Chapter 18
The Circulatory System: Blood

• Introduction
• Erythrocytes
• Blood types
• Leukocytes
• Platelets
• Hemostasis – the control of bleeding
Functions of Circulatory System

• Transport
  – $O_2$, $CO_2$, nutrients, wastes, hormones, and heat

• Protection
  – WBCs, antibodies, and platelets

• Regulation
  – fluid regulation and buffering
Blood

• Adults have 4-6 L of blood
  – plasma, a clear extracellular fluid
  – formed elements (blood cells and platelets)
• Centrifuge blood to separate components
Properties of Blood

• Viscosity - resistance to flow
  – whole blood 5 times as viscous as water

• Osmolarity
  – total molarity of dissolved particles
    • sodium ions, protein, and RBCs
  – high osmolarity
    • causes fluid absorption into blood, raises BP
  – low osmolarity
    • causes fluid to remain in tissues, may result in edema
Formed Elements of Blood
Plasma and Plasma Proteins

• Plasma – liquid portion of blood
  – serum remains after plasma clots
• 3 major categories of plasma proteins
  – albumins - most abundant
    • contributes to viscosity and osmolarity, influences blood pressure, flow and fluid balance
  – globulins (antibodies)
    • provide immune system functions
    • alpha, beta and gamma globulins
  – fibrinogen
    • precursor of fibrin threads that help form blood clots
• Plasma proteins formed by liver
  – except globulins (produced by plasma cells)
Nonprotein Components of Plasma

- Nitrogenous compounds
  - amino acids
    - from dietary protein or tissue breakdown
  - nitrogenous wastes (urea)
    - toxic end products of catabolism
    - normally removed by the kidneys

- Nutrients
  - glucose, vitamins, fats, minerals, etc

- $O_2$ and $CO_2$

- Electrolytes
  - $Na^+$ makes up 90% of plasma cations
Iron Absorption, Transport, Storage

1. Mixture of Fe$^{2+}$ and Fe$^{3+}$ is ingested

2. Stomach acid converts Fe$^{3+}$ to Fe$^{2+}$

3. Fe$^{2+}$ binds to gastroferritin

4. Gastroferritin transports Fe$^{2+}$ to small intestine and releases it for absorption

5. In blood plasma, Fe$^{2+}$ binds to transferrin

6. In liver, some transferrin releases Fe$^{2+}$ for storage

7. Fe$^{2+}$ binds to apoferritin to be stored as ferritin

8. Remaining transferrin is distributed to other organs where Fe$^{2+}$ is used to make hemoglobin, myoglobin, etc.
Nutritional Needs for Erythropoiesis

- Vitamin B12 and folic acid
  - rapid cell division

- Vitamin C and copper
  - cofactors for enzymes synthesizing RBCs
Erythrocytes (RBCs)

- Disc-shaped cell with thick rim
  - 7.5 μM diameter and 2.0 μm thick at rim
  - blood type determined by surface glycoprotein and glycolipids
  - cytoskeletal proteins give membrane durability
Erythrocytes (RBCs) Function

• Gas transport - major function
  – increased surface area/volume ratio
    • due to loss of organelles during maturation
    • increases diffusion rate of substances
  – 33% of cytoplasm is hemoglobin (Hb)
    • O₂ delivery to tissue and CO₂ transport to lungs

• Carbonic anhydrase (CAH)
  – produces carbonic acid from CO₂ and water
  – important role in gas transport and pH balance
Erythrocytes

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Hemoglobin (Hb) Structure

• Heme groups
  – conjugate with each protein chain
    • hemoglobin molecule can carry four O₂
  – binds oxygen to ferrous ion (Fe²⁺)

• Globins - 4 protein chains
  – 2 alpha and 2 beta chains
    • fetal Hb - gamma replace beta chains; binds O₂ better
Erythrocytes and Hemoglobin

- RBC count and hemoglobin concentration indicate amount of $O_2$ blood can carry
  - hematocrit (packed cell volume) - % of blood composed of cells
    - men 42-52% cells; women 37-48% cells
  - hemoglobin concentration of whole blood
    - men 13-18g/dL; women 12-16g/dL
  - RBC count
    - men 4.6-6.2 million/$\mu$L; women 4-2-5.4 million/$\mu$L

- Values are lower in women
  - androgens stimulate RBC production
  - women have periodic menstrual losses
Hemopoiesis

- Adult produces 400 billion platelets, 200 billion RBCs and 10 billion WBCs every day

- Hemopoietic tissues produce blood cells
  - yolk sac produces stem cells
    - colonize fetal bone marrow, liver, spleen and thymus
  - liver stops producing blood cells at birth
  - spleen remains involved with WBC production
    - lymphoid hemopoiesis occurs in widely distributed lymphoid tissues (thymus, tonsils, lymph nodes, spleen and peyers patches in intestines)
  - red bone marrow
    - pluripotent stem cells
    - myeloid hemopoiesis produces RBCs, WBCs and platelets
Erythrocyte Homeostasis

• **Negative feedback control**
  – drop in RBC count causes kidney hypoxemia
  – EPO production stimulates bone marrow
  – RBC count $\uparrow$ in 3 - 4 days

• **Stimulus for erythropoiesis**
  – low levels $O_2$
  – increase in exercise
  – loss of lung tissue in emphysema
Nutritional Needs for Erythropoiesis

- Iron - key nutritional requirement
  - lost daily through urine, feces, and bleeding
    - men 0.9 mg/day and women 1.7 mg/day
  - low absorption requires consumption of 5-20 mg/day
- dietary iron: ferric (Fe$^{3+}$) and ferrous (Fe$^{2+}$)
  - stomach acid converts Fe$^{3+}$ to absorbable Fe$^{2+}$
  - gastroferritin binds Fe$^{2+}$ and transports it to intestine
  - absorbed into blood and binds to transferrin for transport
    » bone marrow for hemoglobin, muscle for myoglobin
    and all cells use for cytochromes in mitochondria
- liver apoferritin binds to create ferritin for storage
Erythrocyte Production

- 2.5 million RBCs/sec
- Development takes 3-5 days
  - reduction in cell size, increase in cell number, synthesis of hemoglobin and loss of nucleus
- First committed cell - erythrocyte colony forming unit
  - has receptors for erythropoietin (EPO) from kidneys
- Erythroblasts multiply and synthesize hemoglobin
- Discard nucleus to form a reticulocyte
  - named for fine network of endoplasmic reticulum
  - 0.5 to 1.5% of circulating RBCs
Erythrocytes Recycle/Disposal

- RBCs lyse in narrow channels in spleen
- Macrophages in spleen
  - digest membrane bits
  - separate heme from globin
    - globins hydrolyzed into amino acids
    - iron removed from heme
      - heme pigment converted to biliverdin (green)
      - biliverdin converted to bilirubin (yellow)
      - released into blood plasma (kidneys - yellow urine)
      - liver secretes into bile
        » concentrated in gall bladder: released into small intestine; bacteria create urobilinogen (brown feces)
Erythrocytes Recycle/Disposal

- Amino acids
- Iron
- Folic acid
- Vitamin B₁₂

Nutrient absorption

Small intestine

Erythropoiesis in red bone marrow

Erythrocytes circulate for 120 days

Expired erythrocytes break up in liver and spleen

Cell fragments phagocytized

Hemoglobin degraded

- Heme
- Globin

- Biliverdin
- Bilirubin

- Iron
- Storage
- Reuse
- Loss by menstruation, injury, etc.

Hydrolyzed to free amino acids

- Bile
- Feces
Erythrocyte Disorders

• Polycythemia - an excess of RBCs
  – primary polycythemia
    • cancer of erythropoietic cell line in red bone marrow
      – RBC count as high as 11 million/μL; hematocrit 80%
  – secondary polycythemia
    • from dehydration, emphysema, high altitude, or physical conditioning
      – RBC count up to 8 million/μL

• Dangers of polycythemia
  – increased blood volume, pressure, viscosity
    • can lead to embolism, stroke or heart failure
Anemia - Causes

- Inadequate erythropoiesis or hemoglobin synthesis
  - inadequate vitamin B12 from poor nutrition or lack of intrinsic factor (pernicious anemia)
  - iron-deficiency anemia
  - kidney failure and insufficient erythropoietin
  - aplastic anemia - complete cessation

- Hemorrhagic anemias

- Hemolytic anemias
Anemia - Effects

- Tissue hypoxia and necrosis (short of breath and lethargic)
- Low blood osmolarity (tissue edema)
- Low blood viscosity (heart races and pressure drops)
Sickle-Cell Disease

• Hereditary Hb ‘defect’ of African Americans
  – recessive allele modifies hemoglobin structure
  – sickle-cell trait - heterozygous for HbS
    • individual has resistance to malaria
      – HbS indigestible to malaria parasites
  – sickle-cell disease - homozygous for HbS
    • individual has shortened life
      – in low O₂ concentrations HbS causes cell elongation and sickle shape
      – cell stickiness causes agglutination and blocked vessels
      – intense pain; kidney and heart failure; paralysis; stroke
      – chronic hypoxemia reactivates hemopoietic tissue
        » enlarging spleen and bones of cranium
Sickle-Cell Diseased Erythrocyte
Antigens and Antibodies

• Antigens
  – unique molecules on cell surface
    • used to distinguish self from foreign
    • foreign antigens generate immune response

• Antibodies
  – secreted by plasma cells
    • as part of immune response to foreign matter

• Agglutination
  – antibody molecule binding to antigens
  – causes clumping
Blood Types

• RBC antigens
  – agglutinogens; A and B
  – on RBC surface
ABO Group

- Your ABO blood type is determined by presence or absence of antigens (agglutinogens) on RBCs
  - type A person has A antigens
  - type B person has B antigens
  - type AB has both antigens
  - type O has neither antigen
    - most common - type O
    - rarest - type AB
Plasma antibodies

- Antibodies (agglutinins); anti-A and -B
- Appear 2-8 months after birth; at maximum concentration at 10 yr.
  - Anti -A and/or -B (both or none) are in plasma
    - you do not form antibodies against your antigens
- Agglutination
  - each antibody can attach to several foreign antigens at the same time
- Responsible for mismatched transfusion reaction
Agglutination of Erythrocytes
Transfusion Reaction

- Agglutinated RBCs block blood vessels and hemolyze
  - free Hb blocks kidney tubules, causes death
Universal Donors and Recipients

• Universal donor
  – Type O
  – lacks RBC antigens
  – donor’s plasma may have antibodies against recipient’s RBCs
    • may give packed cells (minimal plasma)

• Universal recipient
  – Type AB
  – lacks plasma antibodies; no anti- A or B
Rh Group

- Rh (D) agglutinogens discovered in rhesus monkey in 1940
  - Rh\(^+\) blood type has D agglutinogens on RBCs
  - Rh frequencies vary among ethnic groups

- Anti-D agglutinins not normally present
  - form in Rh\(^-\) individuals exposed to Rh\(^+\) blood
    - Rh\(^-\) woman with an Rh\(^+\) fetus or transfusion of Rh\(^+\) blood
    - no problems with first transfusion or pregnancy
Hemolytic Disease of Newborn

• Occurs if mother has formed antibodies and is pregnant with 2\textsuperscript{nd} Rh\textsuperscript{+} child
  – Anti-D antibodies can cross placenta

• Prevention
  – RhoGAM given to pregnant Rh\textsuperscript{-} women
    • binds fetal agglutinogens in her blood so she will not form Anti-D antibodies
Hemolytic Disease of Newborn

Rh antibodies attack fetal blood
- causing severe anemia and toxic brain syndrome
Leukocytes (WBCs)

- 5,000 to 10,000 WBCs/\(\mu L\)
- Conspicuous nucleus
- Travel in blood before migrating to connective tissue
- Protect against pathogens
Leukocyte Descriptions

- **Granulocytes**
  - neutrophils (60-70%)
    - fine granules in cytoplasm; 3 to 5 lobed nucleus
  - eosinophils (2-4%)
    - large rosy-orange granules; bilobed nucleus
  - basophils (<1%)
    - large, abundant, violet granules (obscure a large S-shaped nucleus)

- **Agranulocytes**
  - lymphocytes (25-33%)
    - variable amounts of bluish cytoplasm (scanty to abundant); ovoid/round, uniform dark violet nucleus
  - monocytes (3-8%)
    - largest WBC; ovoid, kidney-, or horseshoe-shaped nucleus
Granulocyte Functions

• Neutrophils (↑ in bacterial infections)
  – phagocytosis of bacteria
  – release antimicrobial chemicals

• Eosinophils (↑ in parasitic infections or allergies)
  – phagocytosis of antigen-antibody complexes, allergens and inflammatory chemicals
  – release enzymes to destroy parasites

• Basophils (↑ in chicken pox, sinusitis, diabetes)
  – secrete histamine (vasodilator)
  – secrete heparin (anticoagulant)
Agranulocyte Functions

• Lymphocytes (↑ in diverse infections and immune responses)
  – destroy cells (cancer, foreign, and virally infected cells)
  – “present” antigens to activate other immune cells
  – coordinate actions of other immune cells
  – secrete antibodies and provide immune memory

• Monocytes (↑ in viral infections and inflammation)
  – differentiate into macrophages
  – phagocytize pathogens and debris
  – “present” antigens to activate other immune cells
Complete Blood Count

- Hematocrit
- Hemoglobin concentration
- Total count for RBCs, reticulocytes, WBCs, and platelets
- Differential WBC count
- RBC size and hemoglobin concentration per RBC
Leukocyte Life Cycle

• Leukopoiesis
  – pluripotent stem cells –
    • myeloblasts – form neutrophils, eosinophils, basophils
    • monoblasts form monocytes
    • lymphoblasts form B and T lymphocytes and NK cells
  – T lymphocytes complete development in thymus

• Red bone marrow stores and releases granulocytes and monocytes

• Circulating WBCs do not stay in bloodstream
  – granulocytes leave in 8 hours and live 5 days longer
  – monocytes leave in 20 hours, transform into macrophages and live for several years
  – WBCs provide long-term immunity (decades)
Leukopoiesis
Leukocyte Disorders

• Leukopenia - low WBC count (<5000/µL)
  – causes: radiation, poisons, infectious disease
  – effects: elevated risk of infection

• Leukocytosis = high WBC count (>10,000/µL)
  – causes: infection, allergy and disease
  – differential count - distinguishes % of each cell type

• Leukemia = cancer of hemopoietic tissue
  – myeloid and lymphoid - uncontrolled WBC production
  – acute and chronic - death in months or ≤ 3 years
  – effects - normal cell % disrupted; impaired clotting
Platelets

- Small fragments of megakaryocyte cytoplasm
  - 2-4 μm diameter; contain “granules”
  - amoeboid movement and phagocytosis
- Normal Count - 130,000 to 400,000 platelets/μL
- Functions
  - secrete clotting factors and growth factors for vessel repair
  - initiate formation of clot-dissolving enzyme
  - phagocytize bacteria
  - chemically attract neutrophils and monocytes to sites of inflammation
Platelet Production -Thrombopoiesis

- Stem cells (that develop receptors for thrombopoietin) become megakaryoblasts

- Megakaryoblasts
  - repeatedly replicate DNA without dividing cytoplasm
  - forms gigantic cell called megakaryocyte (100 μm in diameter, remains in bone marrow)

- Megakaryocyte
  - infoldings of cytoplasm splits off cell fragments that enter bloodstream as platelets (live for 10 days)
  - some stored in spleen
Hemostasis

- All 3 pathways involve platelets
Hemostasis - Vascular Spasm

• Causes
  – pain receptors
    • some directly innervate constrictors
  – smooth muscle injury
  – platelets release serotonin (vasoconstrictor)

• Effects
  – prompt constriction of a broken vessel
    • pain receptors - short duration (minutes)
    • smooth muscle injury - longer duration
  – provides time for other two clotting pathways
Hemostasis - Platelet Plug Formation

• Endothelium smooth, coated with prostacyclin

• Platelet plug formation
  – broken vessel exposes collagen
  – platelet pseudopods stick to damaged vessel and other platelets - pseudopods contract and draw walls of vessel together forming a platelet plug
  – platelets degranulate releasing a variety of substances
    • serotonin is a vasoconstrictor
    • ADP attracts and degranulates more platelets
    • thromboxane A₂, an eicosanoid, promotes aggregation, degranulation and vasoconstriction
  – positive feedback cycle is active until break in vessel is sealed
Hemostasis - Coagulation

• Clotting - most effective defense against bleeding
  – conversion of plasma protein fibrinogen into insoluble fibrin threads to form framework of clot

• Procoagulants (clotting factors) are present in plasma
  – activate one factor and it will activate the next to form a reaction cascade

• Extrinsic pathway
  – factors released by damaged tissues begin cascade

• Intrinsic pathway
  – factors found in blood begin cascade (platelet degranulation)
Coagulation Pathways

- **Extrinsic pathway**
  - initiated by tissue thromboplastin
  - cascade to factor VII, V and X (fewer steps)

- **Intrinsic pathway**
  - initiated by factor XII
  - cascade to factor XI to IX to VIII to X

- **Calcium required for either pathway**
Enzyme Amplification in Clotting

- Rapid clotting - each activated cofactor activates many more molecules in next step of sequence
Completion of Coagulation

- Activation of Factor X
  - leads to production of prothrombin activator

- Prothrombin activator
  - converts prothrombin to thrombin

- Thrombin
  - converts fibrinogen into fibrin

- Positive feedback - thrombin speeds up formation of prothrombin activator
Fate of Blood Clots

• Clot retraction occurs within 30 minutes
• Platelet-derived growth factor secreted by platelets and endothelial cells
  – mitotic stimulant for fibroblasts and smooth muscle to multiply and repair damaged vessel
• Fibrinolysis (dissolution of a clot)
  – factor XII speeds up formation of kallikrein enzyme
  – kallikrein converts plasminogen into plasmin, a fibrin-dissolving enzyme (clot buster)
Blood Clot Dissolution

• Positive feedback occurs
• Plasmin promotes formation of kallikrein
Prevention of Inappropriate Clotting

- **Platelet repulsion**
  - platelets do not adhere to prostacyclin-coating

- **Thrombin dilution**
  - by rapidly flowing blood
    - heart slowing in shock can result in clot formation

- **Natural anticoagulants**
  - heparin (from basophils and mast cells) interferes with formation of prothrombin activator
  - antithrombin (from liver) deactivates thrombin before it can act on fibrinogen
Hemophilia

• Genetic lack of any clotting factor affects coagulation

• Sex-linked recessive (on X chromosome)
  – hemophilia A missing factor VIII (83% of cases)
  – hemophilia B missing factor IX (15% of cases)
  note: hemophilia C missing factor XI (autosomal)

• Physical exertion causes bleeding and excruciating pain
  – transfusion of plasma or purified clotting factors
  – factor VIII produced by transgenic bacteria
Coagulation Disorders

• Embolism - clot traveling in a vessel
• Thrombosis - abnormal clotting in unbroken vessel
  – most likely to occur in leg veins of inactive people
  – pulmonary embolism - clot may break free, travel from veins to lungs
• Infarction may occur if clot blocks blood supply to an organ (MI or stroke)
  – 650,000 Americans die annually of thromboembolism
Medicinal Leeches