of erythrocytes (red blood cells).

- **Side view (cut)**: 2.5 μm
- **Top view**: 7.5 μm
Figure 17.4 Structure of hemoglobin.

(a) Hemoglobin consists of globin (two alpha and two beta polypeptide chains) and four heme groups.

(b) Iron-containing heme pigment.
Function of Erythrocytes (cont.)

- $O_2$ loading in lungs
  - Produces oxyhemoglobin (ruby red)
- $O_2$ unloading in tissues
  - Produces deoxyhemoglobin, or reduced hemoglobin (dark red)
- $CO_2$ loading in tissues
  - 20% of $CO_2$ in blood binds to Hb, producing carbaminohemoglobin
Sickle-Cell Anemia

• Results from a defective gene coding for an abnormal hemoglobin called hemoglobin S (HbS)
  – HbS has a single amino acid substitution in the beta chain
  – This defect causes RBCs to become sickle-shaped in low oxygen situations
Homeostatic Imbalance - Sickle-cell Anemia

- Black people of African malarial belt and descendants
- Protects against **Malaria**
- Sickle-cell gene
  - Two copies $\rightarrow$ Sickle-cell anemia
  - One copy $\rightarrow$ Sickle-cell trait; milder disease; better chance to survive malaria
Sickle-cell Anemia: Treatments

• Acute crisis treated with transfusions; inhaled nitric oxide
• Preventing sickling
  – Hydroxyurea induces fetal hemoglobin (which does not sickle) formation
  – Stem cell transplants
  – Gene therapy
  – Nitric oxide for vasodilation
Hematopoiesis

- Blood cell formation in red bone marrow
- In adult, found in axial skeleton, girdles, and proximal epiphyses of humerus and femur
- Hematopoietic stem cells (Hemocytoblasts)
  - Give rise to all formed elements
Figure 17.5 Erythropoiesis: formation of red blood cells.

Hematopoietic stem cell (hemocytoblast) → Proerythroblast → Basophilic erythroblast → Polychromatic erythroblast → Orthochromatic erythroblast → Reticulocyte → Erythrocyte

Developmental pathway:
- Phase 1: Ribosome synthesis
- Phase 2: Hemoglobin accumulation
- Phase 3: Ejection of nucleus

A reticulocyte image is also shown.
Regulation and Requirements of Erythropoiesis

• Too few RBCs lead to tissue hypoxia
• Too many RBCs increase blood viscosity
• > 2 million RBCs are made per second
• Balance between RBC production and destruction depends on:
  – Hormonal controls
  – Adequate supplies of iron, amino acids, and B vitamins
Figure 17.6 Erythropoietin mechanism for regulating erythropoiesis.

**Stimulus:** Hypoxia (inadequate O₂ delivery) due to
- Decreased RBC count
- Decreased amount of hemoglobin
- Decreased availability of O₂

1. **Enhanced erythropoiesis increases RBC count.**
2. **Kidney (and liver to a smaller extent) releases erythropoietin.**
3. **Erythropoietin stimulates red bone marrow.**
4. **O₂-carrying ability of blood rises.**
5. **Homeostasis: Normal blood oxygen levels**

**Homeostasis:** Normal blood oxygen levels
Clinical Applications – Possible causes of kidney hypoxia

• Insufficient number of RBC

• Reduced oxygenation of blood

• Increased aerobic demands

• Treatment
Figure 17.7 Life cycle of red blood cells.

1. Low O₂ levels in blood stimulate kidneys to produce erythropoietin.
2. Erythropoietin levels rise in blood.
3. Erythropoietin and necessary raw materials in blood promote erythropoiesis in red bone marrow.
4. New erythrocytes enter bloodstream; function about 120 days.
5. Aged and damaged red blood cells are engulfed by macrophages of spleen, liver, and bone marrow; the hemoglobin is broken down.

- Hemoglobin
- Heme
- Globin
- Iron is stored as ferritin or hemosiderin.
- Amino acids

Iron is bound to transferrin and released to blood from liver as needed for erythropoiesis.

Billirubin is secreted into intestine in bile where it is metabolized to stercobilin by bacteria.

- Stercobilin is excreted in feces.
- Food nutrients (amino acids, Fe, B₁₂, and folic acid) are absorbed from intestine and enter blood.

Circulation

- Bilirubin is picked up by the liver.

Raw materials are made available in blood for erythrocyte synthesis.
Disorders that produce jaundice

- Liver malfunction – cirrhosis and hepatitis
- Gallstones
- Erythroblastosis fetalis
- Newborn jaundice
Erythrocyte Disorders

• Most erythrocyte disorders are classified as either **anemia** or **polycythemia**

• **Anemia**
  – Blood has abnormally low O$_2$-carrying capacity that is too low to support normal metabolism
  – Sign of problem rather than disease itself
  – Symptoms: fatigue, pallor, dyspnea, and chills
  – Three groups based on cause
    • Blood loss
    • Not enough RBCs produced
    • Too many RBCs being destroyed
Anemias - OYO

- Hemorrhagic anemia
- Iron-deficiency anemia
- Pernicious anemia
- Renal anemia
- Aplastic anemia
- Hemolytic anemia
- Sickle Cell anemia
- Thalasemia
• Polycythemia
  – Abnormal excess of RBCs; increases blood viscosity, causing sluggish blood flow
  – *Polycythemia vera*: Bone marrow cancer leading to excess RBCs
    • Hematocrit may go as high as 80%
    • Treatment: therapeutic phlebotomy
  – *Secondary polycythemia*: caused by low O$_2$ levels (example: high altitude) or increased EPO production
17.6 Hemostasis

- **Hemostasis**: fast series of reactions for stoppage of bleeding
- Requires **clotting factors** and substances released by platelets and injured tissues
- Three steps involved
  - Step 1: Vascular spasm
  - Step 2: Platelet plug formation
  - Step 3: Coagulation (blood clotting)
Figure 17.13 Events of hemostasis.

1. **Vascular spasm**
   - Smooth muscle contracts, causing vasoconstriction.

2. **Platelet plug formation**
   - Injury to lining of vessel exposes collagen fibers; platelets adhere.
   - Platelets release chemicals that make nearby platelets sticky; platelet plug forms.

3. **Coagulation**
   - Fibrin forms a mesh that traps red blood cells and platelets, forming the clot.
Step 3: Coagulation (cont.)

• Phase 1: Two pathways to prothrombin activator
  – Initiated by either **intrinsic** or **extrinsic** pathway (usually both)
    • Triggered by tissue-damaging events
    • Involves a series of procoagulants
    • Each pathway cascades toward and ends with the activation of factor X
  – Factor X then complexes with Ca\(^{2+}\), PF\(_3\) (platelet factor 3), and factor V to form prothrombin activator
Figure 17.14-1 The intrinsic and extrinsic pathways of blood clotting (coagulation).

**Phase 1**

**Intrinsic pathway**
- Vessel endothelium ruptures, exposing underlying tissues (e.g., collagen)
- Platelets cling and their surfaces provide sites for mobilization of factors

**Extrinsic pathway**
- Tissue cell trauma exposes blood to
  - Tissue factor (TF)

**Intrinsic pathway**
- XI
- XII
- IX
- IXa/VIIIa complex
- VIII
- VIIIa complex
- X
- Xa

**Extrinsic pathway**
- VII
- VIIa
- Ca2+
- TF/VIIa complex

**Phospholipid surfaces of aggregated platelets**

**Prothrombin activator** consists of factors Xa, V, Ca2+, and phospholipid surface.
• Phase 2: Pathway to thrombin
  – Prothrombin activator catalyzes transformation of prothrombin to active enzyme thrombin
Figure 17.14-2 The intrinsic and extrinsic pathways of blood clotting (coagulation).

Phase 2

- Prothrombin (II)
- Thrombin (IIa)

Phase 3

- Fibrinogen (I) (soluble)
- Fibrin (insoluble polymer)
- Cross-linked fibrin mesh

- Ca^{2+}
- XIII
- XIIIa
Step 3: Coagulation (cont.)

• Phase 3: Common pathway to the fibrin mesh
  – Thrombin converts soluble fibrinogen to fibrin
  – Fibrin strands form structural basis of clot
  – Fibrin causes plasma to become a gel-like trap catching formed elements
  – Thrombin (along with Ca\(^{2+}\)) activates factor XIII (fibrin stabilizing factor), which:
    • Cross-links fibrin
    • Strengthens and stabilizes clot
  – Anticoagulants: factors that normally dominate in blood to inhibit coagulation
Figure 17.14-2 The intrinsic and extrinsic pathways of blood clotting (coagulation).

Phase 2
- Prothrombin (II)
- Thrombin (IIₐ)

Phase 3
- Fibrinogen (I) (soluble)
- Fibrin (insoluble polymer)
- Cross-linked fibrin mesh
- Ca²⁺
- XIII
- XIIIₐ
Figure 17.14 The intrinsic and extrinsic pathways of blood clotting (coagulation).

**Phase 1**

**Intrinsic pathway**
- Vessel endothelium ruptures, exposing underlying tissues (e.g., collagen)
- Platelets cling and their surfaces provide sites for mobilization of factors

**Extrinsic pathway**
- Tissue cell trauma exposes blood to
- Tissue factor (TF)

**Phase 2**

**Prothrombin (II)**
- Thrombin (IIa)

**Phase 3**

**Fibrinogen (I)** (soluble)
- Fibrin (insoluble polymer)
- Cross-linked fibrin mesh

**Prothrombin activator** consists of factors XIa, V, Ca²⁺, and phospholipid surface.

Ca²⁺

XII

XI

IX

Ca²⁺

IXa

Ca²⁺

Ca²⁺

VIII

IX, VIII complex

Prothrombin activator

Ca²⁺

X

Ca²⁺

VII

Ca²⁺

Ca²⁺

Ca²⁺

Ca²⁺

Ca²⁺

Ca²⁺

Ca²⁺

Ca²⁺

Ca²⁺
Figure 17.15 Scanning electron micrograph of erythrocytes trapped in a fibrin mesh.
Clot Retraction and Fibrinolysis

• Clot must be stabilized and removed when damage has been repaired

• Clot retraction
  – Actin and myosin in platelets contract within 30–60 minutes
  – Contraction pulls on fibrin strands, squeezing serum from clot
    • Serum is plasma minus the clotting proteins
  – Draws ruptured blood vessel edges together
• Vessel is healing even as clot retraction occurs

• **Platelet-derived growth factor (PDGF)** is released by platelets
  – Stimulates division of smooth muscle cells and fibroblasts to rebuild blood vessel wall

• **Vascular endothelial growth factor (VEGF)** stimulates endothelial cells to multiply and restore endothelial lining
• **Fibrinolysis**
  – Process whereby clots are removed after repair is completed
  – Begins within 2 days and continues for several days until clot is dissolved
  – **Plasminogen**, plasma protein that is trapped in clot, is converted to **plasmin**, a fibrin-digesting enzyme
    • **Tissue plasminogen activator** (**tPA**), factor XII, and thrombin all play a role in conversion process
Clinical Application – Thrombolytic Agents

- Thrombolytic Agents – Clot busting drugs
  - tPA – alteplase, streptokinase, urokinase
    - Given for ischemic strokes and myocardial infarctions up to 4.5 hours after onset of event.
Factors Limiting Clot Growth or Formation

• Two mechanisms limit clot size
  – Swift removal and dilution of clotting factors
  – Inhibition of activated clotting factors

• Thrombin bound onto fibrin threads

• Antithrombin III inactivates unbound thrombin

• Heparin in basophil and mast cells inhibits thrombin by enhancing antithrombin III
Factors Preventing Undesirable Clotting

• Platelet adhesion is prevented by
  – Smooth endothelium of blood vessels prevents platelets from clinging
  – Antithrombic substances nitric oxide and prostacyclin secreted by endothelial cells
  – Vitamin E quinone acts as potent anticoagulant
Prevention of Undesirable Clots

- Substances used to prevent undesirable clots include:
  - **TPA** – given in stoke and heart attack
  - **Heparin** – an anticoagulant used clinically for pre- and postoperative cardiac care
  - **Warfarin (Coumadin)** – used for those prone to atrial fibrillation
  - **Aspirin** – an antiprostaglandin that inhibits thromboxane A₂ – How does this reduce odds of heart attack and stroke??????
  - **Dabigatran**
Disorders of Hemostasis

• Two major types of disorders
  – **Thromboembolic disorders**: result in undesirable clot formation
  – **Bleeding disorders**: abnormalities that prevent normal clot formation

• **Disseminated intravascular coagulation (DIC)**
  – Involves both types of disorders
• Thromboembolic conditions
  – Thrombi and emboli
    • Thrombus:
    • Embolus:
    • Embolism:
    • Risk factors: atherosclerosis, inflammation, slowly flowing blood or blood stasis from immobility

• How can these be prevented?
Thrombus vs. Embolus

How pulmonary embolism occurs

1. A blood clot forms in a vein and breaks free from the vessel wall.
2. The embolus travels through bloodstream and heart into the vessels of the lung.
3. The embolus obstructs a vessel in the lung and deprives tissue of blood.

Deep vein thrombosis

Sitting too long in one position can cause deadly blood clots in the legs, a condition known as deep vein thrombosis. It can be serious if the clot ultimately blocks blood flow in the lungs.

Embolization

Emboli can travel through the heart to an artery in the lung, where it can block blood flow and cause potentially fatal complications.

Clot formation

When the legs are inactive for a long period of time, blood can pool, causing a clot.

Explosion

As the clot grows in size, it will shed pieces known as emboli.
Bleeding Disorders - OYO

- Thrombocytopenia
- Vitamin K Deficiency
- Cirrhosis
- Hepatitis
- Hemophilia