Chapter 11
The Hematopoietic and Lymphatic Systems

Learning Objectives (1 of 2)
• Describe composition and functions of blood, and functions of the lymphatic system
• Explain classification of anemia
• List and describe causes and treatment of hypochromic microcytic anemia and macrocytic anemia
• List causes and treatment of anemia from bone marrow damage and anemia from accelerated blood destruction
• Describe causes and effects of polycythemia and thrombocytopenia

Learning Objectives (2 of 2)
• Describe causes and clinical manifestations of infectious mononucleosis
• List common causes of lymph node enlargement
• Explain role of spleen in protecting the body against infection
• Describe effect of splenectomy on body’s defenses

Composition of Human Blood (1 of 6)
• Transports substances to tissues:
  – Oxygen, nutrients, hormones, leukocytes, red cells, platelets, antibodies
  – Carbon dioxide and other waste products of cell metabolism to the excretory organs of the body
• Volume of blood: about 5 quarts, but varies according to size of individual
• Almost half of blood consists of cellular elements suspended in plasma (viscous fluid)

Composition of Human Blood (2 of 6)
• Stem cells: precursor cells in bone marrow and differentiate to form red cells, white cells, and platelets
• Cellular elements are:
  – Red cells
  – Leukocytes
  – Neutrophils
  – Monocytes
  – Eosinophils
  – Lymphocytes
  – Basophils
  – Platelets

Composition of Human Blood (3 of 6)
• Red cells
  – Primarily concerned with transport of oxygen
  – Most numerous cells
  – Survive 4 months (120 days)
  – Erythroblast: precursor cell in bone marrow
  – Hemoglobin: oxygen-carrying protein formed by the developing red cell
• Leukocytes
  – Less numerous
  – Different types
Composition of Human Blood (4 of 6)

- Lymphocytes may last for several years
- Lymphocytes also produced in the bone marrow but mainly produced in lymph nodes and spleen
- Types of leukocytes
  - Neutrophils
    - Most numerous in adults
    - Make up 70% of total circulating white cells
    - Predominant in inflammatory reactions
  - Monocytes
    - Actively phagocytic
    - Increased in certain types of chronic infection

Composition of Human Blood (5 of 6)

- Eosinophils
  - Increased in allergic reactions
  - Increased in presence of animal-parasite infections
- Lymphocytes
  - Next most common leukocytes in adults
  - Predominant leukocytes in children
  - Mostly located in lymph nodes, spleen, lymphoid tissues
  - Take part in cell-mediated and humoral defense reactions

Composition of Human Blood (6 of 6)

- Platelets
  - Essential for blood coagulation
  - Much smaller than leukocytes
  - Represent bits of the cytoplasm of megakaryocytes, largest precursor cells in the bone marrow
  - Short survival, about 10 days

Normal Hematopoiesis (1 of 4)

- Hematopoiesis: formation and development of blood cells
- Bone marrow replenishes the blood cells
- Substances necessary for hematopoiesis
  - Protein
  - Vitamin B₁₂
  - Folic acid (one of the vitamin B group)
  - Iron
- Red cell production: regulated by oxygen content of the arterial blood
- White cell production: not well understood
- Factors that may cause white cell production
  - Products of cell necrosis
  - Hormone secretion by adrenals and endocrine glands

Iron uptake, transport, storage, and utilization for hemoglobin synthesis

- Dietary iron
  - Iron combined with protein (ferriheme) in duodenal mucosa to form ferritin
  - Iron transcribed in blood by transferrin
  - Iron recycled
- Iron storage as ferritin for later use
- Hemoglobin broken down when red cells wear out

Normal Hematopoiesis (2 of 4)

- Red cells: develop from erythroblasts, large precursor cells in bone marrow
- Hemoglobin: tetramer composed of 4 subunits, each one consisting of heme and globin
- Heme: porphyrin ring that contains an iron atom
- Globin: largest part of hemoglobin; forms different chains designated by Greek letters such as alpha, beta, gamma, delta, and epsilon
- Porphyrin ring: produced by the mitochondria; iron inserted to form heme
- Globin chains: produced by the ribosomes; joined to heme to form a hemoglobin unit
Normal Hematopoiesis (3 of 4)

- Four subunits aggregate to form the complete hemoglobin tetramer
- Red cell accumulates increasing amounts of hemoglobin as it matures
- Nucleus extruded when 80% of total hemoglobin has been synthesized; cell discharged from the marrow into the circulation where it completes its maturation process in the next 24 hours
- Reticulocyte: young red cell without a nucleus but retains some of organelles; identified by special stains
- In 24 hours, reticulocyte matures and survives in the circulation for about 4 months

Normal Hematopoiesis (4 of 4)

- Worn out red cells removed in the spleen
  - Hemoglobin degraded and excreted as bile by liver
  - Porphyrin ring cannot be salvaged
  - Globin chains broken down and used to make other proteins
  - Iron extracted and saved to make new hemoglobin
- Red cell production regulated by O₂ content of arterial blood
  - Reduced O₂ supply stimulates erythropoiesis
  - Reduced O₂ tension does not act directly on bone marrow but mediated by the kidneys, which produce erythropoietin

Anemia: Etiologic Classification (1 of 2)

- Reduction in red blood cells or subnormal level of hemoglobin
- Inadequate production of red cells
- Insufficient raw materials
  - Iron deficiency
  - Vitamin B₁₂ deficiency
  - Folic acid deficiency
- Inability to deliver adequate red cells into circulation due to marrow damage or destruction (aplastic anemia), replacement of marrow by foreign or abnormal cells

Anemia: Etiologic Classification (2 of 2)

- Excessive loss of red cells
  - External blood loss (hemorrhage)
  - Shortened survival of red cells in circulation
  - Defective red cells: hereditary hemolytic anemia
  - Accelerated destruction of cells from antibodies to red blood cell or by mechanical trauma to circulating red cells

Classification of anemia based on the "bone marrow factory" concept

- Inadequate production of red cells
  - Caused by inadequate raw materials
    - Iron deficiency
    - Vitamin B₁₂ deficiency
    - Folic acid deficiency
  - Caused by impaired function of bone marrow factory
    - Anemia of chronic disease
    - Bone marrow damaged or destroyed (aplastic anemia)
    - Bone marrow replaced by foreign or abnormal cells (bone marrow replacement anemia)

Etiologic Classification of Anemia
Etiologic Classification of Anemia

- Excessive loss of red cells
  - Caused by external blood loss (hemorrhage)
  - Caused by shortened survival of red cells in circulation
  - Defective red cells (hereditary hemolytic anemia)
    - Abnormal red cell shape
    - Abnormal hemoglobin within red cells
    - Defective hemoglobin synthesis within red cells
    - Deficient red cell enzymes
  - “Hostile environment”
    - Anti-red cell antibodies
    - Mechanical trauma to circulating red cells

Defective red cells (hereditary hemolytic anemia)

- Abnormal red cell shape
- Abnormal hemoglobin within red cells
- Defective hemoglobin synthesis within red cells
- Deficient red cell enzymes
- "Hostile environment"
- Anti-red cell antibodies
- Mechanical trauma to circulating red cells

Anemia: Morphologic Classification

- Classification based on red cell appearance suggests the etiology of the anemia:
  - Normocytic anemia: normal size and appearance
  - Macrocytic anemia: cells larger than normal
  - Folic acid deficiency
  - Vitamin B12 deficiency
  - Microcytic anemia: cells smaller than normal

Anemia: Morphologic Classification (2 of 2)

- Hypochromic anemia: reduced hemoglobin content
- Hypochromic microcytic anemia: smaller than normal and reduced hemoglobin content

Iron-Deficiency Anemia (1 of 2)

- Most common type of anemia
- Hypochromic microcytic anemia
- Iron absorbed from duodenum, transferred via transferrin, stored as ferritin
- Pathogenesis
  - Inadequate iron intake in diet
  - Infants during periods of rapid growth
  - Adolescents subsisting on inadequate diet
  - Inadequate reutilization of iron present in red cells due to chronic blood loss
- Laboratory tests
  - Serum ferritin
  - Serum iron
  - Serum iron-binding capacity

Iron-Deficiency Anemia (2 of 2)

- Characteristic laboratory profile
  - Low serum ferritin and serum iron
  - Higher than normal serum iron-binding protein
  - Lower than normal percent iron saturation
- Treatment
  - Primary focus: learn cause of anemia
  - Direct treatment towards cause than symptoms
  - Administer supplementary iron
- Examples
  - Infant with a history of poor diet
  - Adults: common cause is chronic blood loss from GIT (bleeding ulcer or ulcerated colon carcinoma)
  - Women: excessive menstrual blood loss
  - Too-frequent blood donations

Normal red cells
Vitamin B₁₂ Deficiency Anemia
(1 of 2)
- Vitamin B₁₂: meat, liver, and foods rich in animal protein
- Folic acid: green leafy vegetables and animal protein foods
  - Both required for normal hematopoiesis and normal maturation of many other types of cells
- Vitamin B₁₂: for structural and functional integrity of nervous system; deficiency may lead to neurologic disturbances

(2 of 2)
- Absence or deficiency of vitamin B₁₂ or folic acid
  - Abnormal red cell maturation or megaloblastic erythropoiesis with formation of large cells called megaloblasts
  - Mature red cells formed are larger than normal or macrocytes; corresponding anemia is called macrocytic anemia
  - Abnormal development of white cell precursors and megakaryocytes: leukopenia, thrombocytopenia

Pernicious Anemia
- Lack of intrinsic factor results in macrocytic anemia
  - Vitamin B₁₂ in food combines with intrinsic factor in gastric juice
  - Vitamin B₁₂ intrinsic factor complex absorbed in ileum
- Causes
  - Gastric mucosal atrophy; also causes lack of secretion of acid and digestive enzymes
  - Gastric resection and bypass: vitamin B₁₂ not absorbed
  - Distal bowel resection or disease: impaired absorption of vitamin B₁₂ intrinsic factor complex
  - May develop among middle-aged and elderly
  - Associated with autoantibodies against gastric mucosal cells and intrinsic factor

Folic Acid Deficiency Anemia
- Relatively common
- The body has very limited stores, which rapidly become depleted if not replenished continually
- Pathogenesis
  - Inadequate diet: encountered frequently in chronic alcoholics
  - Poor absorption caused by intestinal disease
  - Occasionally occurs in pregnancy with increased demand for folic acid

Diagnostic Evaluation of Anemia
- History and physical examination
- Complete blood count: to assess degree of anemia, leukopenia, and thrombocytopenia
- Blood smear: determine if normocytic, macrocytic, or hypochromic microcytic
- Reticulocyte count: assess rate of production of new red cells
- Lab tests: determine iron, B₁₂, folic acid
- Bone marrow study: study characteristic abnormalities in marrow cells
- Evaluation of blood loss from gastrointestinal tract to localize site of bleeding
Bone Marrow Suppression, Damage, or Infiltration (1 of 2)

- Conditions that depress bone marrow function:
  - Anemia of chronic disease: mild suppression of bone marrow function
  - Aplastic anemia: marrow injured by radiation, anticancer drugs, chemicals, or autoantibodies
  - Marrow infiltrated by tumor or replaced by fibrous tissue

Bone Marrow Suppression, Damage, or Infiltration (2 of 2)

- Treatment depends on cause
  - Blood and platelet transfusions
  - Immunosuppressive drugs
  - Bone marrow transplant in highly selected cases of aplastic anemia
  - In many cases, there is no specific treatment

Hemolytic Anemia (1 of 2)

- Hereditary hemolytic anemia
  - Genetic abnormality prevents normal survival
- Abnormal shape: hereditary spherocytosis
- Abnormal hemoglobin: hemoglobin S (sickle hemoglobin); hemoglobin C; both found predominantly in persons of African descent
- Defective hemoglobin synthesis: thalassemia minor and major; globin chains are normal but synthesis is defective (Greek and Italian ancestry)
- Enzyme defects: glucose-6-phosphatase dehydrogenase deficiency predisposes to episodes of acute hemolysis

Hemolytic Anemia (2 of 2)

- Acquired hemolytic anemia
  - Normal red cells but unable to survive due to a "hostile environment"
  - Attacked and destroyed by antibodies
  - Destruction of red cells by mechanical trauma
  - Passing through enlarged spleen (splenomegaly)
  - In contact with some part of artificial heart valve

Distortion of red cells containing sickle hemoglobin when incubated under reduced oxygen tension.

Distortion of red cells containing sickle hemoglobin when incubated under reduced oxygen tension. Higher magnification view.
A stained blood film from subject with hereditary spherocytosis

Polycythemia (1 of 2)
- Secondary polycythemia
  - Reduced arterial O₂ saturation leads to compensatory increase in red blood cells (increased erythropoietin production)
  - Emphysema, pulmonary fibrosis, congenital heart disease; increased erythropoietin production by renal tumor
- Primary/Polycthyemia vera
  - Manifestation of diffuse marrow hyperplasia of unknown etiology
  - Overproduction of red cells, white cells, and platelets
  - Some cases evolve into granulocytic leukemia

Polycythemia (2 of 2)
- Complications
  - Clot formation due to increased blood viscosity and platelet count
- Treatment
  - Primary polycythemia: treated by drugs that suppress marrow function
  - Secondary polycythemia: periodic removal of excess blood

Hemochromatosis
- Common genetic disease transmitted as autosomal recessive trait
- Iron overload but excreted with difficulty
- Iron accumulation leads to organ damage followed by scarring and permanent derangement of organ function
- Manifestations of disease take years to develop
  - Tan to brown skin
  - Diabetes
  - Cirrhosis
  - Heart failure
- Treatment: periodic removal of blood (phlebotomy) until iron stores are depleted

Thrombocytopenia
- Secondary thrombocytopenic purpura
  - Damage to bone marrow from drugs or chemicals
  - Bone marrow infiltrated by leukemic cells or metastatic carcinoma
- Primary thrombocytopenic purpura
  - Associated with platelet antibodies
  - Bone marrow produces platelets but are rapidly destroyed
  - Encountered in children and subsides spontaneously after a short time
  - Tends to be chronic in adults

Lymphatic System (1 of 2)
- Primary function: provide immunologic defenses against foreign material via cell-mediated and humoral defense mechanisms
- Structure
  - Lymph nodes: bean-shaped structures consisting of a mass of lymphocytes supported by a meshwork of reticular fibers in which are scattered phagocytic cells
  - As lymph flows through the nodes, phagocytic cells filter out and destroy microorganisms and foreign matter
  - Clustered where lymph channels are located
Lymphatic System (2 of 2)

- **Spleen**: specialized to filter blood
  - Compact mass of lymphocytes and network of sinusoids (capillaries with wide lumens)
  - For antibody formation and phagocytosis of senescent red cells
- **Lymphoid tissue**: present in thymus, tonsils, adenoids, lymphoid aggregates in intestinal mucosa, respiratory tract, and bone marrow
- **Thymus**: overlies base of heart; large during infancy and childhood; undergoes atrophy in adolescence
  - Essential in prenatal development of lymphoid system and in formation of body’s immunologic defense mechanisms

Lymphatic System Diseases (1 of 2)

- **Lymphadenitis**: inflamed and enlarged lymph nodes
- **Infectious mononucleosis**: caused by Epstein-Barr virus, EBV
  - Infection of B lymphocytes causes diffuse lymphoid hyperplasia of spleen, lymph nodes, lymphoid tissues
  - Cytotoxic (CD8+) lymphocytes and antibodies produced by plasma cells destroy most of infected B cells
  - Characterized by enlarged and tender lymph nodes
  - Mostly encountered by young adults transmitted by close contact, usually kissing
  - Avoid body contact sports until spleen is no longer enlarged to avoid risk of splenic rupture
  - Persons with compromised immune system, unrestrained B cell proliferation may give rise to B cell lymphoma

Lymphatic System Diseases (2 of 2)

- **Neoplasms**
  - Metastatic tumors: breasts, lung, colon, other sites
  - Nodes first affected lie in immediate drainage area of tumor
  - Tumor spreads to more distant lymph nodes through lymphatic channels
  - **Malignant lymphoma**
    - Hodgkin’s lymphoma
    - Non-Hodgkin’s lymphoma
  - **Lymphocytic leukemia**: from lymphoid precursor cells; acute (primitive forms) or chronic (mature cells)

Large lymphocyte from subject with infectious mononucleosis

Spleen

- **Phagocytosis**
- **Antibody formation**: prompt elimination of pathogenic organisms
- **Reasons for splenectomy**
  - Traumatic injury: to prevent fatal hemorrhage
  - Blood diseases: excessive destruction of blood cells in the spleen (hereditary hemolytic anemia)
  - Patients with Hodgkin’s disease prior to treatment
- **Effects**
  - Less-efficient elimination of bacteria
  - Impaired production of antibodies
  - Predisposed to systemic infections
- **Treatment**: antibacterial vaccines; antibiotic prophylaxis

Discussion

- **A patient has an enlarged lymph node**
  - What types of diseases could produce lymph node enlargement?
  - How does the physician arrive at a diagnosis when a patient presents with enlarged lymph node?
  - What is the EB virus? What is its relationship to infectious mononucleosis? What are the clinical manifestations, complications, and treatment for infectious mononucleosis?