CHAPTER 10

Blood and Circulatory System Disorders

Review of the Circulatory System and Blood

Anatomy, Structures, and Components

Blood Vessels

Blood Composition

Blood Cells and Hematopoiesis

Blood Clotting

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Disseminated Intravascular Coagulation

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The Leukemias

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Chapter Summary

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LEARNING OBJECTIVES

After studying this chapter, the student is expected to:

1. Define the terms describing abnormalities in the blood.
2. Describe and compare the pathophysiology, etiology, manifestations, diagnostic tests, and treatment for each of the specified anemias: iron-deficiency, pernicious, aplastic, sickle cell, and thalassemia.
3. Differentiate between primary and secondary polycythemia, and describe the need for the diagnosis and treatment of these conditions.

5. Discuss the disorder disseminated intravascular coagulation: its pathophysiology, etiology, manifestations, and treatment.
6. Discuss the myeloplastic syndrome and its relationship to other blood disorders.
7. Compare acute and chronic leukemia: the incidence, onset and course, pathophysiology, signs, diagnostic tests, and treatment.

KEY TERMS

achlorhydria
agglutination
autoregulation
bilirubin
cyanotic
demyelination
dehysemoglobin
diabetes
erythraemia
erythropoietin
feritin
ferritin
gastroctomy
glossitis
hemarthrosis
hemacrit
hematopoiesis
hemolysis
hemoptysis
hemoglobin
hepatosplenomegaly
hypochromic
leukocytosis
leukopenia
leukopenia
leukopenia
leukopenia
macrophages
malabsorption
megaloblasts
microcytic
morphology
myeloidosis
myelosis
myelophthisic
myelosplastic
neutropenia
orthochromic
pallor
pancytopenia
peripheral
phlebotomy
plasmacytoma
plastic
plastic
reticuloocyte
serum
spenicomegaly
stomatitis
symptom
thrombocytopenia

Blood vessels

The arteries, capillaries, and veins constitute a closed system for the distribution of blood throughout the body. Major blood vessels, most of which are paired left and right, are shown in Figures 10-1 and 10-2.

To review the components of the circulatory system:

- There are two separate circulations—the pulmonary circulation allows the exchange of oxygen and carbon dioxide in the lungs, and the systemic circulation provides for the exchange of nutrients and wastes between the blood and the cells throughout the body.
- Arteries transport blood away from the heart into the lungs or to body tissues.
- Arterioles are the smaller branches of arteries that control the amount of blood flowing into the capillaries in specific areas through the degree of contraction of smooth muscle in the vessel walls (vasoconstriction or dilation).
- Capillaries are very small vessels organized in numerous networks that form the microcirculation. Blood flows very slowly through capillaries, and precapillary sphincters determine the amount of blood flowing from the arteries into the individual capillaries, depending on the metabolic needs of the tissues.
- Small vessels conduct blood from the capillary beds toward the heart.
- Larger vessels collect blood draining from the veins. Normally a high percentage of the blood (approx. 70%) is located in the veins at any one time; hence, the veins are called capacitance vessels. Blood flow in the veins depends on skeletal muscle action, respiratory movements, and gravity. Valves in the larger veins in the arms and legs have an important role in keeping the blood flowing toward the heart. Respiratory movements assist the movement of blood through the trunk.

The walls of arteries and veins are made up of three layers.

1. The tunica intima, an endothelial layer, is the inner layer.
2. The tunica media, a layer of smooth muscle that controls the diameter and lumen size (diameter) of the blood vessel, is the middle layer.
3. The tunica adventitia, or externa, is the outer connective tissue layer and contains elastic and collagen fibers.

The vasa vasorum consists of tiny blood vessels that supply blood to the tissues of the wall itself. Normally the large arteries are highly elastic in order to adjust to the changes in blood volume that occur during the cardiac cycle. For example, the aorta must expand during systole to prevent systolic pressure from rising too high, and during diastole the walls must recoil to maintain adequate diastolic pressure. Veins have thinner walls than arteries and less smooth muscle (Fig. 10-3).

Localized vasodilation or vasoconstriction in arterioles is controlled by autoregulation, a reflex adjustment in a small area of a tissue or an organ, which varies depending on the needs of the area. For example, a decrease in pH, an increase in carbon dioxide, or a decrease in oxygen leads to local vasodilation. Release of chemical mediators such as histamine or an increase in temperature at a specific area can also cause vasodilation. These local changes do not affect the systemic blood pressure.

Neointima: and epinephrine increase systemic vasoconstriction by stimulating alpha-adrenergic receptors in the arteriolar walls. Angiotensin is another powerful systemic vasoconstrictor. At times, even at rest, vascular or vasoconstrictor tone is maintained by constant input from the SNS that results in partial vasoconstriction throughout the body to ensure continued circulation of blood.

Capillary walls consist of a single endothelial layer to facilitate the exchange of fluid, oxygen, carbon dioxide, electrolytes, glucose and other nutrients, and wastes between the blood and the interstitial fluid. Capillary exchange and abnormal electrolyte shifts are discussed in Chapter 2.
Blood

Blood provides the major transport system of the body for essentials such as oxygen, glucose and other nutrients, hormones, electrolytes, and cell wastes. It serves as a critical part of the body's defenses, carrying antibodies and white blood cells for the rapid removal of any foreign material. As a vehicle promoting homeostasis, blood provides a mechanism for controlling body temperature by distributing core heat throughout the peripheral tissues. Blood is the medium through which body fluid levels and blood pressure are measured and adjusted by various controls, such as hormones. Clotting factors in the circulating blood are readily available for hemostasis. Buffer systems in the blood maintain a stable pH of 7.35 to 7.45 (see discussion of acid-base balance in Chapter 2).

Composition of Blood

The adult body contains approximately 5 liters of blood. Blood consists of water and its dissolved solutes, which make up about 55% of the whole blood volume; the remaining 45% is composed of the cells or formed elements, the erythrocytes, along with leukocytes, and thrombocytes or platelets. Hematocrit refers to the proportion of cells (essentially the erythrocytes) in blood and indicates the viscosity of the blood. Males have a higher hematocrit, average 42% to 52%, than females, 37% to 47%. An elevated hematocrit could indicate dehydration (loss of fluid) or excess red blood cells. A low hematocrit might result from blood loss or anemia. Plasma is the clear yellowish fluid remaining after the cells have been removed, and serum refers to the fluid and solutes remaining after the cells and fibrinogen have been removed. The plasma proteins include albumin, which maintains osmotic pressure in the blood;
### Blood Cells and Hematopoiesis

All blood cells originate from the red bone marrow. In the adult, red bone marrow is found in the flat and irregular bones, ribs, vertebrae, sternum, and pelvis. The iliac crest in the pelvic bone is a common site for a bone marrow aspiration for biopsy. The various blood cells develop from a single stem cell (pluripotential hematopoietic stem cell) during the process of hematopoiesis or hemopoiesis (Fig. 10-5). From this basic cell, the differentiation process forms committed stem cells for each type of blood cell. These cells then proliferate and mature, providing the specialized functional cells needed by the body. A pathological condition of the blood that usually refers to disorders involving the cellular components of blood is called dyscrasia. A number of specific blood dyscrasias are addressed later in the chapter.

**Erythrocytes** or red blood cells (RBCs) are biconcave, flexible discs (like doughnuts but with thin centers rather than holes) that are non-nucleated when mature and contain hemoglobin (Fig. 10-6). The size and structure are essential for easy passage through small capillaries. The hormone erythropoietin, originating from the kidney, stimulates erythrocyte production in the red bone marrow in response to tissue hypoxia, or insufficient oxygen available to cells. Normally RBCs (4.2 to 6.2 million/mm³) constitute most of the cell volume in blood. Adequate RBC production and maturation depend on the availability of many raw materials, including amino acids, iron, vitamin B₁₂, vitamin B₉, and folate acid.
**Hemoglobin** consists of the globin portion, two pairs of amino acid chains, and four heme groups, each containing a ferrous iron atom, to which the oxygen molecule (O₂) can attach (Fig. 10-16A). Heme provides the red color associated with hemoglobin. Normally, hemoglobin becomes fully saturated with oxygen in the lungs. Oxygenated hemoglobin is a bright red color, which distinguishes arterial blood from venous blood. As the blood circulates through the body, oxygen dissociates from hemoglobin, depending on local metabolism (see Fig. 13-6). Deoxygenated hemoglobin (deoxygenated hemoglobin or reduced hemoglobin) is dark or bluish-red in color and is found in venous blood. Only a small proportion of the carbon dioxide (CO₂) in blood is carried by hemoglobin (carboxyhemoglobin) attached to nitrogen in an amino acid group at a different site from that for oxygen. Most carbon dioxide is transported in blood as bicarbonate ion (in the buffer pair). Oxygen can easily be displaced from hemoglobin by carbon monoxide, which binds tightly to the iron, thus causing a fatal hypoxia (deficit of oxygen). Carbon monoxide poisoning can be recognized by the bright cherry-red color in the lips and face. The lifespan of a normal RBC is approximately 120 days. As it ages, the cell becomes rigid and fragile and finally succumbs to phagocytosis in the spleen or liver and is broken down into globin and heme (Fig. 10-7). Globin is broken down into amino acids, which can be recycled in the amino acid pool, and the iron can be returned to the bone marrow and liver to be reused in the synthesis of more hemoglobin. Excess iron can be stored as ferritin or hemosiderin in the liver, blood, and other body tissues. A genetic disorder, hereditary spherocytosis, otherwise known as iron overload, results in large amounts of hemosiderin accumulating in the liver, heart, and other organs, causing serious organ damage.

The balance of the hemolytic component is converted to bilirubin and transported by the blood to the liver, where it is conjugated (or combined) with glucuronic acid to make it more soluble, and then excreted in the bile. Excessive hemolysis or destruction of RBCs may cause elevated serum bilirubin levels, which result in jaundice, the yellow color in the sclera of the eye and of the skin.

**Hemoly sis**

Leukocytes, which number 5 to 10,000/mm³, make up only about 1% of blood volume. They are subdivided into three types of granulocytes and two types of agranulocytes. All types develop and differentiate from the original stem cell in bone marrow (see Fig. 10-8). Leukocytes, or production of white blood cells (WBCs), is stimulated by colony-stimulating factors (CSFs) produced by cells such as macrophages and T lymphocytes. For example, granulocyte CSF or multi-CSF (interleukin-3; IL-3) may be produced in response to the production of various types of WBCs during an inflammatory response (see Chapter 5). White blood cells may leave the capillaries and enter the tissues by diapedesis or amoeboid action (movement through an intact capillary wall) when they are needed for defensive purposes.

The five types of leukocytes vary in physical characteristics and functions (Fig. 10-4). Some examples of WBCs are visible as large, nucleated cells (purple stain) in the blood smear in Figure 10-8.

**Platelet plug** that seals small breaks in blood vessels, or they can adhere to rough surfaces and foreign material. The common drug ASA (aspirin) reduces this adhesion and can lead to an increased bleeding tendency. Thrombocytes can also initiate the coagulation process.

**Blood Clotting**

Homostasis consists of three steps:

1. First, the immediate response of a blood vessel to injury is vasoconstriction or vascular spasms. In small blood vessels, this decreases blood flow and may allow a platelet plug to form.

2. Second, thrombocytes tend to adhere to the underlying tissue at the site of injury and, if the blood vessel is small, can form a platelet plug in the vessel.

3. The blood-clotting or coagulation mechanism is required in larger vessels, by which the clotting factors that are present in inactive forms in the circulating blood are activated through a sequence of reactions (Fig. 10-9). Reagents, additional coagulation factor activity, and the cascade of reactions is referred to as the basis for coagulation.

**Clot formation (coagulation)** requires a sequence or cascade of events as summarized:

1. Damaged tissue and platelets release factors that stimulate a series of reactions involving numerous clotting factors, finally producing prothrombin activator (PTA).

2. Pro thrombin factor II (inactive in the plasma) is converted into thrombin.

3. Fibrinogen (factor I) is converted into fibrin threads.

4. A fibrin mesh forms to trap cells, making up a solid clot, or thrombus, and stopping the flow of blood (Fig. 10-10).

5. The clot gradually shrinks or retracts, pulling the edges of damaged tissue closer together and sealing the site.

The circulating clotting factors are produced primarily in the liver. Their numbers relate to the order of their discovery, not to the step in the clotting process. Vitamin K, a fat-soluble vitamin, is required for the synthesis of many clotting factors. Calcium ions are essential for many steps in the clotting process.

Other measures can be used by a person to facilitate this clotting process. For example, applying pressure and cold (a vasoconstrictor) to the site reduces blood flow in the area, or thrombin solution can be applied directly to speed up clotting.
Intrinsic Pathway
(Activated by endothelial injury in blood vessel)

- XI (Hageman factor) → X → IX → Xla → V → VIII

Extrinsic Pathway
(Activated by tissue and platelet injury)

- III (Tissue thromboplastin) → V → VIII → Vla → X → Xa

Ca<sup>2+</sup> required

Plasminogen

- Activated by tissue plasminogen activator (tPA) and streptokinase through a sequence of reactions, into plasmin.
- Plasmin, then breaks down fibrin and fibrinogen. This fibrinolysis is a localized event only, because plasmin is quickly inactivated by plasmin inhibitor. These numerous checks and balances are essential in the regulation of defense mechanisms.

Antigenic Blood Types
An individual's blood type (e.g., ABO and Rh groups) is determined by the presence of specific antigens on the cell membranes of that person's erythrocytes. ABO groups are an inherited characteristic that depends on the presence of type A or B antigens or antigen combinations (Table 10-1). Shortly after birth, antibodies that can react with different antigens on another person's RBCs form in the blood of the newborn infant. Such an antigen-antibody reaction would occur with, for example, an incompatible blood transfusion, resulting in agglutination (clumping) and hemolysis of the recipient's RBCs (Fig. 10-11).

Blood types of both donor and recipient are carefully checked before transfusion. Persons with O blood

<table>
<thead>
<tr>
<th>TABLE 10-1</th>
<th>ABO Blood Groups and Transfusion Compatibility</th>
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</thead>
<tbody>
<tr>
<td>Blood Group</td>
<td>RBC Antigens</td>
</tr>
<tr>
<td>O</td>
<td>None</td>
</tr>
<tr>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>B</td>
<td>B</td>
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<td>AB</td>
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**Fibrinolysis**

A delicate balance is always necessary between the tendency to clot to prevent blood loss and the tendency to form clots unnecessarily and cause infections. Some individuals tend to form clots very readily; others are predisposed to excessive bleeding. To prevent inappropriate thrombus formation, coagulation inhibitors such as antithrombin III circulate in the blood. Though thrombin, a prostaglandin is released to prevent platelets sticking to nearby undamaged tissue. Heparin, an anticoagulant, is released from basophils or mast cells in the tissues and exerts its major action by blocking thrombin. Heparin, as a drug, may be administered intravenously to patients at risk for thrombus formation. It does not dissolve clots, but will prevent further growth of the thrombus.

**Also,** there is a natural fibrinolytic process that can break down newly formed clots. Inactive plasminogen circulates in the blood. Following injury, it can be converted by tissue plasminogen activator (tPA) and streptokinase through a sequence of reactions, into plasmin. The product, plasmin, then breaks down fibrin and fibrinogen. This fibrinolysis is a localized event only, because plasmin is quickly inactivated by plasmin inhibitor. These numerous checks and balances are essential in the regulation of defense mechanisms. Application of this mechanism with "clot-buster" drugs such as streptokinase (Streptase) is proving very successful in minimizing the tissue damage resulting from blood clots causing strokes (cardiovascular accidents, CVAs) and heart attacks (myocardial infarctions, MIs). However, constant monitoring of blood-clotting times and careful administration technique are essential to prevent excessive bleeding or hematoma formation. New protocols for anticoagulant medications are under development in the United States to ensure greater safety for patients.

**APPLY YOUR KNOWLEDGE 10-2**

Predict three ways that normal blood clotting could be impaired.

Predict three ways that inappropriate blood clotting could be promoted.
lack A and B antigens and therefore are considered universal donors. Persons with type AB blood are universal recipients. Signs of a transfusion reaction include a feeling of warmth in the involved vein, flushed face, headache, fever and chills, pain in the chest and abdomen, decreased blood pressure, and rapid pulse.

Another inherited factor in blood is the Rh factor, which can cause blood incompatibility if the mother is Rh-negative and the fetus is Rh positive (see Fig. 22-2). Rh blood incompatibility between maternal and fetal blood is reviewed in Chapter 22.

Plasma or colloidal volume-expanding solutions can be administered without risk of a reaction because they are free of antigens and antibodies.

Diagnostic Tests

The basic diagnostic test for blood is the complete blood count (CBC), which includes total RBCs, WBCs, platelet counts, and indices of size and shape. A white blood cell count for WBCs, hemoglobin, and hematocrit values (see normal values inside the front cover of this book). These tests are useful screening tools. For example, leukopenia, an increase in WBCs in the circulation, is often associated with inflammation or infection. Leukopenia, a decrease in leukocytes, occurs with some viral infections as well as with radiation and chemotherapy. An increase in eosinophils is common with allergic responses. The characteristics of the individual cells observed in a blood smear, including size and shape, uniformity, maturity, and amount of hemoglobin, are very important. Different types of anemia are distinguished by the characteristic size and shape of the cell, and presence of a nucleus in the RBC. More specialized tests are available. A summary of the most common diagnostic tests is provided in Ready Reference 5.

The hematocrit shows the percentage of blood volume composed of RBCs and indicates fluid and cell content. It may be an indicator of anemia, a low RBC count. Hemoglobin is measured, and the amount of hemoglobin per cell is shown by the mean corpuscular volume (MCV). MCV indicates the oxygen-carrying capacity of the blood. Bone marrow function can be assessed by the reticulocyte (immature non-nucleated RBC) count, plus a bone marrow aspiration and biopsy. Chemical analysis of the blood can determine the serum levels of such components as iron, vitamin B12 and folic acid, cholesterol, uric acid, and bilirubin. The test can indicate metabolic disorders and disorders within various other body systems.

Blood-clotting disorders can be differentiated by tests such as bleeding time (measures platelet function—the time it takes to form a primary clot or a skin puncture wound); prothrombin time or INR International Normalized Ratio (measures the extrinsic pathway); and partial thromboplastin time (PTT—intrinsic pathway), which measure the function of various factors in the coagulation process. They are also used to monitor anticoagulant therapy. The reference values for these tests are best established for individual patients based on their health history.

Blood Therapies

• Whole blood, packed red blood cells, or packed platelets may be administered when severe anemia or thrombocytopenia is present.

• Plasma or colloidal volume-expanding solutions can be administered without risk of a reaction because they are free of antigens and antibodies.

• Artificial blood products are available, but none can perform all the complex functions of normal whole blood. They are compatible with all blood types. Hemolink is made from human hemoglobin, whereas Hemopure is made from cow hemoglobin. Oxygen is a synthetic, genetically engineered blood substitute. Other agents, such as MP4, which is undergoing clinical testing, are combined with blood to increase the oxygen transfer from RBCs to tissues. Polyethylene glycol (PEG) is also being tested by various companies to bind and stabilize hemoglobin molecules, thus decreasing the problem of the dissociation of hemoglobin that occurs in storage. Although promising, none of these artificial blood products have yet received approval from the United States Food and Drug Administration (USFDA).

• Epoetin alfa (Procrit, Eprex) is a form of erythropoietin produced through the use of recombinant DNA technology. It may be administered by injection to stimulate production of red blood cells before certain surgical procedures (e.g., hip replacement) and for patients with anemia related to cancer or chronic renal failure. This reduces the risk of infections or immune reactions associated with multiple blood transfusions.

• Bone marrow or stem cell transplants are used to treat many cancers, severe immune deficiency, or severe blood cell diseases. For success, a close match in tissue or human leukocyte antigen (HLA) type is required. The marrow stem cells are extracted from the donor's pelvic bone, filtered, and infused into the recipient's veins. Normal cells should appear in several weeks. In cases of malignant disease, pretreatment with chemotherapy or radiation is required to destroy tumor cells before the transplant.

• For patients suffering from a lack of blood clotting capability, there are drugs available to aid in the clotting process. Xeljaz is a drug that has been recently approved by the FDA that directly stimulates platelet production by the bone marrow. Novoseven is a drug developed primarily to treat factor VIII deficiency for use in treating combat trauma. Although these drugs are in use today, problems with unintentional clots that may form during their use continue to be a dangerous problem that must be considered.

Blood Dyscrasias

The Anemias

Anemias cause a reduction in oxygen transport in the blood due to a decrease in hemoglobin content. The low hemoglobin level may result from declining production of the protein, a decrease in the number of erythrocytes, or a combination of these factors. Anemias may be classified by common cell characteristics such as size and shape (morphology) or by etiology, for example, the hemolytic anemias.

The oxygen deficit leads to a sequence of events:

• Less energy is produced in all cells; cell metabolism and reproduction are diminished.

• Compensation mechanisms to improve the oxygen supply include tachycardia and peripheral vasoconstriction.

• These changes lead to the general signs of anemia, which include fatigue (excessive tiredness), pallor (pale face), dyspnea (difficulty breathing), and tachycardia (rapid heart rate).

• Decreased regeneration of epithelial cells causes the digestive tract to become inflamed and ulcerated, leading to stomatitis (ulcers in the oral mucosa), inflamed and cracked lips, and dysphagia (difficulty swallowing); the hair and skin may show degenerative changes.

• Severe anemia may lead to angina (chest pain) during stressful situations if the oxygen supply to the heart is sufficiently reduced. Chronic severe anemia may cause congestive heart failure.

Anemias may occur when there is a deficiency of a required nutrient, bone marrow function is impaired, or blood loss or excessive destruction of erythrocytes occurs. This section of the chapter covers a few examples of different types of anemias.

Iron Deficiency Anemia

Pathophysiology

Insufficient iron impairs the synthesis of hemoglobin, thereby reducing the amount of oxygen transported in the blood (see Fig. 10-14A for a diagram showing four hemoglobin molecules). This results in microcytic (small cell), hypochromic (less color) erythrocytes owing to a low concentration of hemoglobin in each cell (see Fig. 10-12). Iron deficiency is common; it ranges from mild to severe and occurs in all age groups. An estimated one in five women is affected, and the proportion increases for pregnant women. Because iron deficiency anemia is frequently a sign of an underlying problem, it is important to determine the specific cause of the deficiency. There is no normal serum iron, as indicated by decreased serum ferritin, decreased hemosiderin, and decreased iron-containing histiocytosis in the bone marrow.

Etiology

An iron deficit can occur for many reasons:

• Dietary intake of iron-containing vegetables or meat may be below the minimum requirement, particularly during the adolescent growth spurt or during pregnancy and breastfeeding, when needs increase. Normally, only 5% to 10% of ingested iron is absorbed, but this can increase to 20% when there is a deficit.

• Chronic blood loss from a bleeding ulcer, hemmorhoids, cancer, or excessive menstrual flow is a common cause of iron deficiency. Continuous blood loss, even small amounts of blood, means that less iron is recycled to maintain an adequate production of hemoglobin (Fig. 10-13).

• Duodenal absorption of iron may be impaired by many disorders, including malabsorption syndromes such as regional ileitis and achlorhydria (lack of hydrochloric acid in the stomach).

• Severe liver disease may affect both iron absorption and iron storage. An associated protein deficit would further impede hemoglobin synthesis.

• In the form of iron deficiency anemia associated with some infections and cancers, iron is present but is not well used, leading to low hemoglobin levels but high iron storage levels.

Signs and Symptoms

Mild anemias are frequently asymptomatic. As the hemoglobin value drops, the general signs of anemia become apparent: