The Cardiovascular System

The components of the cardiovascular system include the blood, heart, and blood vessels. Blood flows through a network of thousands of miles of vessels within the body, transporting nutrients, gases, wastes, hormones, and electrolytes and redistributing the heat generated by active tissues. The exchange of materials between the blood and peripheral tissues occurs across the walls of tiny capillaries that are situated between the arterial and venous systems. The total capillary surface area for exchange is truly enormous, averaging around 6300 square meters, 50 percent larger than the area of a football field.

Because the cardiovascular system plays a key role in supporting all other systems, disorders of this system will affect virtually every cell in the body. One method of organizing the many potential disorders involving this system is by the nature of the primary problem, whether it affects the blood, the heart, or the vascular network. Figure A-34 provides an overview of major blood disorders, and Figure A-35 summarizes heart and blood vessel disorders that are discussed in the text and in later sections of the Applications Manual.

THE PHYSICAL EXAMINATION AND THE CARDIOVASCULAR SYSTEM

Individuals with cardiovascular problems often seek medical attention with one or more of the following as chief complaints:

1. Weakness and fatigue: These symptoms develop when the cardiovascular system can no

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**Figure A-34 Blood Disorders**
longer meet tissue demands for oxygen and nutrients. These symptoms may occur because cardiac function is impaired, as in heart failure (p. 115) or cardiomyopathy (p. 104), or because the blood is unable to carry normal amounts of oxygen, as in the various forms of anemia (p. 102). In the early stages of these conditions, the individual feels healthy at rest, but becomes weak and fatigued with any significant degree of exertion because the cardiovascular system cannot keep pace with the rising tissue oxygen demands. In more advanced stages of these disorders, weakness and fatigue are chronic problems that continue, even at rest.

2. Cardiac pain: This is a deep pain felt in the substernal region and often radiating down the left arm or up into the shoulder and neck. There are two major causes of cardiac pain:

- Constant severe pain can result from inflammation of the pericardial sac, a condition known as pericarditis. This pericardial pain may superficially resemble the pain experienced in a myocardial infarction (MI), or heart attack. Pericardial pain differs from the pain of an MI in that (a) it may be relieved by leaning forward, (b) a fever may be present, and (c) the pain does not respond to the administration of drugs, such as nitroglycerin, that dilate coronary blood vessels. Nitroglycerin, which is effective in relieving angina pectoris, does not relieve the pain associated with pericarditis.

- Cardiac pain can also result from inadequate blood flow to the myocardium. This type of pain is called myocardial ischemic pain. Ischemic pain occurs in angina pectoris and in a myocardial infarction. Angina pectoris (p. 106) most often results from the constriction of coronary blood vessels by atherosclerosis. The associated pain appears during physical exertion, when myocardial oxygen demands increase, and the pain is relieved by drugs such as nitroglycerin, which dilate coronary vessels and improve coronary blood flow. The pain associated with a myocardial infarction is usually felt as a heavy weight or a constriction of the chest. The pain of an MI is also distinctive because (a) it is not necessarily
linked to exertion, (b) it is not relieved by nitroglycerin or other coronary vasodilators, and (c) nausea, vomiting, and sweating may occur during the attack.

3. Palpitations: Palpitations are a person's perception of an altered heart rate. The individual may complain of the heart “skipping a beat” or “racing.” The most likely cause of palpitations is an abnormal pattern of cardiac activity known as an arrhythmia. The detection and analysis of arrhythmias are considered in a later section (p. 108).

4. Pain on movement: Individuals with advanced atherosclerosis often experience pain in the extremities during muscle use. The pain may become so severe that the person is unwilling or unable to walk or perform other common activities. The underlying problem is constriction or partial occlusion of major arteries, such as the external iliac arteries to the lower limbs, by plaque formation.

These are only a few of the many symptoms that can be caused by cardiovascular disorders. In addition, the individual may notice the appearance of characteristic signs of other cardiovascular problems. A partial listing of important cardiovascular signs includes the following:

- **Edema** is an increase of fluid in the tissues that occurs when (a) the pumping efficiency of the heart is decreased, (b) the plasma protein content of the blood is reduced, or (c) venous pressures are abnormally high. The tissues of the lungs and the legs are most often affected, and individuals experience swollen feet and ankles. When edema is so severe that pressing on the affected area leaves an indentation, the sign is called **pitting edema**. Edema is discussed in Chapter 13 of the text (p. 397).

- **Breathlessness**, or **dyspnea**, occurs when cardiac output is inadequate for tissue oxygen demands. Dyspnea may also occur with **pulmonary edema**, a buildup of fluid within the alveoli of the lungs. Pulmonary edema and dyspnea are often associated with **congestive heart failure** (p. 115).

- **Varicose veins** are dilated superficial veins that are visible at the skin surface. This condition, which develops when venous valves malfunction, can be caused or exaggerated by increased systemic venous pressures. Varicose veins are considered further on p. 112.

- There may be characteristic and distinctive changes in skin coloration. For example, **pallor** is the lack of normal red or pinkish color to the skin of a Caucasian or the conjunctiva and oral mucosa of darker-skinned individuals. Pallor accompanies many forms of anemia, but may also be the result of inadequate cardiac output, shock (p. 113), or circulatory collapse. **Cyanosis** is the bluish color of the skin occurring with a deficiency of oxygen to the tissues. Cyanosis usually results from either cardiovascular or respiratory disorders.

- **Vascular skin lesions** were introduced in the discussion of skin disorders on p. 38. Characteristic vascular lesions may occur in primary clotting disorders (p. 104) and as a result of **leukemia** (p. 102). For example, abnormal bruising may be the result of a disorder affecting the clotting system, platelet production, or vessel structure. **Petechiae**, which appear as purple spots on the skin surface, are often seen in certain types of leukemia or other diseases associated with low platelet counts.

### CARDIOVASCULAR DISORDERS AND DIAGNOSTIC PROCEDURES

Often the initial detection of a cardiovascular disorder occurs during the assessment stage of a physical examination.

1. When the vital signs are taken, the pulse is checked for vigor, rate, and rhythm. Weak or irregular heart beats will often be noticed at this time.

2. The blood pressure is monitored with a stethoscope, blood pressure cuff, and sphygmomanometer. Unusually high or low readings can alert the examiner to potential problems with cardiac or vascular function. However, a diagnosis of hypotension or hypertension is not made on the basis of a single reading, but after several readings over a period of time. Hypertension and hypotension are discussed in detail on p. 112.

3. The heart sounds are monitored by auscultation with a stethoscope:

   - Cardiac rate and rhythm can be checked and arrhythmias detected.

   - Abnormal heart sound, or **murmurs**, may indicate problems with atrioventricular or semilunar valves. Murmurs are noted in relation to their location in the heart (as determined by the position of the stethoscope on the chest wall), the time of occurrence in the cardiac cycle, and whether the sound is low or high pitched.

   - Nothing is usually heard during auscultation of normal vessels of the circulatory system. **Bruit**s are the sounds resulting from turbulent blood flow around an obstruction within a vessel. Bruits are typically heard where large atherosclerotic plaques have formed.

   Functional abnormalities of the heart and blood vessels can often be detected through physi-
cal assessment and the recognition of characteristic signs and symptoms. The structural basis for these problems is usually determined through the use of scans, X-rays, and the monitoring of electrical activity in the heart. For problems with a hematological basis, laboratory tests performed on blood samples usually provide the information necessary to reach a diagnosis.

Polycythemia

EAP p. 347

An elevated hematocrit with a normal blood volume constitutes polycythemia (po-le-si-THE-mé-uh). There are several different types of polycythemia. Erythrocytosis (é-rith-ro-si-TÖ-sis), a polycythemia affecting only red blood cells, will be considered later in the chapter. Polycythemia vera (“true polycythemia”) results from an increase in the numbers of all blood cells. The hematocrit may reach 80–90, at which point the tissues become oxygen-starved because red blood cells are blocking the smaller vessels. This condition seldom strikes young people; most cases involve patients age 60–80. There are several treatment options, but none cures the condition. The cause of polycythemia vera is unknown, although there is some evidence that the condition is linked to radiation exposure.

Thalassemia

EAP p. 349

The thalassemias are a diverse group of inherited blood disorders caused by an inability to produce adequate amounts of the normal protein subunits of hemoglobin. Each hemoglobin molecule has two alpha (α) chains and two beta (β) chains. A specific condition is categorized as an α-thalassemia or β-thalassemia depending on whether the α or β hemoglobin subunits are affected. Normal individuals inherit two alpha chain genes from each parent, and alpha-thalassemia develops when one or more of these genes are missing or inactive. The severity of the symptoms varies depending on how many normal alpha chain genes remain functional. For example, an individual with three normal alpha chain genes will not develop symptoms at all, but this person can be a carrier, passing the defect to the next generation. A child born of parents who are both carriers is likely to develop a more severe form of the disease:

- Individuals with two copies of the normal alpha chain gene, rather than four copies, have somewhat impaired hemoglobin synthesis. The red blood cells are small and contain less than the normal quantity of hemoglobin. This condition, known as α-thalassemia trait, affects roughly 2 percent of African Americans and many Southeast Asians.
- Individuals with one copy of the alpha chain gene have very small (microcytic) red blood cells that are relatively fragile.
- Individuals with no functional copies of the alpha chain gene usually die shortly after birth, because the hemoglobin synthesized cannot bind and transport oxygen normally. The incidence of fatal α-thalassemia is highest among Southeast Asians.

Each person inherits only one gene for the beta hemoglobin chain from each parent. If an individual does not receive a copy of the normal gene from either parent, the condition of beta-thalassemia major, or Cooley’s disease, develops. Symptoms of this condition include severe anemia; microcytosis; a low hematocrit (under 20); and enlargement of the spleen, liver, heart, and areas of red bone marrow. Potential treatments for those with severe symptoms include transfusions, splenectomy (to slow the rate of RBC recycling), and bone marrow transplantation. Inheriting one normal gene results in beta-thalassemia minor, or beta-thalassemia trait, which seldom produces clinical symptoms. The rates of hemoglobin synthesis are depressed by roughly 15 percent, but this decrease does not affect their functional abilities, and no treatment is necessary.

Sickle Cell Anemia

EAP p. 349

Sickle cell anemia (SCA) results from the production of an abnormal form of hemoglobin. The β chains are involved, and the abnormal subunit is called hemoglobin S. Sickle cell anemia affects 60,000–80,000 African Americans today; this represents roughly 0.14 percent of the African-American population.

An individual with sickle-cell anemia carries two copies of the abnormal gene, one from each parent. If only one copy is present, the individual has a sickling trait. One African American in 12 carries the sickling trait. Although it is now known that the genes are present in Americans of Mediterranean, Middle Eastern, and East Indian ancestry, statistics on the incidence of sickling trait and SCA in these groups are as yet unavailable.

In individuals with the sickling trait, most of the hemoglobin is of the normal form and the erythrocytes function normally. But the presence of the abnormal hemoglobin gives the individual the ability to resist the parasitic infections that cause malaria, a mosquito-borne illness. The malaria parasites enter the bloodstream when an individual is bitten by an infected mosquito. The microorganisms then invade and reproduce within the erythrocytes. But when they enter an erythrocyte from a person with the sickling trait, the cell responds by sickling. Either the sickling itself kills the parasite, or the sickling attracts the attention of a phagocyte that engulfs the RBC and kills the parasite. In either event the individual remains unaffected by the disease, while normal individuals sicken and often die.

Symptoms of sickle cell anemia include pain and damage to a variety of organs and systems,
depending on the location of the obstructions. In addition, the trapped red blood cells eventually die and break down, producing a characteristic anemia. Transfusions of normal blood can temporarily prevent additional complications, and there are experimental drugs that can control or reduce sickling. *Hydroxyurea* is an anticancer drug that stimulates production of fetal hemoglobin, a slightly different form of hemoglobin produced during development. It is effective, but has toxic side effects (not surprising for an anticancer drug). The food additive *butyrate*, found in butter and other foods, appears to be even more effective in promoting the synthesis of fetal hemoglobin. In clinical trials it has been effective in treating sickle cell anemia and other conditions caused by abnormal hemoglobin structure, such as *beta-thalassemia*.

### Bilirubin Tests and Jaundice

When hemoglobin is broken down, the heme units (minus the iron) are converted to bilirubin. Normal serum bilirubin concentrations range from 0.1 to 1.2 mg/dl. Of that amount, roughly 85 percent will be metabolized and removed by the liver. Several different clinical conditions are characterized by an increase in the total plasma bilirubin concentration. In such conditions, bilirubin diffuses into peripheral tissues, giving them a yellow coloration that is most apparent in the skin and over the sclera of the eyes. This combination of signs (yellow skin and eyes) is called *jaundice* (JAWN-dis).

Jaundice can have many different causes, but blood tests that determine the concentration of different forms of bilirubin can provide useful diagnostic clues. For example, *hemolytic jaundice* results from the destruction of large numbers of red blood cells. When this occurs, phagocytes release massive quantities of one form of bilirubin (unconjugated) into the blood. Because the liver cells accelerate the secretion of bilirubin in the bile, the blood concentration of another form of bilirubin (conjugated) does not increase proportionately. A blood test from a patient with hemolytic jaundice would reveal (1) elevated total bilirubin, (2) high concentrations of unconjugated bilirubin, and (3) conjugated bilirubin contributing much less than 15 percent to the total bilirubin concentration.

These results are quite different from those seen in *obstructive jaundice*. In this condition, the ducts that remove bile from the liver are constricted or blocked. Liver cells cannot get rid of conjugated bilirubin, and large quantities diffuse into the blood. In this case, diagnostic tests would show (1) elevated total bilirubin, (2) unconjugated bilirubin contributing much less than 85 percent to the total bilirubin concentration, and (3) high concentrations of conjugated bilirubin.

### Iron Deficiencies and Excesses

If dietary supplies of iron are inadequate, hemoglobin production slows down, and symptoms of *iron deficiency anemia* appear. This form of anemia can also be caused by any condition that produces a blood loss, since the iron in the lost blood cannot be recycled. As the red blood cells are replaced, iron reserves must be mobilized for use in the synthesis of new hemoglobin molecules. If those reserves are exhausted, or dietary sources are inadequate, symptoms of iron deficiency appear. In iron deficiency anemia, the red blood cells are unable to synthesize functional hemoglobin, and they are unusually small when they enter the circulation. The hematocrit declines, and the hemoglobin content and oxygen-carrying capacity of the blood are substantially reduced. Symptoms include weakness and a tendency to fatigue easily.

Women are especially dependent on a normal dietary supply of iron, because their iron reserves are smaller than those of men. The body of a normal man contains around 3.5 g of iron in the ionic form Fe$^{2+}$. Of that amount, 2.5 g are bound to the hemoglobin of circulating red blood cells, and the rest is stored in the liver and bone marrow. In women, the total body iron content averages 2.4 g, with roughly 1.9 g incorporated into red blood cells. Thus a woman’s iron reserves consist of only 0.5 g—half that of a typical man.

Because their reserves are relatively small, women are dependent on a reliable dietary supply of iron. When the demand for iron increases out of proportion with dietary supplies, iron deficiency develops. An estimated 20 percent of menstruating women in the United States show signs of iron deficiency. Pregnancy also stresses iron reserves, for the woman must provide the iron needed to produce both maternal and fetal erythrocytes.

Good dietary sources of iron include liver, red meats, kidney beans, egg yolks, spinach, and carrots. Iron supplements can help prevent iron deficiency, but too much iron can be as dangerous as too little. Iron absorption across the digestive tract normally keeps pace with physiological demands. When the diet contains abnormally high concentrations of iron, or hereditary factors increase the rate of absorption, the excess iron gets stored in peripheral tissues. This is called *iron loading*. Eventually cells begin to malfunction as massive iron deposits accumulate in the cytoplasm. For example, iron deposits in pancreatic cells can lead to diabetes mellitus; deposits in cardiac muscle cells lead to abnormal heart contractions and heart failure. (There is evidence that iron deposits in the heart caused by the overconsumption of red meats may contribute to heart disease.) Liver cells become nonfunctional, and liver cirrhosis may develop.

Comparable symptoms of iron loading may appear following repeated transfusions of whole
blood, because each unit of whole blood contains roughly 250 mg of iron. For example, as noted above, the various forms of thalassemia result from a genetic inability to produce adequate amounts of one of the four globin chains in hemoglobin. Erythrocyte production and survival are reduced, and so is the oxygen-carrying capacity of the blood. Individuals with severe untreated thalassemia usually die in their twenties, but not because of the anemia. These patients are treated for severe anemia. These patients are treated for severe anemia with frequent blood transfusions that prolong life, but the excessive iron loading eventually leads to fatal heart problems.

**Erythrocytosis and Blood Doping**

In **erythrocytosis** (e-rith-ró-si-TÖ-sis), the blood contains abnormally large numbers of red blood cells. Erythrocytosis usually results from the massive release of erythropoietin by tissues (especially the kidneys) deprived of oxygen. People moving to high altitudes usually experience erythrocytosis following their arrival, because the air contains less oxygen than it does at sea level. The increased number of red blood cells compensates for the fact that individually each RBC is carrying less oxygen than it would at sea level. Mountainers and those living at altitudes of 10,000–12,000 feet may have hematocrits as high as 65.

Individuals whose hearts or lungs are functioning inadequately may also develop erythrocytosis. For example, this condition is often seen in heart failure and emphysema, two conditions discussed in later chapters. Whether the blood fails to circulate efficiently or the lungs do not deliver enough oxygen to the blood, peripheral tissues remain oxygen-poor despite the rising hematocrit. Having a higher concentration of red blood cells increases the oxygen-carrying capacity of the blood, but it also makes the blood thicker and harder to push around the circulatory system. This increases the workload on the heart, making a bad situation even worse.

The practice of **blood doping** was temporarily widespread among competitive athletes involved in endurance sports such as cycling. The procedure entails removing whole blood from the athlete in the weeks before an event. The packed red cells are separated from the plasma and stored. By the time of the race, the competitor’s bone marrow will have replaced the lost blood. Immediately before the event the packed red cells are reinfused, increasing the hematocrit. The objective is to elevate the oxygen-carrying capacity of the blood, and so increase endurance. The consequence is that the athlete’s heart is placed under a tremendous strain. The long-term effects are unknown, but the practice obviously carries a significant risk. Once EPO became available, its ease of use replaced blood doping. Both have been banned in amateur sports. Attempts to circumvent this rule by the use of EPO in 1992–1993 resulted in the tragic deaths of 18 European cyclists.

**Blood Tests and RBCs**

This section describes several common blood tests that assess circulating RBCs.

**Reticulocyte Count.** Reticulocytes are immature red blood cells that are still synthesizing hemoglobin. Most reticulocytes remain in the bone marrow until they complete their maturation, but some enter the circulation. Reticulocytes normally account for around 0.8 percent of the erythrocyte population. Values above 1.5 percent or below 0.5 percent indicate that something is wrong with the rates of RBC survival or maturation.

**Hematocrit (Hct).** The hematocrit value is the percentage of whole blood occupied by cells. Normal adult hematocrits average 46 for men and 42 for women, with ranges of 42–52 for men and 37–47 for women.

**Hemoglobin Concentration (Hb).** This test determines the amount of hemoglobin in the blood, expressed in grams per deciliter (g/dl). Normal ranges are 14–18 g/dl in males and 12–16 g/dl in females. The differences in hemoglobin concentration reflect the differences in hematocrit. For both sexes, a normal RBC contains 27–33 picograms (pg) of hemoglobin.

**RBC Count.** Calculations of the RBC count, the number of RBCs per microliter of blood, are based on the hematocrit and hemoglobin content, and can be used to develop a better picture of the condition of the RBCs. Values often reported in blood screens include:

- Mean corpuscular volume (MCV), the average volume of an individual red blood cell, in cubic micrometers. It is calculated by dividing the volume of red cells per microliter by the RBC count, using the formula
  \[
  MCV = \frac{Hct \times 10}{RBC \text{ count (in millions)}}
  \]

Normal values range from 80 to 98. For a representative hematocrit of 46 and an RBC count of 5.2 million, the mean corpuscular volume would be

\[
MCV = \frac{46 \times 10}{5.2} = 88.5 \mu m^3
\]

Cells of normal size are **normocytic**, whereas larger-than-normal or smaller-than-normal RBCs are called **macrocytic** or **microcytic**, respectively.
1. Hemorrhagic anemia results from severe blood loss. Erythrocytes are of normal size, and contain a normal amount of hemoglobin. Reticulocyte count is low, and as a result they are unusually small. A blood test therefore shows a low hematocrit, low hemoglobin content, low MCV, and low MCHC, but a normal reticulocyte count. An estimated 60 million women worldwide have iron deficiency anemia. (See the discussion on iron deficiencies and excesses on p. 100.)

4. In pernicious anemia, normal red blood cell maturation ceases because of an inadequate supply of vitamin B₁₂. Erythrocyte production declines, and the red blood cells are abnormally large and may develop a variety of bizarre shapes. Blood tests from a person with pernicious anemia indicate a low hematocrit with a very high MCV and a low reticulocyte count.

### Hemolytic Disease of the Newborn

Hemolytic disease of the newborn results from the maternal production of anti-Rh antibodies that cross the placenta to attack fetal Rh-positive red blood cells. Within 6 months after delivery, roughly 20 percent of Rh-negative mothers who were pregnant with Rh-positive children have become sensitized and produce anti-Rh antibodies. For the entire sequence of events, see Figure A-36. Without treatment, the fetus will probably die before delivery or shortly thereafter.

A newborn with severe HDN is anemic, and the high concentration of circulating bilirubin produces jaundice. Because the maternal antibodies remain active for 1 to 2 months after delivery, the infant’s entire blood volume may need to be replaced by an exchange transfusion. Blood replacement removes most of the maternal antibodies as well as the affected erythrocytes, reducing the complications and the chance the infant will die.

When there is a danger that the fetus may not survive to full term, premature delivery may be induced after 7 to 8 months of development. In a severe case affecting a fetus at an earlier stage, one or more transfusions can be given while the fetus continues to develop within the uterus.

To avoid the problem, the maternal production of Rh antibodies is prevented by administering Rh antibodies (available under the name RhoGam) after delivery or miscarriage or abortion. These “foreign” antibodies quickly destroy any fetal red blood cells that enter the maternal circulation. Thus there are no exposed antigens to stimulate the maternal immune system, sensitization does not occur, and Rh antibodies are not produced. This relatively simple procedure could almost entirely prevent HDN mortality caused by Rh incompatibilities.

### The Leukemias

Leukemias characterized by the presence of abnormal granulocytes or other cells of the bone marrow are called myeloid; leukemias that involve abnor-

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**Table A-20 RBC Tests and Anemias**

<table>
<thead>
<tr>
<th>Anemia type</th>
<th>Hct</th>
<th>Hb</th>
<th>MCV</th>
<th>MCHC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhagic</td>
<td>low</td>
<td>low</td>
<td>normal</td>
<td>normal</td>
</tr>
<tr>
<td>Aplastic</td>
<td>low</td>
<td>very low</td>
<td>normal</td>
<td>normal</td>
</tr>
<tr>
<td>Iron deficiency</td>
<td>low</td>
<td>normal</td>
<td>normal</td>
<td>low</td>
</tr>
<tr>
<td>Pernicious</td>
<td>low</td>
<td>very low</td>
<td>high</td>
<td>high</td>
</tr>
</tbody>
</table>
mal lymphocytes are termed lymphoid. The first symptoms appear as immature and abnormal white blood cells appear in the circulation. As their numbers increase, they travel through the circulation, invading tissues and organs throughout the body.

These cells are extremely active, and they require abnormally large amounts of energy. As in other cancers, described in Chapter 3 of the text and elsewhere in this Applications Manual (p. 33), invading leukemic cells gradually replace the normal cells, especially in the bone marrow. Red blood cell, normal WBC, and platelet formation decline, with resulting anemia, infection, and impaired blood clotting. Untreated leukemias are invariably fatal.

Leukemias are classified as acute (short and severe) or chronic (prolonged). Acute leukemias may be linked to radiation exposure, hereditary susceptibility, viral infections, or unknown causes. Chronic leukemias may be related to chromosomal abnormalities or immune system malfunctions. Survival in untreated acute leukemia averages about three months; individuals with chronic leukemia may survive for years.

FIGURE A-36  Rh Factors and Pregnancy

When an Rh-negative woman has her first Rh-positive child, mixing of fetal and maternal blood occurs at delivery when the placental connection breaks down. The appearance of Rh-positive blood cells in the maternal circulation sensitizes the mother, stimulating the production of anti-Rh agglutinins. If another pregnancy occurs with an Rh-positive fetus, maternal agglutinins can cross the placental barrier and attack fetal blood cells, producing symptoms of HDN (hemolytic disease of the newborn).
Effective treatments exist for some forms of leukemia and not others. For example, when acute lymphoid leukemia is detected early, 85–90 percent of patients can be held in remission for 5 years or longer, but only 10–15 percent of patients with acute myeloid leukemia survive 5 years or more. The yearly mortality rate for leukemia (all types) in the United States has not declined appreciably in the past 30 years, remaining at around 6.8 per 100,000 population. However, new treatments are being developed that show promise when used against specific forms of leukemia. For example, administration of α-interferon, a hormone of the immune system, has been very effective in treating hairy cell leukemia and chronic myeloid leukemia.

One option for treating acute leukemias is to perform a bone marrow transplant. In this procedure, massive chemotherapy or radiation treatment is given, enough to kill all the cancerous cells. Unfortunately, this also destroys the patient’s blood cells and stem cells in the bone marrow and other blood-forming tissues. The individual then receives an infusion of healthy bone marrow cells that repopulate the blood and marrow tissues.

If the bone marrow is extracted from another person (an heterologous marrow transplant), care must be taken to ensure that the blood types and tissue types are compatible (see Chapters 11 and 14 of the text). If they are not, the new lymphocytes may attack the patient’s tissues, with potentially fatal results. Best results are obtained when the donor is a close relative. In an autologous marrow transplant bone marrow is removed from the patient, cleansed of cancer cells, and reintroduced after radiation or chemotherapy treatment. Although there are fewer complications, the preparation and cleansing of the marrow are technically difficult and time consuming.

Bone marrow transplants are also performed to treat patients whose bone marrow has been destroyed by toxic chemicals or radiation. For example, heterologous transplants were used successfully in the USSR to treat survivors of the Chernobyl nuclear reactor accident in 1986.

### Testing the Clotting System

Several clinical tests check the efficiency of the clotting system:

**BLEEDING TIME.** This test measures the time it takes for a small skin wound to seal itself. There are several variations on this procedure, with normal values ranging from 1 to 9 minutes. The nonprescription drug aspirin prolongs the bleeding time by affecting platelet function and suppressing the extrinsic pathway.

**COAGULATION TIME.** In this test, a sample of whole blood is allowed to stand under controlled conditions until a visible clot has formed. Normal values range from 3 to 15 minutes. The test has several potential sources of error, and so is not very accurate. Nevertheless, it is the simplest test that can be performed on a blood sample.

**PARTIAL THROMBOPLASTIN TIME (PTT).** In this test, a plasma sample is mixed with chemicals that mimic the effects of activated platelets. Calcium ions are then introduced, and the clotting time is recorded. Clotting normally occurs in 35–50 seconds if the enzymes and clotting factors of the intrinsic pathway are present in normal concentrations.

**PLASMA PROTHROMBIN TIME (PROTHROMBIN TIME, PT).** This test checks the performance of the extrinsic pathway. The procedure is similar to that in the PTT test, but the clotting process is triggered by exposure to a combination of tissue thromboplastin (formerly called thromboplastin) and calcium ions. Clotting normally occurs in 12–14 seconds.

### Infection and Inflammation of the Heart

EAP p. 369

Many different microorganisms may infect heart tissue, leading to serious cardiac abnormalities. **Carditis** (kar-di-tis) is a general term indicating inflammation of the heart. Clinical conditions resulting from cardiac infection are usually identified by the primary site of infection. For example, those affecting the endocardium produce symptoms of **endocarditis**. Endocarditis primarily affects the chordae tendineae and heart valves, and the mortality rate may reach 21–35 percent. The most severe complications result from the formation of blood clots on the damaged surfaces. These clots subsequently break free, entering the circulation as drifting emboli (see p. 361 of the text) that may cause strokes, heart attacks, or kidney failure. Destruction of heart valves by infection may lead to valve leakage, heart failure, and death.

Bacteria, viruses, protozoa, and fungal pathogens that either attack the myocardium directly or release toxins that do, produce **myocarditis**. The microorganisms implicated include those responsible for many of the conditions discussed in earlier chapters, including diphtheria, syphilis, polio, and malaria. The membranes of infected heart muscle cells become facilitated, and the heart rate may rise dramatically. Over time, abnormal contractions may appear, the heart muscle weakens, and these may eventually prove fatal.

### The Cardiomyopathies

EAP p. 370

The cardiomyopathies (kar-de-ô-mi-OP-a-théz) include an assortment of diseases with a common symptom: the progressive, irreversible degeneration of the myocardium. Cardiac muscle fibers are damaged and replaced by fibrous tissue, and the muscular walls of the heart become thin and weak. As muscle tone declines, the ventricular chambers become greatly enlarged. When the remaining fibers cannot develop enough force to maintain cardiac output, symptoms of heart failure develop.
Chronic alcoholism and coronary artery disease are probably the most common causes of cardiomyopathy in the United States. Infectious agents, including viruses, bacteria, fungi, and protozoans, can also produce cardiomyopathies. Diseases affecting neuromuscular performance, such as muscular dystrophy (discussed elsewhere in this manual), can also damage cardiac muscle fibers, as can starvation or chronic variations in the extracellular concentrations of calcium or potassium ions.

There are also several inherited forms of cardiomyopathy. **Hypertrophic cardiomyopathy (HCM)** is an inherited disorder that makes the wall of the left ventricle thicken to the point at which it has difficulty pumping blood. Most people with HCM do not become aware of it until relatively late in life. However, HCM can also cause a fatal arrhythmia: it has been implicated in the sudden deaths of several young athletes. The implantation of an electronic cardiac pacemaker has proved to be beneficial in controlling these arrhythmias.

Finally, there are a significant number of cases of **idiopathic cardiomyopathy**, a term used when the primary cause cannot be determined.

### Heart Transplants and Assist Devices

Individuals with severe cardiomyopathy may be considered as candidates for heart transplants. This surgery involves the complete removal of the weakened heart and its replacement with a heart taken from a suitable donor. To survive the surgery, the recipient must be in otherwise satisfactory health. Because the number of suitable donors is limited, the available hearts are usually assigned to individuals younger than age 50. Out of the 8,000–10,000 U.S. patients each year who have potentially fatal cardiomyopathies, only about 1,000 receive heart transplants. After successful transplantation, there is an 80–85 percent one-year survival rate and a 50–70 percent five-year survival rate. These rates are quite good, considering that these patients would have died if the transplant had not been performed.

Many individuals with cardiomyopathy who are initially selected for transplant surgery succumb to the disease before a suitable donor becomes available. For this reason there continues to be considerable interest in the development of an artificial heart. One model, the **Jarvik-7**, had limited clinical use in the 1980s. Attempts to implant it on a permanent basis were unsuccessful, primarily because of the formation of blood clots on the mechanical valves and infections involving its external power source. When the clots broke free, they formed drifting emboli that plugged peripheral vessels, producing strokes, kidney failure, and other complications. In 1989 the federal government prohibited further experimental use of the Jarvik-7 as a permanent heart implant. Modified versions of this unit and others now under development may still be used to maintain transplant candidates while awaiting the arrival of a donor organ. These are called **left ventricular assist devices (LVAD)**. As the name implies, these devices assist, rather than replace, the damaged heart. A mechanical left ventricular assist device has been used to support a patient awaiting a transplant.

An experimental approach, which has yet to be tried with human patients, involves the insertion of fetal heart muscle cells in a damaged adult heart. The fetal cells appear to adapt to their surroundings and differentiate into functional contractile cells.

### RHD and Valvular Stenosis

**Rheumatic (roo-MA-tik) fever** is an inflammatory condition that may develop following untreated infection by streptococcal bacteria (“strep throat”). Rheumatic fever most often affects children of age 5–15 years; symptoms include high fever, joint pain and stiffness, and a distinctive full-body rash. Obvious symptoms usually persist for less than 6 weeks, although severe cases may linger for 6 months or more. The longer the duration of the inflammation, the more likely it is that carditis will develop. The carditis that does develop in 50–60 percent of patients often escapes detection, and scar tissue forms gradually in the myocardium and the heart valves. Valve condition deteriorates over time, and valve problems serious enough to affect cardiac function may not appear until 10–20 years after the initial infection.

Over the interim the affected valves become thickened and often calcified to some degree. This thickening narrows the opening guarded by the valves, producing a condition called **valvular stenosis** (ste-NÖ-sis; *stenos*, narrow). The resulting clinical disorder is known as **rheumatic heart disease**, or RHD. The thickened cusps stiffen in a partially closed position, but the valves do not completely block the circulation; instead, the edges of the cusps are rough and irregular (Figure A-37). Regurgitation may occur, and much of the blood pumped out of the heart may flow right back in. The abnormal valves are also much more susceptible to bacterial infection, a type of **endocarditis**.

**Mitrail stenosis** and **aortic stenosis** are the most common forms of valvular heart disease. About 40 percent of patients with RHD develop mitral stenosis, and two-thirds of them are women. The reason for the correlation between gender and mitral stenosis is unknown. In mitral stenosis blood enters the left ventricle at a slower than normal rate, and when the ventricle contracts, blood flows back into the left atrium as well as into the aortic trunk. As a result, the left ventricle has to work much harder to maintain adequate systemic circulation. The right and left ventricles discharge identical amounts of blood with each beat, and as the output of the left ventricle declines, blood “backs up” in the pulmonary circuit. Venous pressures then rise in the pulmonary circuit, and the right...
ventricle must develop greater pressures to force blood into the pulmonary trunk. In severe cases of mitral stenosis, the ventricular musculature is not up to the task. The heart weakens, and peripheral tissues begin to suffer from oxygen and nutrient deprivation. (This condition, called heart failure, is discussed in more detail in a later section.)

Symptoms of aortic stenosis develop in roughly 25 percent of patients with RHD; 80 percent of these individuals are males. Symptoms of aortic stenosis are initially less severe than those of mitral stenosis. Although the left ventricle enlarges and works harder, normal circulatory function can often be maintained for years. Clinical problems develop only when the opening narrows enough to prevent adequate blood flow. Symptoms then resemble those of mitral stenosis.

One reasonably successful treatment for severe stenosis involves the replacement of the damaged valve with a prosthetic (artificial) valve. Figure A-37a shows a stenotic heart valve; two possible replacements are a valve from a pig (Figure A-37b) and a synthetic valve (Figure A-37c), one of a number of designs that have been employed. Pig valves do not require anticoagulant therapy, but may wear out and begin leaking after roughly 10 years in service. The plastic or stainless steel components of the artificial valve are more durable but activate the clotting system of the recipient, leading to inflammation, clot formation, and other potential complications. Synthetic valve recipients must take anticoagulant drugs to prevent strokes and other disorders caused by embolus formation. Valve replacement operations are quite successful, with about 95 percent of the surgical patients surviving for 3 years or more and 70 percent surviving over 5 years.

Coronary Artery Disease

The term coronary artery disease (CAD) refers to degenerative changes in the coronary circulation. Cardiac muscle fibers need a constant supply of oxygen and nutrients, and any reduction in coronary circulation produces a corresponding reduction in cardiac performance. Such reduced circulatory supply, known as coronary ischemia (is-KÉ-mé-uh), usually results from partial or complete blockage of the coronary arteries. The usual cause is the formation of a fatty deposit, or plaque, in the wall of a coronary vessel. The plaque, or an associated thrombus, then narrows the passageway and reduces blood flow. Spasms in the smooth muscles of the vessel wall can further decrease blood flow or even stop it altogether. Plaque development and growth are considered in Chapter 13.

One of the first symptoms of CAD is often angina pectoris (an-JI-nuh PEK-tor-is; angina, pain spasm + pectoris, of the chest). In the most common form of angina, temporary insufficiency and ischemia develop when the workload of the heart increases. Although the individual may feel comfortable at rest, any unusual exertion or emotional stress can produce a sensation of pressure, chest constriction, and pain that may radiate from the sternal area to the arms, back, and neck.

Angina can often be controlled by a combination of drug treatment and changes in lifestyle. Lifestyle changes to combat angina include (1) limiting activities known to trigger angina attacks, such as strenuous exercise, and avoiding stressful situations; (2) stopping smoking; and (3) modifying the diet to lower fat consumption. Medications useful for controlling angina include drugs that block sympathetic stimulation (propranolol or metoprolol); vasodilators such as nitroglycerin (ni-tró-GLIS-er-in); and drugs that block calcium movement into the cardiac muscle cells (calcium channel blockers).

Angina can also be treated surgically. A single, soft plaque may be reduced with the aid of a slender, elongate catheter (KATH-e-ter). The catheter, a small-diameter tube, is inserted into a large artery and guided into a coronary artery to the plaque. A variety of surgical tools can be slid into the catheter, and the plaque can then be removed with...
laser beams or chewed to pieces by a miniature version of the Roto-Rooter machine. Debris created during plaque destruction is sucked up by the catheter, preventing blockage of smaller vessels.

In **balloon angioplasty** (AN-jē-ō-plas-tē; angeion, vessel) the catheter tip is inflated with an inflatable balloon. Once in position, the balloon is inflated, pressing the plaque against the vessel walls. This procedure works best in small (under 10 mm) soft plaques. Several factors make this a highly attractive treatment: (1) The mortality rate during surgery is only around 1 percent; (2) the success rate is over 90 percent; and (3) it can be performed on an outpatient basis. Although in about 20 percent of patients the plaque deposit returns to its original size within 6 months, the process can be repeated as needed.

A **coronary artery bypass graft (CABG)** involves taking a small section from either a small artery (often the **internal thoracic artery**) or a peripheral vein (such as the **great saphenous vein** of the leg) and using it to create a detour around the obstructed portion of a coronary artery. As many as four coronary arteries can be rerouted this way during a single operation. The procedures are named according to the number of vessels repaired, so one speaks of **single, double, triple, or quadruple coronary bypass operations**. The mortality rate during surgery for operations performed before significant heart damage has occurred is relatively low (1–2 percent). Under these conditions the procedure completely eliminates the angina symptoms in 70 percent of the cases and provides partial relief in another 20 percent.

Although it does offer certain advantages, recent studies have shown that for mild angina, coronary bypass surgery does not yield significantly better results than drug therapy. Current recommendations are that coronary bypass surgery be reserved for cases of severe angina that do not respond to other treatment.

**Heart Attacks**

In a **myocardial** (mi-ō-KAR-de-al) **infarction** (MI), or **heart attack**, the coronary circulation becomes blocked and the cardiac muscle cells die from lack of oxygen. The affected tissue then degenerates, creating a nonfunctional area known as an **infarct**. Heart attacks most often result from severe coronary artery disease. The consequences depend on the site and nature of the circulatory blockage. If it occurs near the base of one of the coronary arteries, the damage will be widespread and the heart will probably stop beating. If the blockage involves one of the smaller arterial branches, the individual may survive the immediate crisis, but there are many potential complications, all unpleasant. As scar tissue forms in the damaged area, the heartbeat may become irregular and other vessels can become constricted, creating additional circulatory problems.

Myocardial infarctions are most often associated with pre-existing fixed partial blockages, such as those seen in CAD. When the crisis develops because of complete blockage by a thrombus (clot) formation at a plaque, the condition is called **coronary thrombosis**. A vessel already narrowed by plaque formation may also become blocked by a sudden spasm in the smooth muscles of the vascular wall. The individual then may experience intense pain, similar to that of an angina attack but persisting even at rest. However, pain does not always accompany a heart attack. These **silent heart attacks** may be even more dangerous, because the condition may not be diagnosed and treated before a fatal MI occurs. Roughly 25 percent of heart attacks are not recognized when they occur.

The cytoplasm of a damaged cardiac muscle cell differs from that of a normal muscle cell. As the supply of oxygen decreases, the cells become more dependent on anaerobic metabolism to meet their energy needs. Over time the cytoplasm accumulates large numbers of enzymes involved with anaerobic energy production.

As the cardiac muscle cell membranes deteriorate, these enzymes leak into the surrounding intercellular fluids. The appearance of such enzymes in the circulation thus indicates that an infarct has occurred. The enzymes tested for in a diagnostic blood test include **lactate dehydrogenase (LDH)**, **serum glutamic oxaloacetic transaminase (SGOT, also called aspartate aminotransferase)**, **creatine phosphokinase (CPK, or CK)**, and a special form of creatine phosphokinase found only in cardiac muscle (CK-MB).

Roughly 25 percent of MI patients die before obtaining medical assistance, and 65 percent of MI deaths among those under age 50 occur within an hour after the initial infarct. The goals of treatment are to limit the size of the infarct and prevent additional complications by preventing irregular contractions, improving circulation with vasodilators, providing additional oxygen, reducing the cardiac workload, and, if possible, eliminating the cause of the circulatory blockage. Anticoagulants may help prevent the formation of additional thrombi, and clot-dissolving enzymes, such as t-PA, may reduce the extent of the damage if they are administered within 6 hours after the MI has occurred. Follow-up treatment with heparin or aspirin or both is recommended; without further treatment the circulatory blockages will reappear in roughly 20 percent of patients.

A number of factors increase the risk of a heart attack: smoking, high blood pressure, high blood cholesterol levels, high circulating levels of **low-density lipoproteins** (LDL), diabetes, increasing age, male gender (below age 70), and obesity. The role of lipoproteins and cholesterol in plaque formation and heart disease are considered in Chapter 13. Hereditary factors may also predispose an individual to coronary artery disease. Although the rate of heart attacks of women under age 70 is lower than that of men, their mortality rate is actually higher—perhaps because heart disease in women is...
neither diagnosed as early nor treated as aggressively as is heart disease in men. The presence of two risk factors more than doubles the risk, so eliminating as many risk factors as possible will improve one’s chances of preventing or surviving a heart attack. Changes in diet to limit cholesterol, exercise to lower weight, not smoking, and seeking treatment for high blood pressure are steps in the right direction. As public health knowledge and education about risk factors for heart disease and treatment for hypertension and high cholesterol have improved death rates have declined. Data from the CDC shows a drop of death rates from coronary artery disease from over 200 per 100,000 to 134 per 100,000 between 1963 and 1996. In 1996, they estimate there were 621,000 fewer deaths from CAD than would have been expected had the rates stayed as high.

Diagnosing Abnormal Heartbeats

Damage to the conduction pathways caused by mechanical distortion, ischemia, infection, or inflammation can affect the normal rhythm of the heart. The resulting condition is called a conduction deficit, or heart block. Heart blocks of varying severity are illustrated in Figure A-38. In a first-degree heart block (Figure A-38b), the AV node and proximal portion of the AV bundle slow the passage of impulses heading for the ventricular myocardium. As a result, a pause appears between the atrial and ventricular contractions. Although a delay exists, the regular rhythm of the heart continues, and each atrial beat is followed by a ventricular contraction.

If the delay lasts long enough, the nodal cells will still be repolarizing from the previous beat when the next impulse arrives from the pacemaker. The arriving impulse will then be ignored, the ventricles will not be stimulated, and the normal “atria-ventricles, atria-ventricles” pattern will disappear. This condition is a second-degree heart block (Figure A-38c). A mild second-degree block may produce only an occasional skipped beat, but with more substantial delays the ventricles will follow every second atrial beat. The resulting pattern of “atria-ventricles, atria, atria-ventricles” is known as a two-to-one (2:1) block. Three-to-one or even four-to-one blocks are also encountered.

In a third-degree heart block, or complete heart block, the conducting pathway stops functioning altogether (Figure A-38d). The atria and ventricles continue to beat, but their activities are no longer synchronized. The atria follow the pace set by the SA node, beating 70–80 times per minute, and the ventricles follow the commands of the AV node, beating at a rate of 40–60 per minute. A temporary heart block can be induced by stimulating the vagus nerve. In addition to slowing the rate of impulse generation by the SA node, such stimulation inhibits the AV nodal cells to the point that they cannot respond to normal stimulation. Comments such as “my heart stopped” or “my heart skipped a beat” usually refer to this phenomenon. The pause typically lasts for just a few seconds. Longer delays end when a conducting cell, usually one of the Purkinje fibers, depolarizes to threshold. This phenomenon is called ventricular escape because the ventricles are escaping from the control of the SA node. Ventricular escape can be a lifesaving event if the conduction system is damaged. Even without instructions from the SA or AV nodes, the ventricles will continue to pump blood at a slow but steady rate.

Tachycardia and Fibrillation

Additional important examples of arrhythmias are shown in Figure A-39. Premature atrial contractions (PACs), indicated in Figure A-39b, often occur in normal individuals. In a PAC the normal atrial rhythm is momentarily interrupted by a “surprise” atrial contraction. Stress, caffeine, and various drugs may increase the frequency of PAC incidence, presumably by increasing the permeabilities of the SA pacemakers. The impulse
spreads along the conduction pathway, and a normal ventricular contraction follows the atrial beat.

In **paroxysmal atrial tachycardia** (par-ok-SIZ-mal), or PAT (Figure A-39c), a premature atrial contraction triggers a flurry of atrial activity. The ventricles are still able to keep pace, and the heart rate jumps to about 180 beats per minute. In **atrial flutter** the atria are contracting in a coordinated manner, but the contractions are occurring very frequently. During a bout of **atrial fibrillation** (fibri-LÅ-shun), Figure A-39d, the impulses are moving over the atrial surface at rates of perhaps 500 beats per minute. The atrial wall quivers instead of producing an organized contraction. The ventricular rate in atrial flutter or atrial fibrillation cannot follow the atrial rate, and may remain within normal limits. Despite the fact that the atria are now essentially nonfunctional, the condition may go unnoticed, especially in older individuals leading sedentary lives. PACs, PAT, atrial flutter, and even atrial fibrillation are not considered very dangerous unless they are prolonged or associated with some more serious indications of cardiac damage, such as coronary artery disease or valve problems.

In contrast, ventricular arrhythmias may be serious and even fatal. Because the conduction system functions in one direction only, a ventricular arrhythmia is not linked to atrial activities. **Premature ventricular contractions** (PVCs; Figure A-39e) occur when a Purkinje cell or ventricular myocardial cell depolarizes to threshold and triggers a premature contraction. The cell responsible is called an **ectopic pacemaker**. The frequency of PVCs can be increased by exposure to epinephrine and other stimulatory drugs or to ionic changes that depolarize cardiac muscle fiber membranes. Similar factors may be responsible for periods of **ventricular tachycardia**, also known as VT, or V-tach (Figure A-39f).

Multiple PVCs and VT often precede the most serious type of arrhythmia, **ventricular fibrillation** (VF; Figure A-39g). The resulting condition, known as **cardiac arrest**, is rapidly fatal because the heart quivers and stops pumping blood. During ventricular fibrillation, cardiac muscle fibers are overly sensitive to stimulation and the impulses are traveling from cell to cell around and around the ventricular walls. A normal rhythm cannot become established, because the ventricular muscle fibers are stimulating one another at a rapid rate. The problem is exaggerated by a sustained rise in free intracellular calcium ion concentrations due to massive stimulation of alpha and beta receptors following sympathetic activation.

A **defibrillator** is a device that attempts to eliminate ventricular fibrillation and restore normal cardiac rhythm. Two electrodes are placed in contact with the chest, and a powerful electrical shock is administered. The electrical stimulus depolarizes the entire myocardium simultaneously. With luck, after repolarization the SA node will be the first area of the heart to reach threshold. Thus the primary goal of defibrillation is not just to stop the fibrillation, but to give the ventricles a chance to respond to normal SA commands. Early defibrillation can result in dramatic recovery of an unconscious cardiac arrest victim.

In treating arrhythmias there are several medications that can slow down rapid heart rates, or the abnormal portions of the conducting system can be destroyed. Pacemakers are used to accelerate slow heart rates. Implantable pacemakers able to sense ventricular fibrillation and deliver an immediate defibrillating shock have been successful in preventing sudden death in patients with previous episodes of ventricular tachycardia and ventricular fibrillation.

**Aneurysms**

An **aneurysm** (AN-ü-rizm) is a bulge in the weakened wall of a blood vessel, usually an artery. This bulge resembles a bubble in the wall of a tire, and like a bad tire, the affected artery may...
suffer a catastrophic blowout. The most dangerous aneurysms are those involving arteries of the brain, where they cause strokes, and of the aorta, where a blowout will cause fatal bleeding in a matter of seconds.

Aneurysms are most often caused by chronic high blood pressure, although any trauma or infection that weakens vessel walls can lead to an aneurysm. Some aortic aneurysms have been linked to inherited disorders, such as Marfan’s syndrome, that have weakened connective tissues in vessel walls. It is not known whether other genetic factors are involved in the development of other aneurysms.

An aneurysm usually forms gradually, as vessel walls become less elastic. When a weak point develops, the arterial pressures distort the wall, creating an aneurysm. Unfortunately, because they are often painless, they are likely to go undetected.

When aneurysms are detected by ultrasound or other scanning procedures, the risk of rupture can sometimes be estimated on the basis of their size. For example, an aortic aneurysm larger than 6 cm has a 50:50 chance of rupturing in the next 10 years. Treatment often begins with the reduction of blood pressure by means of vasodilators or beta-blockers (drugs that decrease heart rate and force of concentration). An aneurysm in an accessible area, such as the abdomen, may be surgically removed and the vessel repaired. Figure A-40 shows a large aortic aneurysm before and after surgical repair with a synthetic patch.

**Arteriosclerosis**

Arteriosclerosis (ar-té-rē-ō-skle-Rō-sis) is a thickening and toughening of arterial walls. Although this condition may not sound life-threatening, complications related to arteriosclerosis account for roughly one-half of all deaths in the United States. There are many different forms of arteriosclerosis: for example, arteriosclerosis of coronary vessels is responsible for coronary artery disease (CAD), and arteriosclerosis of arteries supplying the brain can lead to strokes.

There are two major forms of arteriosclerosis:

- **Focal calcification** is the gradual degeneration of smooth muscle in the tunica media and the subsequent deposition of calcium salts. This process typically involves arteries of the limbs. Some focal calcification occurs as part of the aging process, and it may develop in association with atherosclerosis. Rapid and severe calcification may occur as a complication of diabetes mellitus, an endocrine disorder considered in Chapter 10.

- **Atherosclerosis** (ath-er-ō-skle-Rō-sis) is associated with damage to the endothelial lining and the formation of lipid deposits in the tunica media. This is the most common form of arteriosclerosis.

Many factors may be involved in the development of atherosclerosis. One major factor is lipid levels in the blood. Atherosclerosis tends to develop
in persons whose blood contains elevated levels of plasma lipids, specifically cholesterol. Circulating cholesterol is transported to peripheral tissues in lipoproteins, protein-lipid complexes. (The various types of lipoproteins and their interrelationships are discussed in Chapter 17.) Recent evidence indicates that many forms of atherosclerosis are associated with either (1) low levels of apolipoprotein-E (ApoE), a transport protein whose lipids are associated with either (1) low levels of lipoprotein(a), a low-density lipoprotein (LDL) that is removed at a much slower rate.

When ApoE levels are low, or lipoprotein(a) levels are high, cholesterol-rich lipoproteins remain in circulation for an extended period. Circulating monocytes then begin removing them from the bloodstream. Eventually the monocytes become filled with lipid droplets. Now called foam cells, they attach themselves to the endothelial walls of blood vessels, where they release growth factors. These cytokines stimulate the divisions of smooth muscle fibers near the tunica interna, thickening the vessel wall.

Other monocytes then invade the area, migrating between the endothelial cells. As these changes occur, the monocytes, smooth muscle fibers, and endothelial cells begin phagocytizing lipids as well. The result is a plaque, a fatty mass of tissue that projects into the lumen of the vessel. At this point the plaque has a relatively simple structure, and there is evidence that the process can be reversed if appropriate dietary adjustments are made.

If the conditions persist, the endothelial cells become swollen with lipids, and gaps appear in the endothelial lining. Platelets now begin sticking to the exposed collagen fibers, and the combination of platelet adhesion and aggregation leads to the formation of a localized blood clot that will further restrict blood flow through the artery. The structure of the plaque is now relatively complex. Plaque growth may be halted, but the structural changes are usually permanent.

Typical plaques can be seen in Figure A-41. Elderly individuals, especially elderly men, are most likely to develop atherosclerotic plaques. There is evidence that estrogens may slow plaque formation; this may account for the lower incidence of coronary artery disease, myocardial infarctions (MIs), and strokes in younger women. After menopause, when estrogen production declines, the risk of CAD, MIs, and strokes in women increases markedly.

In addition to advanced age and male sex, other important risk factors include high blood cholesterol levels, high blood pressure, and cigarette smoking. Roughly 20 percent of middle-aged men have all three of these risk factors; these individuals are four times more likely to experience an MI or cardiac arrest than are other men in their age group. Although fewer women develop this condition, elderly women smokers with high blood cholesterol and high blood pressure are at much greater risk than other women. Other factors that promote development of atherosclerosis in both men and women include diabetes mellitus, obesity, and stress. There is also evidence that at least some forms of atherosclerosis may be linked to chronic infection with Chlamydia pneumoniae, a bacterium responsible for several types of respiratory infections, including some forms of pneumonia.

Potential treatments for atherosclerotic plaques, such as catheterization, balloon angioplasty and stents, and bypass surgery, were discussed on p. 106. In cases where dietary modifications do not lower circulating LDL levels sufficiently, there are drug therapies that can bring them under control. Genetic engineering techniques have recently been used to treat an inherited form of hypercholesterolemia (high blood cholesterol) linked to extensive plaque formation. (The patients were unable to absorb and recycle cholesterol in the liver.) In this experimental procedure, circulating cholesterol levels declined after copies of appropriate genes were inserted into some of the individual's liver cells.

Without question, the best approach to atherosclerosis is to try to avoid it by eliminating or reducing associated risk factors. Suggestions include: (1) reducing the amount of dietary cholesterol and saturated fats by restricting consumption of fatty meats (such as beef, lamb, and pork), egg yolks, and cream; (2) giving up smoking (or never starting to begin with); (3) checking your blood pressure and taking steps to lower it if necessary; (4) having your blood cholesterol levels checked at annual physical examinations; (5) controlling your weight; and (6) exercising regularly.

**Problems with Venous Valve Function**

Chapter 4 of the text notes that one of the consequences of aging is a loss of elasticity and resilience in connective tissues throughout the body. Blood vessels are no exception, and with age the walls of veins begin to sag. This change usually

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**FIGURE A-41. A Plaque Blocking a Peripheral Artery**

(a) A section of a coronary artery narrowed by plaque formation. (b) Sectional view of a large plaque. (LM × 18)
affects the superficial veins of the legs first, because at these locations gravity opposes blood flow. The situation is aggravated by a lack of exercise or an occupation requiring long hours standing or sitting. Because there is no muscular activity to help keep the blood moving, venous blood pools on the proximal (heart) side of each valve. As the venous walls are distorted, the valves become less effective, and gravity can then pull blood back toward the capillaries. This further impedes normal blood flow, and the veins become grossly distended. These sagging, swollen vessels are called varicose (VAR-i-kos) veins. Varicose veins are relatively harmless but unsightly; surgical procedures are sometimes used to remove or constrict the offending vessels.

Varicose veins are not limited to the extremities, and another common site involves a network of veins in the walls of the anus. Pressures within the abdominopelvic cavity rise dramatically when the abdominal muscles are tensed. Straining to force defecation can force blood into these veins, and repeated incidents leave them permanently distended. These distended veins, known as hemorrhoids (HEM-ö-roydz), can be uncomfortable and in severe cases extremely painful.

Hemorrhoids are often associated with pregnancy, due to changes in circulation and abdominal pressures. Minor cases can be treated by the topical application of drugs that promote contraction of smooth muscles within the venous walls. More severe cases may require the surgical removal or destruction of the distended veins.

**Hypertension and Hypotension**

EAP p. 395

Elevated blood pressure is considered primary hypertension, or essential hypertension, if no obvious cause can be determined. Known risk factors include a hereditary history of hypertension, sex (males are at higher risk), high plasma cholesterol, obesity, chronic stresses, and cigarette smoking. Secondary hypertension appears as the result of abnormal hormonal production outside the cardiovascular system. For example, a condition resulting in excessive production of antidiuretic hormone (ADH), renin, aldosterone, or epinephrine will probably produce hypertension, and many forms of kidney disease will lead to hypertension caused by fluid retention or excessive renin production.

Hypertension significantly increases the work load on the heart, and the left ventricle gradually enlarges. More muscle mass requires a greater oxygen demand, and when the coronary circulation cannot keep pace, symptoms of coronary ischemia appear.

Increased arterial pressures also place a physical stress on the walls of blood vessels throughout the body. This stress promotes or accelerates the development of arteriosclerosis and increases the risks of aneurysms, heart attacks, and strokes. Vessels supplying the retinas of the eyes are often affected, and hemorrhages and associated circulatory changes can produce disturbances in vision. Because these vessels are examined in a normal physical exam, retinal changes may provide the first evidence that hypertension is affecting peripheral circulation.

One of the most difficult aspects of hypertension is that there are usually no obvious symptoms. As a result, clinical problems do not appear until the condition has reached the crisis stage. There is, therefore, considerable interest in early detection and prompt treatment of hypertension.

Treatment consists of a combination of life-style changes and physiological therapies. Quitting smoking, getting regular exercise, and restricting dietary intake of salt, fats, and calories will improve peripheral circulation, prevent increases in blood volume and total body weight, and reduce plasma cholesterol levels. These strategies may be sufficient to control hypertension if it has been detected before significant cardiovascular damage has occurred. Therapies usually involve antihypertensive drugs, such as calcium channel blockers, beta-blockers, diuretics, and vasodilators, singly or in combination. Beta-blockers eliminate the effects of sympathetic stimulation on the heart, and the unopposed parasym pathetic system lowers the resting heart rate and blood pressure. Diuretics promote the loss of water and sodium ions at the kidneys, lowering blood volume, and vasodilators further reduce blood pressure. A new class of antihypertensive drugs lowers blood pressure by preventing the production of angiotensin II. These angiotensin-converting enzyme (ACE) inhibitors, such as captopril, are being used to treat chronic hypertension and congestive heart failure.

In hypotension, blood pressure declines, and peripheral systems begin to suffer from oxygen and nutrient deprivation. One clinically important form of hypotension can develop following the administration of antihypertensive drugs. Problems may appear when the individual changes position, going from lying down to sitting, or sitting to standing. Normally each time you sit or stand, blood pressure in the carotid sinus drops, for the heart must suddenly counteract gravity to push blood up to the brain. The fall in pressure triggers the carotid reflex, and blood pressure returns to normal. But if the carotid response is blunted by beta-blockers or other drugs, blood pressure at the brain may fall so low that the individual becomes weak, dizzy, disoriented, or unconscious. This condition is known as orthostatic hypotension (or-tho-STAT-ik; orthos, straight + statikos, causing to stand), or simply orthostasis (or-tho-STÄ-sis). Most readers will have experienced brief episodes of orthostasis when standing up suddenly after reclining for an extended period. The carotid reflex frequently slows with age, and older people learn to sit and stand more carefully to avoid the effects of orthostatic hypotension.
**Shock** EAP p. 404

**Shock** is an acute circulatory crisis marked by low blood pressure (hypotension) and inadequate peripheral blood flow. Severe and potentially fatal symptoms develop as vital tissues become starved for oxygen and nutrients. Common causes of shock are (1) a fall in cardiac output after hemorrhaging or other fluid losses, (2) damage to the heart, (3) external pressure on the heart, and (4) extensive peripheral vasodilation.

**Circulatory Shock** A severe loss of blood volume produces symptoms of **circulatory shock**. Symptoms of circulatory shock appear after fluid losses of about 30 percent of the total blood volume. The cause can be hemorrhaging or fluid losses to the environment, as in dehydration or after severe burns. All cases of circulatory shock share the same basic symptoms:

1. Hypotension, with systolic pressures below 90 mm Hg.
2. Pale, cool, and moist (“clammy”) skin. The skin is pale and cool because of peripheral vasoconstriction; the moisture reflects sympathetic activation of the sweat glands.
3. Frequent confusion and disorientation, due to a fall in blood pressure at the brain.
4. Rapid, weak pulse.
5. No urination, because the reduced blood flow to the kidneys slows or stops urine production.
6. A drop in blood pH (acidosis), due to lactic acid generation in oxygen-deprived tissues.

Circulatory shock is often divided into compensated, progressive, and irreversible stages.

**The Compensated Stage (Stage I)** During the **compensated stage** homeostatic adjustments can cope with the situation; the short-term and long-term responses detailed in Figure A-42 are part of the compensation process. During the period of compensation, peripheral blood flow is reduced but remains within tolerable limits.

**The Progressive Stage (Stage II)** When blood volume declines by more than 35 percent, the individual enters the **progressive stage** of circulatory shock. Homeostatic mechanisms are now unable to cope with the situation. Despite sustained vasoconstriction and the mobilization of the venous reserve, blood pressure remains abnormally low, venous return is reduced, and cardiac output is inadequate. A vicious cycle begins when the low cardiac output causes myocardial damage. This damage leads to a further reduction in cardiac output and subsequent reductions in blood pressure and venous return. The sequence is diagrammed in Figure A-42a.

When the mean arterial blood pressure falls to about 50 mm Hg, carotid sinus baroreceptors trigger a massive activation of the vasomotor centers. In essence, the goal now is to preserve the circulation to the brain at any cost. Blood flow to cerebral vessels is not affected, and the blood pressure in the carotid arteries remains relatively high (70 mm Hg). But in other organs sympathetic output causes a sustained and maximal vasoconstriction. This reflex, called the **central ischemic response**, reduces peripheral circulation to an absolute minimum.

The central ischemic response is a last-ditch effort that maintains adequate blood flow to the brain at the expense of other tissues. Unless prompt treatment is provided, the condition will soon prove fatal. Treatment must concentrate on (1) preventing further fluid losses and (2) giving a transfusion of whole blood, plasma expanders, or blood substitutes.

**The Irreversible Stage (Stage III)** In the absence of treatment, progressive shock will soon turn into irreversible shock (Figure A-42b). At this point, conditions in the heart, liver, kidneys, and CNS are rapidly deteriorating to the point that death will occur, even with medical treatment.

Irreversible shock begins when conditions in the tissues become so abnormal that the arteriolar smooth muscles and precapillary sphincters become unable to contract, despite the commands of the vasomotor center. The result is a widespread peripheral vasodilation and an immediate and fatal decline in blood pressure. This event is called **circulatory collapse**. The blood pressure in many tissues then falls so low that the capillaries collapse like deflating balloons. Blood flow through these capillary beds then stops completely, and the cells in the affected tissues die. The dying cells release more abnormal chemicals, and the effect quickly spreads throughout the body.

**Other Types of Shock** EAP p. 404

Although the text focuses on circulatory shock caused by low blood volume, shock can develop when the blood volume is normal. **Cardiogenic** (kar-de-o-JEN-ik) shock occurs when the heart becomes unable to maintain a normal cardiac output. The most common cause is failure of the left ventricle as a result of a myocardial infarction. Between 5 and 10 percent of patients surviving a heart attack must be treated for cardiogenic shock. The use of thrombolytic drugs, such as t-PA and streptokinase, can be very effective in restoring coronary circulation and ventricular function, thereby relieving the peripheral symptoms. Cardiogenic shock may also be the result of arrhythmias, valvular heart disease, advanced coronary artery disease, cardiomyopathy, or ventricular arrhythmias (see p. 109).

In **obstructive shock**, ventricular output is reduced because tissues or fluids are restricting the expansion and contraction of the heart. For example, fluid buildup in the pericardial cavity
cardiac tamponade) due to infection or trauma can compress the heart and limit ventricular filling.

**Distributive shock** results from a widespread, uncontrolled vasodilation. This produces a dramatic fall in blood pressure that leads to a reduction in blood flow and the onset of shock. Three important examples are neurogenic shock, septic shock, and anaphylactic shock.

**Neurogenic** (noo-rō-JEN-ik) shock can be caused by general or spinal anesthesia and by trauma or inflammation of the brain stem. The underlying problem is damage to the vasomotor center or to the sympathetic tracts or nerves, leading to a loss of vasomotor tone.

**Septic shock** results from the massive release of endotoxins, poisons derived from the cell walls of bacteria during a systemic infection. These compounds cause a vasodilation of precapillary sphincters throughout the body, resulting in a drop in peripheral resistance and a decline in blood pressure. Symptoms of septic shock generally resemble those of other types of shock, but the skin is flushed and the individual may have a high fever. For this reason septic shock is also known as “warm shock.” One interesting example of septic shock, called **toxic shock syndrome (TSS)**, results from an infection by the bacterium Staphylococcus aureus. This disease was unrecognized before 1978, when it appeared in a group of children. Since that time there have been more cases in the United States, most (95 percent) affecting women. Although other sources of infection are possible, infection most often appears to occur during menstruation, and the chances of infection are increased with the use of superabsorbent tampons. (The brands involved have been taken off the market, and the incidence has declined steadily since 1980.)
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tricular muscle (see the discussion of myocardial infarctions on p. 107) or high arterial pressures (hypertension, p. 112). In effect, the left ventricle can no longer keep pace with the right ventricle, and blood backs up into the pulmonary circuit. This venous congestion is responsible for the term **congestive heart failure**. The right ventricle now needs to work harder, elevating pulmonary arterial pressures and forcing blood through the lungs and into the weakened left ventricle.

At the capillaries of the lungs, arterial and venous pressures are now elevated. This elevated pressure pushes additional fluid out of the capillaries and into the interstitial fluids. The fluid buildup and compression of the airways reduces the effectiveness of gas exchange, leading to shortness of breath, often the first obvious sign of congestive failure. This fluid buildup begins at a postcapillary pressure of around 25 mm Hg. At a capillary pressure of around 30 mm Hg, fluid not only enters the tissues of the lungs but crosses the alveolar walls and begins filling the airspaces. This condition is called **pulmonary edema**.

Over time, the less muscular right ventricle may become unable to generate enough pressure to force blood through the pulmonary circuit. Venous congestion now occurs in the systemic circuit, and cardiac output declines further. When the reduction in systemic pressures lowers blood flow to the kidneys, renin and erythropoietin are released. This in turn elevates blood volume, due to increased salt and water retention at the kidneys, and accelerated red blood cell production. This rise in blood volume actually complicates the situation, as it tends to increase venous congestion and cause widespread edema.

The increased volume of blood in the venous system leads to a distension of the veins, making superficial veins more prominent. When the heart contracts, the rise in pressure at the right atrium produces a pressure pulse in the large veins. This venous pulse can be seen and palpated most easily over the right external jugular vein.

Treatment of congestive heart failure often includes:

- **Restriction of salt intake**. The expression “water follows salt” applies here, because when sodium and chloride ions are absorbed across the lining of the digestive tract, water is also absorbed by osmosis.
- **Administration of drugs to promote fluid loss**. These drugs, called **diuretics** (di-ú-RET-iks; diouretikos, promoting urine), increase salt and water losses at the kidneys.
- **Extended bed rest, to enhance venous return to the heart, coupled with physical therapy to maintain good venous circulation**.
- **Administration of drugs that enhance cardiac output**. These drugs may target the heart, the peripheral circulation, or some combination of the two. When the heart has been weakened, drugs related to digitals, an extract from the

Extensive peripheral vasodilation also occurs in **anaphylactic** (an-a-fi-LAK-tik) **shock**, a dangerous allergic reaction involving circulating histamine and prostaglandins.

**Heart Failure** EAP p. 404

A condition of heart failure exists when the cardiac output is insufficient to meet the circulatory demand. The initial symptoms of heart failure vary depending on whether the problem is restricted to the left ventricle or the right ventricle, or involves both. However, over time these differences are eliminated; for example, the major cause of right ventricular failure is left ventricular failure. Figure A-43 provides a simplified flow chart for heart failure and indicates potential therapies.

Suppose that the left ventricle cannot maintain normal cardiac output, due to damage to the ven-
leaves of the foxglove plant, are often selected. Digitoxin, digoxin, and ouabain are examples. These compounds increase the force of cardiac muscle cell contractions. When high blood pressure is a factor, some type of vasodilator is given to lower peripheral resistance.

- Administration of drugs that reduce peripheral vascular resistance, such as hydralazine or ACE (angiotensin-converting enzyme) inhibitors. The drop in peripheral resistance reduces the work load of the left ventricle and improves cardiac output.

**Treatment of Cerebrovascular Disease**

Symptoms of cerebrovascular disease usually appear when atherosclerosis reduces the circulatory supply to the brain. If the circulation to a portion of the brain is completely shut off, a cerebrovascular accident (CVA), or stroke, occurs. The most common causes of strokes include ischemia from either cerebral thrombosis (clot formation at a plaque) or cerebral embolism (drifting blood clots, fatty masses, or air bubbles), and cerebral hemorrhages (rupture of a blood vessel, often following formation of an aneurysm). The observed symptoms and their severity vary depending on the vessel involved and the location of the blockage.

If the circulatory blockage disappears in a matter of minutes, the effects are temporary, and the condition is called a transient ischemic attack, or TIA. TIAs often indicate that cerebrovascular disease exists, and preventive measures can be taken to forestall more serious incidents. For example, taking aspirin each day slows blood-clot formation in patients experiencing TIAs, and this reduces the risks of cerebral thrombosis and cerebral embolism.
If the blockage persists for a longer period, neurons die and the area degenerates. Stroke symptoms are initially exaggerated by the swelling and distortion of the injured neural tissues; if the individual survives, there is often a gradual improvement in brain function. The management and treatment of strokes is difficult. Early recognition of symptoms with rapid CT scan to distinguish between hemorrhagic or ischemic stroke is vital. Surgical removal of the offending clot or blood mass may be attempted, but the results are variable. Recent progress in the emergency treatment of cerebral thromboses and cerebral embolisms has involved the administration of a clot-dissolving enzyme such as tissue plasminogen activator (t-PA; now sold as Alteplase®). Best results are obtained if administered within 3 hours of symptom onset. Subsequent treatment involves anticoagulant therapy, usually with heparin (for one to two weeks) followed by coumadin (for up to a year) to prevent further clot formation. None of these treatments is as successful as preventive surgery, where plaques are removed before a stroke. It should also be noted that the very best solution is to prevent or restrict plaque formation by controlling the risk factors involved. With better public health knowledge and education about risk factors for stroke and improved treatments for hypertension and atherosclerosis, death rates from strokes have declined as they have for coronary heart disease. From 1950 to 1996, the rate dropped 70 percent, from 88 deaths per 100,000 to 26 per 100,000 in 1996.

**Congenital Circulatory Problems**

Minor individual variations in the circulatory network are common. For example, very few individuals have identical patterns of venous distribution. Congenital circulatory problems serious enough to represent a threat to homeostasis are relatively rare. They usually reflect abnormal formation of the heart or problems with the interconnections between the heart and the great vessels. Examples of congenital circulatory defects are illustrated in Figure A-44. All of these conditions can be surgically corrected, although multiple surgeries may be required.

The incomplete closure of the foramen ovale or ductus arteriosus (Figure A-44a) results in the bypassing of the lungs and the recirculation of blood into the pulmonary circuit. Because normal blood oxygenation does not occur, the circulating blood has a deep red color. The skin then develops the blue tones typical of cyanosis, a condition noted in Chapter 5 of the text, and the infant is known as a "blue baby."

Ventricular septal defects (Figure A-44b) are the most common congenital heart problems, affecting 0.12 percent of newborn infants. The opening
between the left and right ventricles has the reverse effect of a connection between the atria: When it beats, the more powerful left ventricle ejects blood into the right ventricle and pulmonary circuit. Pulmonary hypertension, pulmonary edema, and cardiac enlargement are the results.

The tetralogy of Fallot (fa-LÔ) (Figure A-44c) is a complex group of heart and circulatory defects that affect 0.10 percent of newborn infants. In this condition (1) the pulmonary trunk is abnormally narrow, (2) the interventricular septum is incomplete, (3) the aorta originates where the interventricular septum normally ends, and (4) the right ventricle is enlarged.

In the transposition of great vessels (Figure A-44d) the aorta is connected to the right ventricle, and the pulmonary artery is connected to the left ventricle. This malformation affects 0.05 percent of newborn infants.

In an atrioventricular septal defect (Figure A-44e), the atria and ventricles are incompletely separated. The results are quite variable, depending on the extent of the defect and the effects on the atrioventricular valves. This type of defect most often affects infants with Down syndrome, a disorder caused by the presence of an extra copy of chromosome 21.

CRITICAL-THINKING QUESTIONS

6-1. Matt has a tumor that causes him to release excess amounts of ADH. Possible symptoms arising from this elevated hormone would be:
   a. decreased blood volume
   b. increased blood pressure
   c. peripheral vasoconstriction
   d. polycythemia
   e. all of the above

6-2. Tammy visits her physician for a routine physical examination. The doctor notes she is pale and complains of being tired and weak. The physician orders blood tests, and the results of the blood work follow:
   RBC count: 3.5 million/mm³
   Hematocrit: 32
   Hemoglobin: 10 g/dl
   MCV: 70
   MCH: 20 pg
   MCHC: 28
   WBC count: 8000/mm³
   Platelet count: 200,000/mm³
   Reticulocyte count: 1% of total erythrocytes

   These results would indicate
   a. hemorrhagic anemia
   b. aplastic anemia
   c. iron deficiency anemia
   d. pernicious anemia
   e. macrocytic anemia

6-3. Cathy has just given birth to a little girl. When the nurses take the infant back to the nursery and try to feed her, she becomes cyanotic. The episode passes, but when the infant is bathed, she becomes cyanotic again. Blood gas levels are taken, and they show the arterial blood is only 60% saturated. Physical examination indicates that there are no structural deformities involving the respiratory or digestive system. Echocardiography shows a heart defect. What might be the specific cause of the problem?