The heart is a fist-sized muscular pump that has a remarkable capacity to work unceasingly for the 80 or more years of a human lifetime. As demand requires, it can increase its output manyfold, in part because the coronary circulation can augment its blood flow to more than 10 times normal. The ventricles also respond to short-term increases in workload by dilating, in accordance with Starling law of the heart. When an increased workload is imposed for a longer period (e.g., in cases of essential hypertension), the left ventricle hypertrophies, an adaptation that increases its work capacity. However, when this compensatory mechanism reaches its limits, the heart no longer provides an adequate supply of blood to peripheral tissues, and the result is congestive heart failure. Damage to the myocardium, caused mostly by ischemic heart disease, also limits the capacity of the left ventricle to pump blood and similarly results in heart failure.
CORONARY ARTERIES SUPPLY BLOOD TO THE HEART

The right and left main coronary arteries originate in, or immediately above, the sinuses of Valsalva of the aortic valve. The left main coronary artery bifurcates within 1 cm of its origin into the left anterior descending (LAD) and left circumflex coronary arteries. The left circumflex coronary artery rests in the left atrioventricular groove and supplies the lateral wall of the left ventricle (Fig. 11-1). The LAD coronary artery lies in the anterior interventricular groove.

**FIGURE 11-1.** Position of left ventricular infarcts resulting from occlusion of each of the three main coronary arteries. **A.** Posterolateral infarct, which follows occlusion of the left circumflex artery and is present in the posterolateral wall. **B.** Anterior infarct, which follows occlusion of the anterior descending branch (left anterior descending, LAD) of the left coronary artery. The infarct is located in the anterior wall and adjacent two thirds of the septum. It involves the entire circumference of the wall near the apex. **C.** A posterior (“inferior” or “diaphragmatic”) infarct results from occlusion of the right coronary artery and involves the posterior wall, including the posterior third of the interventricular septum and the posterior papillary muscle in the basal half of the ventricle.
and provides blood to the (1) anterior left ventricle, (2) adjacent anterior right ventricle, and (3) anterior half to two thirds of the interventricular septum. In the apical region, the LAD artery supplies the ventricles circumferentially (see Fig. 11-1).

The right coronary artery travels along the right atrioventricular groove and nourishes the bulk of the right ventricle and posteroseptal left ventricle (see Fig. 11-1), including the posterior third to half of the interventricular septum at the base of the heart (also referred to as the “inferior” or “diaphragmatic” wall). From these distributions, one can predict the location of infarcts that result from occlusion of any of the three major epicardial coronary arteries. The epicardial coronary arteries are usually arranged in a so-called right coronary-dominant distribution. The pattern of dominance is determined by the coronary artery that contributes most of the blood to the posterior descending coronary artery. Ten percent of human hearts display a left-dominant pattern with the left circumflex coronary artery supplying the posterior descending coronary artery.

Blood flow in the myocardium occurs inward from epicardium to endocardium. Thus, as a general rule, the endocardium is most vulnerable to ischemia when flow through a major epicardial coronary artery is compromised. The epicardial portion of each coronary artery fills and expands during systole and empties and narrows during diastole. The intramyocardial arteries have the opposite action and are narrowed by the systolic muscular pressure. As a result, blood flow within myocardium, especially in the subendocardial ventricular regions, is decreased or absent during systole.

**MYOCARDIAL HYPERTROPHY AND HEART FAILURE**

During systole, ventricles contract vigorously and eject about 60% of the blood present in the ventricle at the end of diastole (ejection fraction). When a heart is injured, the clinical consequences are similar, regardless of the cause of cardiac dysfunction. If the initial impairment is severe, cardiac output is not maintained despite compensatory changes, and the result is acute, life-threatening, cardiogenic shock. When the functional impairment is less, compensatory mechanisms (see below) maintain cardiac output by increasing diastolic ventricular filling pressure and end-diastolic volume. This situation results in the characteristic signs and symptoms of congestive heart failure. Because of the heart’s capacity to compensate, congestive heart failure is often tolerated for years. The heart’s ability to adapt to injury is based on the same mechanisms that allow cardiac output to increase in response to stress. The fundamental compensatory mechanism is the Frank-Starling mechanism: the cardiac stroke volume is a function of diastolic fiber length and, within certain limits, a normal heart will pump whatever volume is brought to it by the venous circulation. Stroke volume, a measure of ventricular function, is enhanced by increasing ventricular end-diastolic volume secondary to an increase in atrial filling pressure. The most prominent feature of heart failure is the abnormally high atrial filling pressure relative to stroke volume. However, the absolute values of stroke volume and cardiac output are generally well maintained in the failing heart.

**PATHOGENESIS:** Myocardial hypertrophy is an adaptive response that augments myocyte contractile strength. It develops as a compensatory response to hemodynamic overload, which occurs in association with chronic hypertension or valvular stenosis (pressure overload), myocardial injury, valvular insufficiency (volume overload), and other stresses that increase heart workload. A distinction must be made between physiologic hypertrophy of a heart that develops in highly trained athletes and pathologic hypertrophy that occurs in response to injury or overload. Hypertrophic responses feature enlargement of cardiac myocytes and accumulation of sarcomeric proteins without an increase in the number of cardiac myocytes. Hypertrophy initially reflects a compensatory and potentially reversible mechanism, but faced with persistent stress, the myocardium becomes irreversibly enlarged and dilated (Fig. 11-2).

Receptor-mediated myocardial events that are triggered by a stimulus promote the hypertrophic response by autocrine and paracrine mechanisms. Contractile cells respond to mechanical stimuli, such as stretching, by activating receptor-mediated signaling pathways that produce hypertrophy. Among the most important ligands that activate these pathways are (1) angiotensin II, (2) endothelin-1, and (3) various growth factors, including insulin-like growth factor-1 and transforming growth factor-β. Some of these mediators may also act on interstitial fibroblasts in the heart to promote synthesis and deposition of extracellular matrix.

The heart has traditionally been thought of as incapable of growing new myocytes to regenerate or repair damage due to a lack of cardiac stem cells. In this view, cardiac myocytes can respond to injury only by hypertrophy or death. Many controversies remain, but there is now compelling evidence that cardiac stem cells exist in adults. For example, male transplant recipients who have received female hearts exhibit fully differentiated cardiac myocytes bearing the Y chromosome, which must have been derived from the circulation. Moreover, embryonic stem cells and adult bone marrow-derived cells can experimentally repopulate areas of myocardial injury and differentiate into cardiac myocytes. In addition, resident cardiac progenitor cells have
been identified in interstitial “niches” in the heart. Thus, the failing heart is a candidate for potential stem cell therapy (see Chapter 3).

**PATHOLOGY:** Anything that increases cardiac workload for a prolonged period or produces structural damage may eventuate in myocardial failure. Ischemic heart disease is by far the most common condition responsible for cardiac failure, accounting for more than 80% of deaths from heart disease. Most of the remaining deaths are caused by nonischemic forms of heart muscle disease (cardiomyopathies) and congenital heart disease (CHD). Other than changes characteristic of specific disease entities (e.g., ischemic heart disease or cardiac amyloidosis), the morphology of the failing heart is nonspecific.

Ventricular hypertrophy is observed in virtually all conditions associated with chronic heart failure. Initially, only the left ventricle may be hypertrophied, as occurs in compensated hypertensive heart disease. But when the left ventricle fails, some right ventricular hypertrophy usually follows because of the increased workload imposed on the right ventricle by the failing left ventricle. In most cases of clinically apparent heart failure, the ventricles are conspicuously dilated. The distribution of end-organ involvement depends on whether the heart failure is predominantly left-sided or right-sided. **Left-sided heart failure** is more common, because the most frequent causes of cardiac injury (e.g., ischemic heart disease and hypertension) primarily affect the left ventricle. To compensate for left ventricular failure, left atrial and pulmonary venous pressures increase, resulting in passive pulmonary congestion. The capillaries in the alveolar septa fill with blood, and small ruptures allow erythrocytes to escape. As a result, alveoli contain many hemosiderin-laden macrophages (so-called heart failure cells). Moreover, if capillary hydrostatic pressure exceeds plasma osmotic pressure, fluid leaks from capillaries into alveoli. The resultant **pulmonary edema** may be massive, with alveoli being “drowned” in a transudate. Interstitial pulmonary fibrosis results when congestion is present over an extended period (see Chapter 10).
Right-sided heart failure commonly complicates left-sided failure, or it can develop independently secondary to intrinsic pulmonary disease or pulmonary hypertension, which create resistance to blood flow through the lungs. As a consequence, right atrial pressure and systemic venous pressure both increase, resulting in jugular venous distention, lower-extremity edema, and congestion of the liver and spleen. Hepatic congestion in heart failure is discussed in Chapter 14.

Diastolic heart failure is seen in up to one third of elderly patients with obvious heart failure. As the heart ages, the ventricles become progressively stiffer and require greater filling (diastolic) pressures. Some patients exhibit signs and symptoms of heart failure although their hearts are normal in size, do not show left ventricular hypertrophy, and have normal systolic contractile function. These patients do not easily tolerate increases in blood volume and are susceptible to developing pulmonary edema in response to a fluid challenge. Microscopically, these hearts typically exhibit interstitial fibrosis, which may contribute to the decreased compliance of ventricular myocardium.

CLINICAL FEATURES: Symptoms of left-sided failure include dyspnea on exertion, orthopnea (dyspnea when lying down), and paroxysmal nocturnal dyspnea. Dyspnea on exertion reflects the increasing pulmonary congestion that accompanies a higher end-diastolic pressure in the left atrium and ventricle. Orthopnea and paroxysmal nocturnal dyspnea result when thoracic blood volume increases, on account of reduced blood volume in the lower extremities during recumbency.

Although much of the clinical presentation of heart failure can be explained by venous congestion (backward failure), certain aspects of congestive failure involve inadequate arterial perfusion of vital organs (forward failure). Most patients with left-sided heart failure retain sodium and water (edema), due to decreased renal perfusion, decreased glomerular filtration rate, and activation of the renin–angiotensin–aldosterone system (see Chapter 7). Inadequate cerebral perfusion can lead to confusion, memory loss, and disorientation. Reduced perfusion of skeletal muscle is associated with fatigue and weakness.

CONGENITAL HEART DISEASE (CHD)

CHD is a consequence of faulty embryonic development, expressed either as misplaced structures (e.g., transposition of the great vessels) or as an arrest in the progression of a normal structure from an early stage to one that is more advanced (e.g., atrial septal defect).

Significant CHD occurs in almost 1% of all live births. This does not include certain common defects that are not functionally important, such as an anatomically patent foramen ovale that is functionally closed by the left atrial flap that covers it. In this circumstance, the foramen ovale remains closed as long as left atrial pressure exceeds that in the right atrium. A bicuspid aortic valve is also common and is usually asymptomatic until adulthood, when it is often associated calcific aortic stenosis. Estimates of the incidence of particular cardiovascular anomalies vary, depending on many factors. A range derived from several sources is shown in Table 11-1.

PATHOGENESIS: The causes of CHD are usually not ascertained. Most congenital heart defects reflect both multifactorial genetic and environmental influences. As in other diseases with multifactorial inheritance (see Chapter 6), the risk of recurrence is increased among siblings of an affected child. Moreover, an infant born to a mother with CHD also has an increased risk of cardiac defects.

Single-gene syndromes are rare causes of CHD. Mutations in Cnx/MKx2-5 in humans have been associated with a spectrum of congenital cardiac malformations. Chromosomal abnormalities associated with an increased incidence of congenital heart anomalies include Down syndrome (trisomy 21), other trisomies, Turner syndrome, and DiGeorge syndrome. Together, these account for no more than 5% of all cases of CHD. The best evidence for intrauterine influence in the occurrence of congenital cardiac defects relates to maternal rubella infection during the first trimester, especially during the first 4 weeks of gestation. Maternal use of certain drugs, including alcohol, phenytoin, amphetamines, lithium, estrogenic steroids and, historically, thalidomide have been associated with an increased risk of CHD, as is maternal diabetes. A contemporary classification divides the cases into the groups shown in Table 11-2 and is based on the pattern of blood shunting.
The fetal heart consists of a single chamber until the fifth week of gestation, after which it is divided by the development of interatrial and interventricular septa and by the formation of atrioventricular valves from endocardial cushions. A muscular interventricular septum grows upward from the apex toward the base of the heart (Fig. 11-3). It is joined by the down-growing membranous septum, separating right and left ventricles. The most common interventricular septal defect is related to failure of the membranous portion of the septum to form in whole or in part.

### Pathology:
Ventricular septal defects occur as (1) a small hole in the membranous septum, (2) a large defect involving more than the membranous region (perimembranous defects), (3) defects in the muscular portion, which are more common anteriorly but can occur anywhere in the muscular septum, or (4) complete absence of the muscular septum (leaving a single ventricle).

### Clinical Features:
A small septal defect may have little functional significance and may actually close spontaneously as the child matures. Closure is accomplished by either hypertrophy of adjacent muscle or adherence of tricuspid valve leaflets to the margins of the defect. In infants with large septal defects, higher left ventricular pressure initially creates a left-to-right shunt. Left ventricular dilation and congestive heart failure are common complications of such shunts. If a defect is small enough to permit prolonged survival, augmented pulmonary blood flow caused by shunting of blood into the right ventricle eventually leads to thickening of pulmonary arteries and increased pulmonary vascular resistance. This increased vascular resistance may be so great that the direction of the shunt is reversed and goes from right to left (Eisenmenger syndrome). A patient with this condition displays late onset of cyanosis (i.e., tardive cyanosis), right ventricular hypertrophy, and right-sided heart failure. Additional complications of ventricular septal defects include (1) infective endocarditis at the site of the defect, (2) paradoxical emboli (moving right to left through a patent foramen ovale), and (3) prolapse of an aortic valve cusp (resulting aortic valve insufficiency). Large ventricular septal defects are repaired surgically, usually in infancy.

### Atrial Septal Defects
Atrial septal defects range in severity from clinically insignificant and asymptomatic anomalies to chronic, life-threatening conditions.

#### Early Left-to-Right Shunt Reflects Higher Pressure on the Left Side of the Heart

#### Ventricular Septal Defect
Ventricular septal defects are the most common congenital heart lesions (see Table 11-1). They occur as isolated defects or in combination with other malformations.

### Pathogenesis:
The embryologic development of the atrial septum occurs in a sequence that permits the continued passage of oxygenated placental blood from the right to the left atrium through the patent foramen until birth. Beginning at the fifth week of intrauterine life, the septum primum extends downward from the roof of the atrium to join with the endocardial cushions, thereby closing the incomplete segment, or “ostium primum” (see Fig. 11-3). Before this closure is complete, the midportion of the septum primum develops a defect, or “ostium secundum,” so that right-to-left flow continues. During the sixth week, a second septum (septum secundum) develops to the right of the septum primum, passing from the roof of the atrium toward the endocardial cushions. This process leaves a patent foramen at about the midpoint of the septum, known as the foramen ovale. The defect persists after birth until it is sealed off by fusion of the septum primum and septum secundum, after which it is termed the fossa ovalis.

### Pathology:
The atrial septum may be defective at a number of sites (see Fig. 11-3).

- **Patent foramen ovale**: Tissue derived from the septum primum situated on the left side of the foramen ovale
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Pathogenesis of ventricular and atrial septal defects. A. The common atrial chamber is being separated into the right and left atria (RA and LA) by the septum primum. Because the septum primum has not yet joined the endocardial cushions, there is an open ostium primum. The ventricular cavity is being divided by a muscular interventricular septum into right and left chambers (right and left ventricles, RV and LV). SVC, superior vena cava; IVC, inferior vena cava. B. The septum primum has joined the endocardial cushions but at the same time, has developed an opening in its midportion (the ostium secundum). This opening is partly overlaid by the septum secundum, which has grown down to cover, in part, the foramen ovale. Simultaneously, the membranous septum joins the muscular interventricular septum to the base of the heart, completely separating the ventricles. C. The sinus venosus type of atrial septal defect is located in the most cephalad region and is adjacent to the inflow of the right pulmonary veins, which thus tend to open into the RA. D. The ostium primum defect occurs just above the atrioventricular (AV) valve ring, sometimes in the presence of an intact valve ring. It may also, in conjunction with a defect of the valve ring and ventricular septum, form an AV canal, as shown in E. This common opening allows free communication between the atria and the ventricles.
functions as a flap valve that normally fuses with the margins of the foramen ovale, thereby sealing the opening. An incomplete seal of the foramen ovale is found in 25% of healthy adults and is not usually functional. If circumstances increase right atrial pressure, as can occur with recurrent pulmonary thromboemboli, a right-to-left shunt will be produced, and thromboemboli from the right-sided circulation will pass directly into the systemic circulation. These paradoxical emboli can produce infarcts in many parts of the arterial circulation, most commonly in the brain, heart, spleen, intestines, kidneys, and lower extremities.

- **Atrial septal defect, ostium secundum type:** This is by far the most common atrial septal defect, accounting for 90% of all cases. It is a true deficiency of the atrial septum and should not be confused with a patent foramen ovale. An ostium secundum defect occurs in the middle portion of the septum and varies from a trivial opening to a large defect of the entire fossa ovalis region. A small defect is usually not functional, but a larger one may allow shunting of sufficient blood from left to right to cause dilation and hypertrophy of the right atrium and ventricle. In this setting, the diameter of the pulmonary artery may exceed that of the aorta.

  - **Lutembacher syndrome,** a variant of the ostium secundum type of atrial septal defect, is the combination of either congenital or rheumatic mitral stenosis and an ostium secundum atrial septal defect.

- **Sinus venosus defect:** This anomaly occurs in the upper portion of the atrial septum, above the fossa ovalis, near the entry of the superior vena cava. It is usually accompanied by drainage of the right pulmonary veins into the right atrium or superior vena cava. This defect represents 5% of atrial septal defects.

- **Atrial septal defect, ostium primum type:** This condition involves the region adjacent to the endocardial cushion and comprises 7% of all atrial septal defects. There are usually clefts in the anterior leaflet of the mitral valve and the septal leaflet of the tricuspid valve, which may be accompanied by an associated defect in the adjacent interventricular septum.

- **Persistent common atrioventricular canal:** This anomaly represents fully developed combined atrial and ventricular septal defects. Although ordinarily uncommon, this defect is frequently encountered in patients with Down syndrome. Incomplete defects are also observed.

**CLINICAL FEATURES:** Young children with atrial septal defects are ordinarily asymptomatic, although they may complain of easy fatigability and dyspnea on exertion. Later in life, usually in adulthood, changes in the pulmonary vasculature may reverse the flow of blood through the defect and create a right-to-left shunt. In such cases, cyanosis and clubbing of the fingers ensue. Complications of atrial septal defects include atrial arrhythmias, pulmonary hypertension, right ventricular hypertrophy, heart failure, paradoxical emboli, and bacterial endocarditis. Symptomatic cases are treated surgically or with closure devices, which can be delivered and placed percutaneously.

### Patent Ductus Arteriosus (PDA)

The ductus arteriosus in the fetus connects the descending aortic arch with the pulmonary artery and conveys most of the pulmonary outflow into the aorta. After birth, the ductus constricts in response to the increased arterial oxygen content and becomes occluded by fibrosis (ligamentum arteriosum).

**PATHOGENESIS:** Persistent PDA is one of the most common congenital cardiac defects and is seen frequently in infants whose mothers were infected with the rubella virus early in pregnancy. In full-term infants with PDA, the ductus has an abnormal endothelium and media and only rarely closes spontaneously.

**CLINICAL FEATURES:** The luminal diameter of a PDA varies greatly. A small shunt has little effect on the heart, whereas a large shunt leads to considerable diversion of blood from the aorta to the low-pressure pulmonary artery. In severe cases, left ventricular hypertrophy and heart failure ensue because of increased demand for cardiac output. The increased volume and pressure of blood in the pulmonary circulation eventually produce pulmonary hypertension and its cardiac complications. Infective endarteritis is a frequent complication of untreated PDA.

PDA can be corrected surgically or by cardiac catheterization. It can be caused to contract and then close by the instillation of prostaglandin synthesis inhibitors (e.g., indomethacin).

### Truncus Arteriosus

Persistent truncus arteriosus refers to a common trunk for the origin of the aorta, pulmonary arteries, and coronary arteries. It results from absent or incomplete partitioning of the truncus arteriosus by the spiral septum. Truncus arteriosus always overrides a ventricular septal defect and receives blood from both ventricles. Several structural variants have been described. The most common (type 1) consists of a single trunk that gives rise to a common pulmonary artery and ascending aorta.

**CLINICAL FEATURES:** Most infants with truncus arteriosus have torrential pulmonary blood flow, causing heart failure, recurrent respiratory
tract infections, and often, early death. Pulmonary vascular disease develops in children with prolonged survival, in which case cyanosis, polycythemia, and clubbing of the fingers appear. Open-heart surgery prior to the development of significant pulmonary vascular changes is an effective treatment.

**Tetralogy of Fallot (Dominant Right-to-Left Shunt) Is the Most Common Cyanotic CHD**

Tetralogy of Fallot represents 10% of all cases of CHD and is the most common cyanotic heart disease in older children and adults.

**PATHOLOGY:** The four anatomical changes that define the tetralogy of Fallot are (Fig. 11-4):

- Pulmonary stenosis
- Ventricular septal defect
- Dextroposition of the aorta so that it overrides the ventricular septal defect
- Right ventricular hypertrophy

The heart is hypertrophied so as to give it a boot shape. Almost half of patients with tetralogy of Fallot have other cardiac anomalies, including ostium secundum atrial septal defects, PDA, left superior vena cava, and endocardial cushion defects. The aortic arch is on the right side in about 25% of cases of tetralogy of Fallot. Patency of the ductus arteriosus is actually protective, because it provides a source of blood to the otherwise deprived pulmonary vascular bed.

**CLINICAL FEATURES:** In the face of severe pulmonary stenosis, right ventricular blood is shunted through the ventricular septal defect into the aorta, resulting in arterial desaturation and cyanosis. Surgical correction is typically performed in the first 2 years of life. In children who are unrepaired, dyspnea on exertion is particularly noticeable, and the affected child often assumes a squatting position to relieve the shortness of breath. Physical development is characteristically retarded. Cerebral thromboses may complicate the disease due to marked polycythemia. Patients are also at risk for bacterial endocarditis and brain abscesses. Without surgical intervention, tetralogy of Fallot has a dismal prognosis. However, total correction is now possible with open-heart surgery, which carries a mortality rate that is less than 10%. After successful surgery, patients are asymptomatic and have an excellent long-term prognosis.

**CHDs Without Shunts Involve Various Cardiovascular Sites**

**Transposition of the Great Arteries (TGA)**

In transposition of the great arteries (TGA), the aorta arises from the right ventricle and the pulmonary artery from the left ventricle. In TGA, the aorta is anterior to the pulmonary artery and to its right (“D” or dextrotransposition) all the way from its origin. The condition shows a male predominance and is more common in offspring of mothers with diabetes. TGA is responsible for more than half of deaths in infants with cyanotic heart disease who are younger than 1 year of age.

**PATHOGENESIS:** Because the venous blood from the right side of the heart flows to the aorta, and the oxygenated blood from the lungs returns to the pulmonary artery, there are, in effect, two independent and parallel blood circuits for the systemic and pulmonary circulations (Fig. 11-5). Survival is possible only if there is a communication between the circuits. Virtually all infants with TGA have an atrial septal defect. One half of patients exhibit a ventricular septal defect and two thirds have a PDA.

**CLINICAL FEATURES:** Before cardiac surgery, the outlook for infants with TGA was hopeless; 90% died in their first year. It is now possible to correct the malformation within the first 2 weeks of life using an arterial-switch operation, with overall survival rate of 90%. Patients in whom corrected TGA is the only malfor-
information are clinically entirely normal. Unfortunately, many cases are complicated by other cardiac anomalies, which require their own specific interventions.

**Coarctation of the Aorta**

Coarctation of the aorta is a local constriction that almost always occurs immediately below the origin of the left subclavian artery at the site of the ductus arteriosus (Fig. 11-6). Rare coarctations can occur at any point from the aortic arch to the abdominal bifurcation. The condition is two to five times more frequent in males than females and is associated with a bicuspid aortic valve in two thirds of cases. Mitral valve malformations, ventricular septal defects, and subaortic stenosis may also accompany coarctation of the aorta. There is a particular association of coarctation with Turner syndrome, and berry aneurysms in the brain are also more common.

**CLINICAL FEATURES:** The clinical hallmark of coarctation of the aorta is a discrepancy in blood pressure between the upper and lower extremities. The pressure gradient produced by the coarctation causes hypertension proximal to the narrowed segment and, occasionally, dilation of that portion of the aorta. Hypertension in the upper part of the body results in left ventricular hypertrophy and may produce dizziness, headaches, and nosebleeds. Hypotension below the coarctation leads to weakness, pallor, and coldness of lower extremities. Radiologic examination of the chest shows **notching of the inner surfaces of the ribs**, produced by increased pressure in markedly dilated intercostal arteries.

Most patients with coarctation of the aorta die by age 40 unless they are treated. Complications include (1) heart failure, (2) rupture of a dissecting aneurysm (secondary to cystic medial necrosis of the aorta), (3) infective endarteritis at the point of narrowing or at the site of jet stream impingement on the wall immediately distal to the coarctation, (4) cerebral hemorrhage, and (5) stenosis or infective endocarditis of a bicuspid aortic valve. Coarctation of the aorta is successfully treated by surgical excision of the narrowed segment, preferably between 1 and 2 years of age for asymptomatic patients.

**Congenital Aortic Stenosis**

Three types of congenital aortic stenosis are recognized: valvular, subvalvular, and supravalvular.

**VALVULAR AORTIC STENOSIS:** The most common congenital aortic stenosis is a bicuspid valve, which arises through the abnormal development of the endocardial cushions. A congenitally bicuspid aortic valve is considerably more frequent (4:1) in males than in females and is associated with other cardiac anomalies (e.g., coarctation of the aorta) in 20% of cases. A bicuspid valve typically features fusion of two of the three semilunar cusps (the right coronary cusp with one of the adjacent two cusps).

**CLINICAL FEATURES:** Many children with bicuspid aortic stenosis are asymptomatic. Over the years, the resulting bicuspid valve tends to become thickened and calcified, generally leading to symptoms in adulthood. More severe forms of congenital aortic stenosis involving unicommissural or valves without commissures cause symptoms in early life. Exertional dyspnea and angina pectoris may be prominent. Sudden death, principally due to ventricular arrhythmias, is a distinct threat for patients with severe obstruction. Bacterial endocarditis sometimes complicates the disease. In symptomatic cases, aortic valvulotomy has had a high degree of success, although valve replacement is occasionally indicated.

**SUBVALVULAR AORTIC STENOSIS:** This defect accounts for 10% of all cases of congenital aortic stenosis. Stenosis results from a membranous diaphragm or fibrous ring that surrounds the left ventricular outflow tract immediately below the aortic valve. It is twice as common in males as in females. In many persons with subvalvular aortic stenosis, thickening and immobility of the aortic cusps develops, with mild aortic regurgitation. Bacterial endocarditis may occur and also aggravate the regurgitation. Surgical treatment of subvalvular aortic stenosis involves excising the membrane or fibrous ridge.
SUPRAVALVULAR AORTIC STENOSIS: This type of stenosis is much less common than the other two and is often associated with defects in the elastin gene, such as are found in Williams syndrome, a congenital disease associated with a deletion of an area of chromosome 7. The syndrome is characterized by idiopathic infantile hypercalcemia, mental retardation, and multiple system disorders.

**Ebstein Malformation**

Ebstein malformation results from downward displacement of an abnormal tricuspid valve into an underdeveloped right ventricle. One or more tricuspid valve leaflets are plastered to the right ventricular wall for a variable distance below the right atrioventricular annulus.

**PATHOLOGY:** Septal and posterior tricuspid valve leaflets are usually affected. They are irregularly elongated and adherent to the right ventricular wall, so that the upper part of the right ventricular cavity (inflow region) functions separately from the distal chamber. Thus, the effective tricuspid valve orifice is displaced downward into the ventricle, thereby dividing it into two separate parts: the “atrialized” ventricle (proximal ventricle) and the functional right ventricle (distal ventricle). In two thirds of cases, conspicuous dilation of the functional ventricle hinders its ability to pump blood efficiently through the pulmonary arteries. The degree of insufficiency of the tricuspid valve depends on the severity and configuration of the defect in the leaflets.

**CLINICAL FEATURES:** Ebstein malformation leads to heart failure, massive right atrial dilation, arrhythmias with palpitations and tachycardia, and sudden death. Surgical treatment has met with variable success.

**Congenital Heart Block**

**PATHOGENESIS:** Congenital complete heart block is usually associated with other cardiac anomalies. In such cases, disruption
in the continuity of the conduction system is probably caused by the accompanying cardiac abnormality. Congenital heart block in the absence of structural heart disease has been linked to maternal connective tissue disease, especially systemic lupus erythematosus (SLE). If maternal SS-A/Ro or SS-B/La autoantibodies are transplacentally transmitted to the fetus, the incidence of congenital complete heart block approaches 100%.

**PATHOLOGY AND CLINICAL FEATURES:** The hearts of patients with congenital heart block tend to show a lack of continuity between the atrial myocardium and the atroventricular node. Alternatively, the defect may consist of a fibrous separation of the atroventricular node from the ventricular conducting tissue. Although the heart rate is abnormally slow, patients with isolated heart block often have little functional difficulty. Later in life, cardiac hypertrophy, attacks of Stokes-Adams syncope (dizziness and unexpected fainting), arrhythmias, and heart failure may develop.

**Endocardial Fibroelastosis**

Endocardial fibroelastosis (EFE) is characterized by thickening of the endocardium of the left ventricle, which may also affect the valves. The disorder is classified as primary or secondary, the latter being far more common.

**SECONDARY ENDOCARDIAL FIBROELASTOSIS:**

This disorder occurs in association with underlying cardiovascular anomalies that lead to left ventricular hypertrophy in the face of an inability to meet the increased myocardial oxygen demands. Thus, secondary EFE is a frequent complication of congenital aortic stenosis (including hypoplastic left ventricle syndrome) and coarctation of the aorta. Presumably, some type of endocardial injury is involved in its pathogenesis.

**PATHOLOGY:** On gross examination, the left ventricle endocardium displays irregular, opaque, grey-white patches, which also may be present on the cardiac valves. Microscopically, these plaques are areas of endocardial fibroelastotic thickening, frequently accompanied by degeneration of adjacent subendocardial myocardocytes. The valves may show collagenous thickening.

**PRIMARY ENDOCARDIAL FIBROELASTOSIS:** Defined as fibroelastosis in the absence of any associated lesion, this disorder is now quite rare. It afflicts infants, usually 4 to 10 months of age. Although it has occurred in siblings, no specific mode of inheritance has been established. Recent evidence links primary EFE to mumps infection, which may explain why this condition is now so rarely encountered.

**Dextrocardia**

Dextrocardia is rightward orientation of the base–apex axis of the heart. It is often associated with a mirror image of the normal left-sided location and configuration. The position of the ventricles is determined by the direction of the embryonic cardiac loop. If the loop protrudes to the right, the future right ventricle develops on the right, and the left ventricle comes to occupy its proper position. If the loop protrudes to the left, the opposite occurs.

**PATHOLOGY:** When dextrocardia occurs without abnormal positioning of the visceral organs (situs inversus), the condition is invariably associated with severe cardiovascular anomalies. These include TGA, a variety of atrial and ventricular septal defects, anomalous pulmonary venous drainage, and many others. In dextrocardia that occurs with situs inversus, the heart is functionally normal, although minor anomalies are not uncommon.

**ISCHEMIC HEART DISEASE**

Ischemic heart disease is, in most cases, a consequence of coronary artery atherosclerosis. It develops when blood flow is inadequate to meet the oxygen demands of the heart. Ischemic heart disease is responsible for at least 80% of all deaths attributable to heart disease in the United States and other industrialized nations, where it remains the leading cause of death. By contrast, atherosclerotic heart disease is far less frequent in developing countries. The principal effects of ischemic heart disease are angina pectoris, myocardial infarction, chronic congestive heart failure, and sudden death.

**ANGINA PECTORIS:** This term refers to the pain resulting from myocardial ischemia. It typically occurs in the substernal portion of the chest and may radiate to the left arm, jaw, and epigastrium. It is the most common symptom of ischemic heart disease. Coronary atherosclerosis usually becomes symptomatic only when the luminal cross-sectional area of the affected vessel is reduced.
by more than 75%. A patient with typical angina pectoris exhibits recurrent episodes of chest pain, usually brought on by increased physical activity or emotional excitement. The pain is of limited duration (1 to 15 minutes) and is relieved by reducing physical activity or by treatment with sublingual nitroglycerin (a potent vasodilator).

Although the most common cause of angina pectoris is severe coronary atherosclerosis, decreased coronary blood flow can result from other conditions, including coronary vasospasm, aortic stenosis, or aortic insufficiency. Angina pectoris is not associated with anatomic changes in the myocardium as long as the duration and severity of ischemic episodes are insufficient to cause myocardial cell necrosis.

**PRINZMETAL ANGINA (VARIANT ANGINA)** is an atypical form of angina that occurs at rest and is caused by coronary artery spasm. The responsible mechanisms are not fully understood. Whereas coronary artery spasm may contribute to the pathogenesis of an acute myocardial infarction or to the size of the infarct, it is generally not the principal cause of infarction.

**UNSTABLE ANGINA**, a variety of chest pain that has a less predictable relationship to exercise than does stable angina and may occur during rest or sleep, is associated with development of nonocclusive thrombi over atherosclerotic plaques. In some cases of unstable angina, episodes of chest pain become progressively more frequent and longer in duration over a 3- to 4-day period. Electrocardiographic changes are not characteristic of infarction, and serum levels of cardiac-specific intracellular proteins, such as MB isoform of CK (MB-Cr) or cardiac troponin T or I (evidence of myocardial necrosis), remain normal. Unstable angina is also termed preinfarction angina, accelerated angina, or “crescendo” angina. Without pharmacologic or mechanical intervention to “open up” the coronary narrowing, many patients with unstable angina progress to myocardial infarction.

**MYOCARDIAL INFARCT**: A myocardial infarct is a discrete focus of ischemic muscle necrosis in the heart. This definition excludes patchy foci of necrosis caused by drugs, toxins, or viruses. The development of an infarct is related to the duration of ischemia and the metabolic rate of the ischemic tissue. In experimental coronary artery ligation, foci of necrosis form after 20 minutes of ischemia and become more extensive as the period of ischemia lengthens.

**CHRONIC CONGESTIVE HEART FAILURE**: Contractile impairment in these patients is due to irreversible loss of myocardium from previous infarcts and hyperfusion of surviving muscle, which leads to chronic ventricular dysfunction. Many patients will develop progressive pump failure and die of multiorgan failure.

**SUDDEN DEATH**: In some patients, the first and only clinical manifestation of ischemic heart disease is sudden death occurring within 1 hour of symptom onset due to spontaneous ventricular fibrillation. **Coronary atherosclerosis underlies most of such cases.** In many cases, lethal arrhythmia is likely triggered by acute ischemia without overt myocardial infarction. However, the presence of a healed infarct or ventricular hypertrophy increases the risk that an episode of acute ischemia will initiate a life-threatening ventricular arrhythmia.

**EPIDEMIOLOGY**: The major risk factors that predispose to coronary artery disease are (1) systemic hypertension, (2) cigarette smoking, (3) diabetes mellitus, and (4) elevated blood cholesterol level. Any one of these factors significantly increases risk of myocardial infarction, but a combination of multiple factors augments risk more than sevenfold (see Chapter 8).

In 1950, the age-adjusted death rate from myocardial infarction was 226 per 100,000 cases; 50 years later, it was 150. This shift reflects many factors, including reduced smoking, lower dietary saturated fat, and new drugs that control hypertension, reduce cholesterol, and lyse coronary thrombi. Multiple studies established that elevated serum LDLs increase the risk of myocardial infarction, whereas elevated levels of high-density lipoproteins (HDLs) decrease the risk. The total cholesterol/HDL cholesterol ratio appears to be a better predictor of coronary artery disease than serum cholesterol level alone. Factors other than blood lipid profile have powerful independent effects. A person with a blood pressure of 160/95 mm Hg has twice the risk of ischemic heart disease as one whose blood pressure is 140/75 mm Hg or less. The risk of ischemic heart disease increases in proportion to the number of cigarettes smoked. Increased levels of plasma factors involved in thrombosis or the inhibition of thrombolysis, such as fibrinogen, plasminogen activator inhibitor-1, homocysteine, and decreased fibrinolytic activity, contribute to the risk of myocardial infarction. Levels of selected serum markers of inflammation such as C-reactive protein are also predictors of ischemic heart disease.

During the past several years, there has been a remarkable increase in the incidence of type II diabetes in the United States, which mirrors a similar increase in obesity (see Chapter 22). Ischemic heart disease is a consequence of both type 1 and type 2 diabetes, and the risk is two- to threefold greater than in nondiabetic individuals. Conversely, atherosclerotic cardiovascular disease (myocardial infarction, stroke, peripheral vascular disease) accounts for 80% of all deaths in patients with diabetes.

Other risk factors for ischemic heart disease include:

- **Obesity**: In a major, longitudinal study of one population (Framingham Heart Study), obesity was an independent risk factor for cardiovascular disease, with an increased risk for obese persons over those who are lean of 2 to 2.5.


**Many Conditions Limit the Supply of Blood to the Heart**

The heart is an aerobic organ, requiring oxidative phosphorylation to provide energy for contraction. The anaerobic glycolysis used by skeletal muscle under conditions of extreme physical exertion is insufficient to sustain cardiac contraction. Ischemic heart disease is caused by an imbalance between the oxygen demands of the myocardium and the supply of oxygenated blood. Any increase in cardiac workload increases the heart’s need for oxygen. Conditions that raise blood pressure or cardiac output, such as exercise or pregnancy, augment oxygen demand by the myocardium, which may lead to angina pectoris or myocardial infarction in the compromised organ. Disorders in this category include valvular disease (mitral or aortic insufficiency, aortic stenosis), infection, and conditions such as hypertension, coarctation of the aorta, and hypertrophic cardiomyopathy (HCM). The increased metabolic rate and tachycardia in patients with hyperthyroidism are also accompanied by increased oxygen demand as well as an increase in the workload of the heart. (Table 11-3).

**Atherosclerosis and Thrombosis**

The pathogenesis of atherosclerosis is detailed in Chapter 10. Here, the features of special importance to ischemic heart disease are briefly discussed. Maximal blood flow to the myocardium is not impaired until about 75% of the cross-sectional area of a coronary artery (~50% of the diameter as assessed during coronary angiography) is compromised by atherosclerosis. However, resting blood flow is not reduced until more than 90% of the lumen is occluded. In patients with long-standing angina pectoris, the extent and distribution of collateral circulation exerts an important influence on the risk of acute myocardial infarction. Although myocardial infarction often occurs during physically demanding activities, such as running or shoveling snow, many infarcts occur at rest or even during sleep. Thus, for most people, conversion of the clinically silent disease of coronary atherosclerosis to the catastrophic event of myocardial infarction involves a sudden, marked decrease in myocardial blood flow, with or without an increase in myocardial oxygen demand. It is now well established that coronary artery thrombosis is the event that usually precipitates an acute myocardial infarction. Thrombosis typically results from spontaneous rupture of an atherosclerotic plaque, usually in a region that contains numerous inflammatory cells and a thin fibrous cap. The initiating event may be hemorrhage into or beneath the plaque.
Myocardial Infarcts May Be Mainly Subendocardial or Transmural

**PATHOLOGY**

**Location of Infarcts**

There are important differences between these two types of infarction.

A *subendocardial infarct* affects the inner one third to one half of the left ventricle. It may arise within the territory of one of the major epicardial coronary arteries or it may be circumferential, involving subendocardial territories of multiple coronary arteries. Subendocardial infarction generally occurs as a consequence of hypoperfusion of the heart. It may result from atherosclerosis in a specific coronary artery or develop in disorders that limit myocardial blood flow globally, such as aortic stenosis, hemorrhagic shock, or hypoperfusion during cardiopulmonary bypass. Most subendocardial infarcts do not involve occlusive coronary thrombi. In the case of circumferential subendocardial infarction caused by global hypoperfusion of the myocardium, coronary artery stenosis need not be present. Because necrosis is limited to the inner layers of the heart, complications arising in transmural infarcts (e.g., pericarditis and ventricular rupture) are generally not seen in subendocardial infarcts.

A *transmural infarct* involves the full left ventricular wall thickness and usually follows occlusion of a coronary artery. As a result, transmural infarcts typically conform to the distribution of one of the three major coronary arteries (see Fig. 11-1).

- **Right coronary artery**: Occlusion of the proximal portion of this vessel results in an infarct of the posterior basal region of the left ventricle and the posterior third to half of the interventricular septum (“inferior” infarct).
- **LAD coronary artery**: Blockage of this artery produces an infarct of the apical, anterior, and anteroseptal walls of the left ventricle.
- **Left circumflex coronary artery**: Obstruction of this vessel is the least common cause of myocardial infarction and leads to an infarct of the lateral wall of the left ventricle.

**Macroscopic Characteristics of Myocardial Infarcts**

Total ischemia for up to 20 to 30 minutes results in reversible cyanosis and bulging during systole. On gross examination, an acute myocardial infarct is not identifiable within the first 12 hours.

- **By 24 hours**, the infarct can be recognized on the cut surface of the involved ventricle by its pallor.
- **After 3 to 5 days**, the infarcted area becomes mottled and more sharply outlined, with a central pale, yellowish, necrotic region bordered by a hyperemic zone (Fig. 11-7).
- **Within 2 to 3 weeks**, the infarcted region is depressed and soft, with a refractile, gelatinous appearance.
- **After several months**, healed infarcts are firm and contracted and have the pale-gray appearance of scar tissue (Fig. 11-8).

**Microscopic Characteristics of Myocardial Infarcts**

**THE FIRST 24 HOURS:** Electron microscopy is required to discern the earliest morphologic features of ischemic injury. After 30 to 60 minutes of ischemia, when myocyte injury has become irreversible, mitochondria are greatly swollen, with disorganized cristae and amorphous matrix densities. The nucleus shows clumping and margination of chromatin, and the sarcolemma is focally disrupted. Loss of...
sarcolemmal integrity leads to release of intracellular proteins, such as myoglobin, LDH, CK, and troponins I and T. The noncontractile ischemic myocytes are stretched with each systole and by light microscopy become “wavy fibers.” After 24 hours, myocytes are deeply eosinophilic (Fig. 11-9) and show the characteristic changes of coagulation necrosis (see Chapter 1). However, it takes several days for the myocyte nucleus to disappear totally.

TWO TO 3 DAYS: Polymorphonuclear leukocytes (PMNs) are attracted to necrotic myocytes. The PMNs accumulate at infarct borders where blood flow is maintained and reach maximal concentration after 2 to 3 days (see Fig. 11-9 and Fig. 11-10). Interstitial edema and microscopic areas of hemorrhage may also appear. Muscle cells are more clearly necrotic, nuclei disappear, and striations become less prominent. Some of the PMNs that were attracted to the area begin to undergo karyorrhexis.

FIVE TO 7 DAYS: By this time, few, if any, PMNs remain. The periphery of the infarcted region shows phagocytosis of dead muscle by macrophages. Fibroblasts begin to proliferate, and new collagen is deposited. Lymphocytes and pigment-laden macrophages are prominent. The process of replacing necrotic muscle with scar tissue is initiated at about 5 days, beginning at the periphery of the infarct and gradually extending toward the center.

ONE TO 3 WEEKS: Collagen deposition proceeds, the inflammatory infiltrate gradually recedes, and the newly sprouted capillaries are progressively obliterated.

MORE THAN 4 WEEKS: Considerable dense fibrous tissue is present. The debris is progressively removed, and the scar becomes more solid and less cellular as it matures (Fig. 11-11).

In estimating the age of a large infarct, it is more accurate to base the interpretation on the outer border where repair begins, rather than on changes in the central region. In fact, in some large infarcts, rather than being removed, dead myocytes remain indefinitely “mummified.”

**Reperfusion of Ischemic Myocardium**

Blood flow may be restored to regions of evolving infarcts either because of spontaneous thrombolysis or in response to pharmacologic or mechanical means of opening up oc-
cluded coronary arteries. When that happens, the infarct’s gross and microscopic appearances change. Reperfused infarcts are typically hemorrhagic, the result of blood flow through a damaged microvasculature. One of the most characteristic features of reperfused infarcts is contraction band necrosis. Contraction bands are thick, irregular, transverse eosinophilic bands in necrotic myocytes. By electron microscopy, these bands are small groups of hypercontracted and disorganized sarcomeres with thickened Z lines. The bands form as a result of massive infusion of Ca$^{2+}$ into the myocytes as a result of sarcolemmal damage mediated by reactive oxygen species.

**CLINICAL FEATURES:**

**Clinical Diagnosis of Acute Myocardial Infarction May Be Complicated by “Silent Disease”**

The onset of acute myocardial infarction is often sudden and associated with severe, crushing substernal, or precordial pain. These symptoms may be accompanied by sweating, nausea, vomiting, and shortness of breath. In some cases, an acute myocardial infarction is preceded by unstable angina of several days’ duration. *One fourth to one half of all nonfatal myocardial infarctions occur without any symptoms,*
and infarcts are identified only later by electrocardiographic changes or at autopsy. These “clinically silent” infarcts are particularly common among diabetic patients with autonomic dysfunction and also in cardiac transplant patients whose hearts are denervated.

Complications of Myocardial Infarction Influence the Clinical Course

Early mortality in acute myocardial infarction (within 30 days) has dropped from 30% in the 1950s to less than 5% today. Nevertheless, the clinical course after acute infarction may be dominated by functional or mechanical complications of the infarct.

ARRHYTHMIAS: Virtually all patients who have a myocardial infarct have an abnormal cardiac rhythm at some time during their illness. Arrhythmias still account for half of all deaths caused by ischemic heart disease, although the advent of coronary care units and defibrillators has greatly reduced early mortality.

LEFT VENTRICULAR FAILURE AND CARDIogenic SHOCK: The development of left ventricular failure soon after myocardial infarction is an ominous sign that generally indicates massive loss of muscle. Fortunately, cardiogenic shock occurs in less than 5% of cases, due to the development of techniques that limit the extent of infarction (thrombolytic therapy, angioplasty) or assist damaged myocardium (intra-aortic balloon pump). Cardiogenic shock tends to develop early after infarction, when 40% or more of the left ventricle has been lost; the mortality rate is as high as 90%.

EXTENSION OF THE INFARCT: Clinically recognizable extension of an acute myocardial infarct occurs in the first 1 to 2 weeks in up to 10% of patients. Such a situation is associated with a doubling of mortality.

RUPTURE OF THE FREE WALL OF THE MYOCARDIum: Myocardial rupture may occur at almost any time during the 3 weeks after acute myocardial infarction but is most common between the first and fourth days, when the infarcted wall is weakest. During this vulnerable period, the infarct is composed of soft, necrotic tissue in which the extracellular matrix has been degraded by proteases released by inflammatory cells but new matrix deposition has not yet occurred. Once scar tissue begins to form, rupture is less likely. Rupture of the free wall is a complication of transmural infarcts. The remaining viable, contractile myocardium adjacent to the infarct produces mechanical forces that can initiate and propagate tearing along the lateral border of the infarct where neutrophils accumulate. Rupture of the left ventricle’s free wall most often leads to hemopericardium and death from cardiac tamponade.

Myocardial rupture accounts for 10% of deaths after acute myocardial infarction in hospitalized patients.

OTHER FORMS OF MYOCARDIAL RUPTURE: A few patients in whom a myocardial infarct involves the interventricular septum develop septal perforation, varying in length from 1 cm or more. The magnitude of the resulting left-to-right shunt and, therefore, the prognosis varies with the size of the rupture. Rupture of a portion of a papillary muscle results in mitral regurgitation. In some cases, an entire papillary muscle is transected, in which case, massive mitral valve incompetence may be fatal.

ANEURYSMS: Left ventricular aneurysms complicate 10% to 15% of transmural myocardial infarcts. After acute transmural infarction, the affected ventricular wall tends to bulge outward during systole in one third of patients. Localized thinning and stretching of the ventricular wall in the region of a healing myocardial infarct has been termed “infarct expansion” but is actually an early aneurysm (Fig. 11-12). Such an aneurysm is composed of a thin layer of necrotic myocardium and collagenous tissue, which expands with each contraction of the heart. As the evolving aneurysm becomes more fibrotic, its tensile strength increases. However, the aneurysm continues to dilate with each beat, thereby “stealing” some of the left ventricular output and increasing the workload of the heart. Mural
Thrombi often develop within aneurysms and are a source of systemic emboli. A distinction should be made between "true" aneurysms (as above) and "false." False aneurysms result from rupture of a portion of the left ventricle that has been walled off by pericardial scar tissue. Thus, the wall of a false aneurysm is composed of pericardium and scar tissue but not left ventricular myocardium.

**MURAL THROMBOSIS AND EMBOLISM:** Half of all patients who die after myocardial infarction have mural thrombi overlying the infarct at autopsy. This occurs particularly often when the infarct involves the apex of the heart. In turn, half of these patients have some evidence of systemic embolization.

**PERICARDITIS:** A transmural myocardial infarct involves the epicardium and leads to inflammation of the pericardium in 10% to 20% of patients. Pericarditis is manifested clinically as chest pain and may produce a pericardial friction rub. One fourth of patients with acute myocardial infarction, particularly those with larger infarcts and congestive heart failure, develop a pericardial effusion, with or without pericarditis.

**Postmyocardial infarction syndrome (Dressler syndrome)** refers to a delayed form of pericarditis that develops 2 to 10 weeks after infarction. A similar disorder may occur after cardiac surgery. Antibodies to heart muscle appear in these patients, and the condition improves with corticosteroid therapy, suggesting that Dressler syndrome may have an immunologic basis.

**Therapeutic Interventions Limit Infarct Size**

Because the amount of myocardium that undergoes necrosis is an important predictor of morbidity and mortality, any therapy that limits infarct size should be beneficial. **Restoration of arterial blood flow** remains the only way to salvage ischemic myocytes permanently, although a number of interventions can delay ischemic injury. Several methods have been developed to restore blood flow to the area of myocardium supplied by an obstructed coronary artery.

- **Thrombolytic enzymes** such as tissue plasminogen activator or streptokinase can be infused intravenously to dissolve the clot causing the obstruction.
- **Percutaneous transluminal coronary angioplasty** is dilation of a narrowed coronary artery by inflation with a balloon catheter. It also allows stent placement in the coronary artery to maintain its patency.
- **Coronary artery bypass grafting** can restore blood flow to the distal segment of a coronary artery with a proximal occlusion.

Procedures that restore blood flow must be performed as quickly as possible, preferably in the first few hours after the onset of symptoms. Beyond 6 hours, it is unlikely that much salvageable ischemic myocardium remains.

**Chronic Congestive Heart Failure Is Most Commonly Related to Ongoing Coronary Artery Disease**

Because the rate of early mortality associated with acute myocardial infarction has fallen to less than 5%, many patients with ischemic heart disease survive longer and eventually develop **chronic congestive heart failure**. In more than 75% of all patients with heart failure, coronary artery disease is the major cause of their condition. Contractile impairment in these patients is due to irreversible loss of myocardium (previous infarcts) and hypoperfusion of surviving muscle. Because coronary artery disease is often so extensive in these patients, and many have already undergone coronary artery bypass surgery, the only treatments available are cardiac transplantation or the use of artificial pumps (ventricular assist devices). In a minority of patients with severe coronary atherosclerosis, myocardial contractility is impaired globally without discrete infarcts. This situation usually reflects a combination of ischemic myocardial dysfunction, diffuse fibrosis, and multiple small healed infarcts. However, there is a group of patients with left ventricular failure in whom cardiac dysfunction occurs without obvious infarction. These patients are said to have **ischemic cardiomyopathy**, which is a condition that results from repetitive episodes of ischemic injury leading to myocyte degeneration.

**HYPERTENSION HEART DISEASE**

**Effects of Hypertension on the Heart**

Hypertension has been defined by the World Health Organization as a persistent increase of systemic blood pressure above 140 mm Hg systolic or 90 mm Hg diastolic, or both (see Chapter 10). Systemic hypertension is one of the most prevalent and serious causes of coronary artery and myocardial disease in the United States. Chronic hypertension leads to pressure overload and results first in compensatory left ventricular hypertrophy and, eventually, cardiac failure. The term **hypertensive heart disease** is used when the heart is enlarged in the absence of a cause other than hypertension.

**PATHOLOGY:** Hypertension causes compensatory left ventricular hypertrophy as a result of the increased cardiac workload. The left ventricular free walls and interventricular septum become thickened uniformly and concentrically (Fig. 11-13), and heart weight increases, exceeding 375 g in men and 350 g in women. Microscopically, hypertrophic myocardial cells have an increased diameter with enlarged, hyperchromatic, and rectangular ("boxcar") nuclei (Fig. 11-14).
CLINICAL FEATURES: Myocardial hypertrophy clearly adds to the ability of the heart to handle an increased workload. However, there is a limit beyond which additional hypertrophy no longer compensates. This upper limit to useful hypertrophy may reflect increasing diffusion distance between the interstitium and the center of each myofiber; if the distance becomes too great, the oxygen supply to the myofiber will be deficient.

Diastolic dysfunction is the most common functional abnormality caused by hypertension and by itself can lead to congestive heart failure. Some interstitial fibrosis typically develops as part of hypertrophy, which further contributes to left ventricular stiffness. Hypertension is also associated with increased severity of coronary artery atherosclerosis. The combination of increased cardiac workload (systolic dysfunction), diastolic dysfunction, and narrowed coronary arteries leads to a greater risk for myocardial ischemia, infarction, and heart failure.

Cause of Death in Patients With Hypertension

Congestive heart failure is the most common cause of death in untreated hypertensive patients. Fatal intracerebral hemorrhage is also common. Death may also result from coronary atherosclerosis and myocardial infarction, dissecting aneurysm of the aorta, or ruptured berry aneurysm of the cerebral circulation. Renal failure may supervene when nephrosclerosis induced by hypertension becomes severe.

COR PULMONALE

Cor pulmonale is right ventricular hypertrophy and dilation due to pulmonary hypertension. Increased pressure in the pulmonary circulation may reflect a disorder of lung parenchyma or, more rarely, a primary disease of the vasculature (e.g., primary pulmonary hypertension, recurrent small pulmonary emboli).

Acute cor pulmonale is the sudden occurrence of pulmonary hypertension, most commonly as a result of sudden, massive pulmonary embolization. This condition causes acute right-sided heart failure and is a medical emergency. At autopsy, the only cardiac findings are severe dilation of the right ventricle and sometimes the right atrium.

Chronic cor pulmonale is a common heart disease, accounting for 10% to 30% of all cases of heart failure. This frequency reflects the prevalence of chronic obstructive pulmonary disease, especially chronic bronchitis and emphysema.

PATHOGENESIS: Chronic cor pulmonale may be caused by any pulmonary disease that interferes with ventilatory mechanics or gas exchange or obstructs the pulmonary vasculature. The most common causes of chronic cor pulmonale are chronic obstructive pulmonary disease and pulmonary fibrosis. In addition to the obliteration of blood vessels in the lung, these disorders also lead to pulmonary arteriolar vasoconstriction, which reduces the effective cross-sectional area of the pulmonary vascular bed without destroying the vessels. Hypoxia, acidosis, and hypercapnia directly cause pulmonary vasoconstriction.

PATHOLOGY: Chronic cor pulmonale is characterized by conspicuous right ventricular hypertrophy (Fig. 11-15) to the extent of exceeding 1.0 cm in thickness (normal range, 0.3 to 0.5 cm). Dilation of the right ventricle and right atrium are often present.
ACQUIRED VALVULAR AND ENDOCARDIAL DISEASES

A variety of inflammatory, infectious, and degenerative diseases damage cardiac valves and impair their function. The valves normally consist of thin flexible membranes, which close tightly to prevent backward blood flow. When they become damaged, leaflets or cusps may be thickened and fused enough to narrow the aperture and obstruct blood flow, a condition labeled valvular stenosis. Diseases that destroy valve tissue may also allow retrograde blood flow, termed valvular regurgitation or insufficiency. In many cases, diseases of the cardiac valves produce both stenosis and insufficiency, but generally one or the other predominates.

Stenosis of a cardiac valve results in hypertrophy of the myocardium proximal (in terms of blood flow) to the obstruction. Once compensatory mechanisms are exhausted, pressure overload eventually causes myocardial dilation and failure of the chamber proximal to the valve. Thus, mitral stenosis leads to left atrial hypertrophy and dilation. As the left atrium decompensates and can no longer force the venous return through the stenotic mitral valve, signs of pulmonary congestion develop, followed by right ventricular hypertrophy and even cor pulmonale. Similarly, aortic stenosis causes left ventricular hypertrophy and eventually left heart failure.

Valvular regurgitation or insufficiency also results in hypertrophy and dilation of the chamber proximal to the valve, due to volume overload. In aortic insufficiency, the left ventricle first hypertrophies and then dilates when it can no longer accommodate the regurgitant volume and provide adequate cardiac output. On the other hand, an incompetent mitral valve leads to hypertrophy and dilation of both the left atrium and left ventricle, because both are subjected to volume overload.

Rheumatic Heart Disease Encompasses Acute Myocarditis and Residual Valvular Deformities

Acute Rheumatic Fever

Rheumatic fever (RF) is a multisystem childhood disease that follows a streptococcal infection and is characterized by an inflammatory reaction involving the heart, joints, and central nervous system.

EPIDEMIOLOGY: RF is a complication of an acute streptococcal infection, almost always pharyngitis (i.e., “strep” throat) (see Chapter 9). The offending agent is Streptococcus pyogenes, also known as group A β-hemolytic Streptococcus. In some epidemics of streptococcal pharyngitis, the incidence of RF has been as high as 3%. RF is principally a disease of childhood, and the median age is 9 to 11 years, although it can occur in adults. Despite its declining importance in industrialized countries, RF is a leading cause of death of heart disease in persons 5 to 25 years old in less-developed regions.

PATHOGENESIS: The pathogenesis of RF remains unclear, and with the exception of the link to streptococcal infection, no theory has been proven unequivocally. Most hypotheses relate rheumatic carditis to antibodies against streptococcal antigens that cross-react with heart antigens, an observation that raises the possibility of an autoimmune etiology related to so-called molecular mimicry (Fig. 11-16).

However, it has not been proved that such antibodies are cytotoxic or that they are directly involved in the pathogenesis of the disease. A direct toxic effect of some streptococcal product on the myocardium has not yet been excluded.

PATHOLOGY: Acute rheumatic heart disease is a pancarditis, involving all three layers of the heart (endocardium, myocardium, and pericardium).

MYOCARDITIS: At the most early stage, the heart tends to be dilated and exhibits a nonspecific myocarditis, in which lymphocytes and macrophages predominate, although a few neutrophils and eosinophils may be evident. Fibrinoid degeneration of collagen, in which fibers become swollen, fragmented, and eosinophilic, is characteristic of this early phase. In severe cases, a few patients may die acutely.

The Aschoff body is the characteristic granulomatous lesion of rheumatic myocarditis (Fig. 11-17), developing...
The upper portion illustrates the initiating β-hemolytic streptococcal infection of the throat, which introduces the streptococcal antigens into the body and may also activate cytotoxic T cells. These antigens lead to the production of antibodies against various antigenic components of the streptococcus, which can cross-react with certain cardiac antigens, including those from the myocyte sarcolemma and glycoproteins of the valves. This may be the mechanism of inflammation of the heart in acute rheumatic fever, which involves all cardiac layers (endocarditis, myocarditis, and pericarditis). This inflammation becomes apparent after a latent period of 2 to 3 weeks. Active inflammation of the valves may eventually lead to chronic valvular stenosis or insufficiency. These lesions involve the mitral, aortic, tricuspid, and pulmonary valves, in that order of frequency.
several weeks after symptoms begin. This structure initially consists of a perivascular focus of swollen eosinophilic collagen surrounded by lymphocytes, plasma cells, and macrophages. With time, the Aschoff body acquires a granulomatous appearance, with a central fibrinoid focus associated with a perimeter of lymphocytes, plasma cells, macrophages, and giant cells. Eventually, the Aschoff body is replaced by a nodule of scar tissue. Anitschkow cells are unusual cells within the Aschoff body, with nuclei that contain a central band of chromatin (see Fig. 11-17). These cells are macrophages that are normally present in small numbers but accumulate and become prominent in certain types of inflammatory diseases of the heart. Anitschkow cells may become multinucleated, in which case they are termed Aschoff giant cells.

PERICARDITIS: Tenacious irregular fibrin deposits are found on both visceral and parietal surfaces of the pericardium during the acute inflammatory phase of RF. These deposits resemble the shaggy surfaces of two slices of buttered bread that have been pulled apart (“bread-and-butter pericarditis”). The pericarditis may be recognized clinically by hearing a friction rub, but it has little functional effect and ordinarily does not lead to constrictive pericarditis.

ENDOCARDITIS: During the acute stage of rheumatic carditis, valve leaflets become inflamed and edematous. All four valves are affected, but left-sided valves are most injured. The result is damage and focal loss of endothelium along the lines of closure of the valve leaflets. This leads to deposition of tiny nodules of fibrin, which can be recognized grossly as “verrucae” along the leaflets (so-called verrucous endocarditis of acute RF).

CLINICAL FEATURES: There is no specific test for RF. The clinical diagnosis is made when either two major or one major and two minor criteria (the Jones criteria) are met. The major criteria of acute RF include carditis (murmurs, cardiomegaly, pericarditis, and congestive heart failure), polyarthritis, chorea, erythema marginatum, and subcutaneous nodules. The minor criteria are previous history of RF, arthralgia, fever, certain laboratory tests indicating an inflammatory process, and electrocardiographic changes.

The acute symptoms of RF usually subside within 3 months, but with severe carditis, clinical activity may continue for 6 months or more. The mortality rate from acute rheumatic carditis is low. The main cause of death is heart failure due to myocarditis, although valvular dysfunction may also play a role. Recurrent attacks of RF are associated with types of group A β-hemolytic streptococci to which the patient has not been previously exposed. In patients with a history of a recent attack of RF, the recurrence rate is as high as 65%, whereas after 10 years, a streptococcal infection is followed by an acute relapse in only 5% of cases. Prompt treatment of streptococcal pharyngitis with antibiotics prevents an initial attack of RF and, less often, a recurrence of the disease. There is no specific treatment for acute RF, but corticosteroids and salicylates are helpful in managing the symptoms.

Chronic Rheumatic Heart Disease

PATHOLOGY: The myocardial and pericardial components of rheumatic pancarditis typically resolve without permanent sequelae. By contrast, the acute valvulitis of RF often results in long-term structural and functional alterations. Severe valvular scarring may develop months or years after a single bout of acute RF. On the other hand, recurrent episodes of acute RF are common and result in repeated and progressively increasing damage to the heart valves. The mitral valve is the most commonly and severely affected valve in chronic rheumatic disease. Chronic mitral valvulitis is characterized by conspicuous, irregular thickening and calcification of the leaflets, often with fusion of the commissures and chordae tendineae (Fig. 11-18). In severe disease, the valve orifice becomes reduced to a fixed narrow opening that has the appearance of a “fish mouth” when viewed from the ventricular aspect (Fig. 11-19). Mitral stenosis is the predominant functional lesion, but such a valve is also regurgitant. Chronic regurgitation produces a “jet” of blood directed at the posterior as-
pect of the left atrium, which damages the atrial endocardium. The aortic valve is the second most commonly involved valve in rheumatic heart disease. Diffuse fibrous thickening of the cusps and fusion of the commissures cause aortic stenosis, which progresses because of the chronic effects of turbulent blood flow across the valve. Often, cusps become rigidly calcified as the patient ages, resulting in stenosis and insufficiency, although either lesion may predominate. In cases of recurrent RF, the tricuspid valve may become deformed, virtually always in association with mitral and aortic lesions. The pulmonic valve is rarely affected.

Complications of Chronic Rheumatic Heart Disease

- **Bacterial endocarditis** follows episodes of bacteremia (e.g., during dental procedures). The scarred valves of rheumatic heart disease provide an attractive environment for bacteria that would bypass a normal valve.
- **Mural thrombi** form in atrial or ventricular chambers in 40% of patients with rheumatic valvular disease. They give rise to thromboemboli, which can produce infarcts in various organs.
- **Congestive heart failure** is associated with rheumatic disease of both mitral and aortic valves.

Collagen Vascular Diseases Affect Both Cardiac Valves and Myocardium

**Systemic Lupus Erythematosus (SLE)**
The heart is often involved in SLE, but cardiac symptoms are usually less prominent than are other manifestations of the disease.

**PATHOLOGY:** The most common cardiac lesion is **fibrinous pericarditis**, usually with an effusion. **Myocarditis** in SLE, in the form of subclinical left ventricular dysfunction, is also common and reflects the severity of the disease in other organs. Microscopically, fibrinoid necrosis of small vessels and focal degeneration of interstitial tissue are seen.

**Endocarditis** is the most striking cardiac lesion of SLE. Verrucous vegetations up to 4 mm across occur on endocardial surfaces and are termed **Libman-Sacks endocarditis**. They are most common on the mitral valve. Ordinarily, Libman-Sacks endocarditis heals without scarring and does not produce a functional deficit.

**Scleroderma (Progressive Systemic Sclerosis)**
Cardiac involvement is second only to renal disease as a cause of death in scleroderma. The myocardium exhibits intimal sclerosis of small arteries, which leads to small in-
farcts and patchy fibrosis. As a result, congestive heart failure and arrhythmias are common. Cor pulmonale secondary to interstitial fibrosis of the lungs and hypertensive heart disease (caused by renal involvement) are also seen.

**Polyarteritis Nodosa**

The heart is involved in up to 75% of cases of polyarteritis nodosa. Necrotizing lesions in branches of the coronary arteries result in myocardial infarction, arrhythmias, or heart block. Cardiac hypertrophy and failure secondary to renal vascular hypertension are common.

**Bacterial Endocarditis Refers to Infection of the Cardiac Valves**

Before the antibiotic era, bacterial endocarditis was untreatable and almost invariably fatal. The infection is classified according to its clinical course as either acute or subacute endocarditis.

**Acute bacterial endocarditis** is an infection of a normal cardiac valve by highly virulent suppurative organisms, typically *Staphylococcus aureus* and *S. pyogenes*. The affected valve is rapidly destroyed, and prior to modern therapy, the patient died within 6 weeks in acute heart failure or of overwhelming sepsis.

**Subacute bacterial endocarditis** is a less fulminant disease in which less-virulent organisms (e.g., *Streptococcus viridans* or *Staphylococcus epidermidis*) infect a structurally abnormal valve, which typically had been deformed by rheumatic heart disease. In these cases, patients typically survived for 6 months or more, and infectious complications were uncommon.

Antimicrobial therapy changed the clinical patterns of bacterial endocarditis, and classical presentations described above are now unusual. The disease is currently classified according to the anatomical location and the etiologic agent (Table 11-4).

**EPIDEMIOLOGY:** The most common predisposing condition for bacterial endocarditis in children now is CHD. Under 10% of cases of bacterial endocarditis in children today are attributable to rheumatic heart disease.

The epidemiology of bacterial endocarditis has also changed in adults. Mitral valve prolapse (MVP) and CHD are today the most frequent bases for bacterial endocarditis in adults, and rheumatic heart disease accounts for few cases. More than half of adults with bacterial endocarditis have no predisposing cardiac lesion. Other predisposing conditions include:

- **Intravenous drug abuse** related to the injection of pathogenic organisms along with illicit drugs. The most common source of bacteria in intravenous drug abusers is the skin, with *S. aureus* causing more than half of the infections.
- **Prosthetic valves** are sites of infection in 15% of all cases of endocarditis in adults, and 4% of patients with pros-

<table>
<thead>
<tr>
<th>TABLE 11–4</th>
<th>Etiologic Factors in Bacterial Endocarditis</th>
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<tbody>
<tr>
<td></td>
<td>Children (%)</td>
</tr>
<tr>
<td></td>
<td>Newborns &lt;15 Years 15–60 Years &gt;60 Years</td>
</tr>
<tr>
<td><strong>Underlying Disease</strong></td>
<td></td>
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<tr>
<td>Congenital heart disease</td>
<td>30 80 10 2</td>
</tr>
<tr>
<td>Rheumatic heart disease</td>
<td>– 5 25 8</td>
</tr>
<tr>
<td>Mitral valve prolapse</td>
<td>– 10 10 10</td>
</tr>
<tr>
<td>Valvular calcification</td>
<td>– – 5 30</td>
</tr>
<tr>
<td>Intravenous drug abuse</td>
<td>– – 15 10</td>
</tr>
<tr>
<td>Other</td>
<td>– – 10 10</td>
</tr>
<tr>
<td>None</td>
<td>70 5 25 30</td>
</tr>
<tr>
<td><strong>Microorganisms</strong></td>
<td></td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>45 25 35 30</td>
</tr>
<tr>
<td>Coagulase-negative staphylococci</td>
<td>10 5 5 10</td>
</tr>
<tr>
<td><em>Streptococci</em></td>
<td>15 45 45 35</td>
</tr>
<tr>
<td>Enterococci</td>
<td>– 5 5 15</td>
</tr>
<tr>
<td>Gram-negative bacteria</td>
<td>10 5 5 5</td>
</tr>
<tr>
<td>Fungi</td>
<td>10 Rare Rare Rare</td>
</tr>
<tr>
<td>Negative culture</td>
<td>5 10 5 5</td>
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</tbody>
</table>

* Five percent of neonatal infections are polymicrobial,
thetic valves have this complication. Staphylococci are again responsible for half of these infections, and most of the rest are caused by gram-negative aerobic organisms.

- **Transient bacteremia** from any procedure may lead to infective endocarditis. Examples include dental procedures, urinary catheterization, gastrointestinal endoscopy, and obstetric procedures. Antibiotic prophylaxis is recommended during such maneuvers for patients at increased risk for bacterial endocarditis (e.g., those with a history of RF or a cardiac murmur).

- **The elderly** also have an increasing tendency to develop endocarditis. A number of degenerative changes in heart valves including calcific aortic stenosis and calcification of the mitral annulus predispose to endocarditis.

### Pathogenesis

Virulent organisms, such as *S. aureus*, can infect apparently normal valves, but the mechanism of such bacterial colonization is poorly understood. The pathogenesis of the infection of a damaged valve by less virulent organisms is initiated by damage to the affected valve’s endothelium by turbulent blood flow. The damage leads to focal deposition of platelets and fibrin, creating small sterile vegetations that are hospitable sites for bacterial colonization and growth (Fig. 11-20). Microorganisms that gain access to the circulation can be deposited within the vegetations. In this protected environment, colony counts upon culture may reach \(10^{10}\) organisms per gram of tissue.

### Pathology

Bacterial endocarditis most commonly involves the mitral valve, the aortic valve, or both. The most common congenital heart lesions that underlie bacterial endocarditis are PDA, tetralogy of Fallot, ventricular septal defect, and bicuspid aortic valve; the last is an increasingly recognized risk factor, especially in men over 60 years of age. Vegetations are composed of platelets, fibrin, cell debris, and masses of organisms. The underlying valve tissue is edematous and inflamed and may eventually become so damaged that a leaflet perforates, causing regurgitation. Lesions vary in size from a small, superficial deposit to bulky, exuberant vegetations. The infective process may spread locally to involve the valve ring or adjacent mural endocardium and chordae tendineae. Infected thromboemboli travel to multiple systemic sites, causing infarcts or abscesses in many organs, including the brain, kidneys, intestine, and spleen.

### Clinical Features

Many patients show early symptoms of bacterial endocarditis within a week of the bacteremic episode, and almost all are symptomatic within 2 weeks. Heart murmurs develop almost invariably, often with a changing pattern during the course of the disease. In cases of more than 6 weeks duration, splenomegaly, petechiae, and clubbing of the fingers are frequent. In one third of patients, systemic emboli are recognized at some time during the illness. One third of the victims of bacterial endocarditis manifest some evidence of neurologic dysfunction, due to the frequency of embolization to the brain.

Antibacterial therapy is effective in limiting the morbidity and mortality of bacterial endocarditis. Most patients defervesce within a week of instituting such therapy. However, the prognosis depends on the offending organism and the stage at which the infection is treated. One third of cases of *S. aureus* endocarditis are still fatal. The most common serious complication of bacterial endocarditis is congestive heart failure, usually due to destruction of a valve. Surgical replacement of a valve destroyed by endocarditis is risky and carries high surgical mortality.

### Nonbacterial Thrombotic Endocarditis (Marantic Endocarditis) Is a Complication of Wasting Diseases

Nonbacterial thrombotic endocarditis (NBTE), also known as marantic endocarditis (from the Greek, marantikos, “wasting away”), refers to sterile vegetations on apparently normal cardiac valves, almost always in association with cancer or some other wasting disease. NBTE affects mitral and aortic valves with equal frequency. Its gross appearance is similar to that of infective endocarditis, but it does not destroy the affected valve, and on microscopic examination, neither inflammation nor microorganisms can be demonstrated. The cause of NBTE is poorly understood. It is seen commonly in complicating adenocarcinomas (particularly of pancreas and lung) and hematologic malignancies.

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**Figure 11-20** Bacterial endocarditis. The mitral valve shows destructive vegetations, which have eroded through the free margins of the valve leaflets.
Calcific Aortic Stenosis Reflects Chronic Damage to the Valve

Calcific aortic stenosis refers to a narrowing of the aortic valve orifice as a result of calcium deposition in the cusps and valve ring.

**PATHOGENESIS AND PATHOLOGY:** Calcific aortic stenosis has three main causes.

- **Rheumatic aortic valve disease**, in which it is characterized by diffuse fibrous thickening and scarring of the cusps, commissural fusion, and deposition of calcium, all of which reduce the valve orifice and limit valve mobility. The disorder is now uncommon due to surgical intervention (see Fig. 11-18).
- **Degenerative (senile) calcific stenosis** develops in elderly patients as a degenerative process that involves a normal symmetric tricuspid aortic valve. Valve cusps become rigidly calcified, but unlike the case in the rheumatic valve, there is no commissural fusion.
- **Congenital bicuspid aortic stenosis** often develops with age and, as above, shows no commissural fusion (Fig. 11-21).

Calcific aortic stenosis in both congenitally malformed valves as well as normal valves is probably related to the cumulative effect of years of trauma, due to turbulent blood flow around the valve. In any of the forms of calcific aortic stenosis, calcification produces nodules restricted to the base and lower half of the cusps, rarely involving free margins.

**CLINICAL FEATURES:** Severe aortic stenosis results in striking concentric left ventricular hypertrophy. Eventually, the heart dilates and fails. The disease is treated with great success (5-year survival rate of 85%) with surgical valve replacement, provided the operation is performed before ventricular dysfunction becomes irreversible. The hypertrophic left ventricle is then restored to its normal size.

**MVP Is the Most Common Indication for Valve Replacement**

MVP is a condition in which mitral valve leaflets become enlarged and redundant, and chordae tendineae become thinned and elongated, such that the billowed leaflets prolapse (protrude) into the left atrium during systole (Fig. 11-22A). Also referred to as “floppy mitral valve syndrome,” MVP is the most frequent cause of mitral regurgitation that requires surgical valve replacement. As much as 5% of the adult population may show echocardiographic evidence of MVP, although most will not have regurgitation severe enough to warrant surgical intervention.

**PATHOGENESIS:** MVP has an important hereditary component and many cases appear to be transmitted as an autosomal dominant trait. Patients with primary MVP exhibit a striking accumulation of myxomatous connective tissue in the center of the valve leaflet (see Fig. 11-22B). Presumably, the extracellular matrix defect allows the leaflets and chordae to enlarge and stretch under the high-pressure conditions they experience during the cardiac cycle.

**PATHOLOGY:** On gross examination, mitral valve leaflets are redundant and deformed (see Fig. 11-22A). On cross-section, they have a gelatinous appearance and slippery texture, due to accumulation of acid mucopolysaccharides (proteoglycans). The myxomatous degenerative process also affects the annulus and chordae tendineae, which increases the degree of prolapse and regurgitation. Although the mitral valve is usually the only valve affected, myxomatous degeneration can develop in the other cardiac valves, especially in patients with Marfan syndrome, 90% of whom have some clinical evidence of MVP.

**CLINICAL FEATURES:** Most patients with MVP are asymptomatic. Endocarditis, both infective and nonbacterial, is sometimes a serious complication, and cerebral emboli are common. Significant mitral regurgitation develops in 15% of patients after 10 to 15 years of MVP, after which mitral valve replacement is indicated.
Carcinoid Heart Disease Affects Right-Sided Valves

Carcinoid heart disease is an unusual condition that uniquely affects the right side of the heart and produces tricuspid regurgitation and pulmonary stenosis. It arises in patients with carcinoid tumors, usually of the small intestine, that have metastasized to the liver.

**PATHOGENESIS:** The pathogenesis of carcinoid heart disease is not fully understood. The valvular and endocardial lesions are thought to be caused by high concentrations of serotonin or other vasoactive amines and peptides produced by the tumor in the liver. Because these moieties are metabolized in the lung, carcinoid heart disease affects the right side of the heart almost exclusively. Use of anorexigenic drugs (such as “fen-phen”) and ergot alkaloids such as methysergide and ergotamine (used to treat migraine headaches) are also associated with cardiac disease strikingly similar to those seen in carcinoid syndrome, except that lesions develop on the left-sided valves. Because these drugs interfere with serotonin metabolism and signaling, it has been suggested that the pathogenesis of drug-related and carcinoid valvular disease is similar.

**PATHOLOGY:** The cardiac lesions are plaque-like deposits of dense, pearly gray, fibrous tissue on the tricuspid and pulmonary valves and on the endocardial surface of the right ventricle. Microscopically, these patches appear “tacked on” to valve leaflets and are not associated with inflammation or apparent damage to underlying valve structures. However, leaflets become deformed, and their surface area is reduced. As a result, the tricuspid leaflets become “stuck down” onto adjacent right ventricular mural endocardium, resulting in tricuspid insufficiency or stenosis. Shrinkage of the pulmonary valve and its annulus leads to pulmonary stenosis.

**MYOCARDITIS**

Myocarditis is inflammation of the myocardium associated with myocyte necrosis and degeneration. This definition specifically excludes ischemic heart disease. Myocarditis can occur at any age but is most common in children between the ages of 1 and 10. It is one of the few heart diseases that can produce acute heart failure in previously healthy children, adolescents, or young adults. Severe myocarditis can cause arrhythmias and even sudden cardiac death.

**Viral Myocarditis May Be Difficult to Demonstrate**

Most cases of myocarditis in North America occur without an easily demonstrable cause but are believed to be viral, although the evidence is usually circumstantial. The most common viruses that cause myocarditis are listed in Table 11-5.

**PATHOGENESIS:** The pathogenesis of viral myocarditis is thought to involve direct viral cytotoxicity or cell-mediated immune reactions directed against infected myocytes. There is substantial evidence for both mechanisms. The stimulus for the immune attack on myocytes is not established but appears to involve major histocompatibility antigens.

**PATHOLOGY:** The hearts of patients with myocarditis who develop clinical heart failure during the active inflammatory phase show biventricular...
dilation and generalized myocardial hypokinesis. At autopsy, these hearts are flabby and dilated. The histologic changes of viral myocarditis vary with the clinical severity of the disease. Most cases show a patchy or diffuse interstitial, predominantly mononuclear, inflammatory infiltrate composed principally of T lymphocytes and macrophages (Fig. 11-23). Multinucleated giant cells may also be present. The inflammatory cells often surround individual myocytes, and focal myocyte necrosis is seen. During the resolving phase, fibroblast proliferation and interstitial collagen deposition predominate.

**CLINICAL FEATURES:** Many persons who develop viral myocarditis may be asymptomatic. When symptoms do occur, they usually begin a few weeks after infection. Most patients recover from acute myocarditis, although a few die of congestive heart failure or arrhythmias. The disease may be unusually severe in infants and pregnant women. Despite resolution of the active inflammatory phase of viral myocarditis, subtle functional impairment may persist for years, and progression to overt cardiomyopathy is well documented. There is no specific treatment for viral myocarditis, and supportive measures usually suffice. In addition to viruses, other microorganisms and parasites that gain access to the bloodstream can infect the heart. Myocarditis may also result from noninfectious etiologies (see Table 11-5).

**METABOLIC DISEASES OF THE HEART**

**Hyperthyroidism Causes High-Output Failure**

Hyperthyroidism causes conspicuous tachycardia and an increased cardiac workload, due to decreased peripheral resistance and increased cardiac output. It may eventually lead to angina pectoris and high-output failure.

**Thiamine Deficiency (Beriberi) Heart Disease is Similar to Hyperthyroidism**

In the United States, thiamine deficiency (beriberi) is occasionally seen in alcoholics or neglected individuals who consume an inadequate amount of thiamine (see Chapter 8). Beriberi heart disease results in decreased peripheral vascular resistance and increased cardiac output, a combination similar to that produced by hyperthyroidism. At autopsy, the heart is dilated and shows only nonspecific microscopic changes.

**Hypothyroid Heart Disease Diminishes Cardiac Output**

Patients with severe hypothyroidism (myxedema) have decreased cardiac output, reduced heart rate, and impaired myocardial contractility—changes that are the reverse of those seen in hyperthyroidism. The hearts of patients with myxedema are flabby and dilated, and the myocardium exhibits myofiber swelling. Basophilic (mucinous) degeneration is common. Interstitial fibrosis may also be present. Despite these changes, myxedema does not produce congestive heart failure in the absence of other cardiac disorders.
CARDIOMYOPATHY

Cardiomyopathy refers to a primary disease of the myocardium and excludes damage caused by extrinsic factors. Dilated cardiomyopathy (DCM) is the most common type of cardiomyopathy and is characterized by biventricular dilation, impaired contractility, and eventually congestive heart failure. DCM can develop in response to a large number of known insults that directly injure cardiac myocytes (“secondary DCM”), or it may be idiopathic (primary).

Idiopathic Dilated Cardiomyopathy Is Characterized by Impaired Contractility

**PATHOGENESIS:** Numerous etiologies have been implicated in idiopathic DCM, but the pathogenesis is unresolved.

Genetic factors now appear to be more important than previously believed. Among patients with idiopathic DCM, at least one-third has a familial disease. Most familial cases seem to be transmitted as an autosomal dominant trait, but autosomal recessive, X-linked recessive, and mitochondrial inheritance patterns have all been described. Mutations in several known genes including those encoding dystrophin, δ-sarcoglycan, troponin T, β-myosin heavy chain, actin, lamin A/C, and desmin have been identified as causing a dilated cardiomyopathic phenotype. A current hypothesis holds that defects in force transmission lead to development of a dilated, poorly contracting heart. Interestingly, mutations in proteins such as actin, troponin T, and β-myosin heavy chain may produce either dilated or HCM phenotypes, perhaps depending on whether they produce a defect in force generation (HCM) or force transmission (dilated cardiomyopathy).

Viral myocarditis may eventually lead to DCM, but how this would develop has not been clear. Interestingly, a protease expressed by cardiotropic enteroviruses has been shown to cleave dystrophin, thereby providing a potential mechanistic link between viral infection and the development of a dilated cardiomyopathy phenotype.

Immunologic abnormalities involving both cellular and humoral effects have been recognized in both myocarditis and idiopathic DCM. Autoantibodies to cardiac antigens that have been identified include those directed against a variety of mitochondrial antigens, cardiac myosin, and β-adrenergic receptors. However, a pathogenic role for immune mechanisms remains to be proved.

**PATHOLOGY:** The pathologic changes in patients with DCM are generally nonspecific and are similar whether the disorder is idiopathic or secondary to a known injurious agent. At autopsy, the heart is invariably enlarged, reflecting conspicuous left and right ventricular hypertrophy. The weight of the heart may be as much as tripled (>900 g). As a rule, all chambers of the heart are dilated, although the ventricles are more severely affected than are the atria (Fig. 11-24). The myocardium is flabby and pale, and small subendocardial scars are occasionally evident. The left ventricular endocardium, especially at the apex (not shown), tends to be thickened. Adherent mural thrombi are often present in this area.

Microscopically, DCM is characterized by atrophic and hypertrophic myocardial fibers. Cardiac myocytes, especially in the subendocardium, often show advanced degenerative changes characterized by myofibrillar loss, an effect that gives cells a vacant, vacuolated appearance. Interstitial and perivascular fibrosis of myocardium is evident, also most prominently in the subendocardial zone.

**CLINICAL FEATURES:** The clinical courses of idiopathic and secondary DCM are comparable. The disease begins insidiously with compensatory ventricular hypertrophy and asymptomatic left ventricular dilation. Commonly, exercise intolerance progresses relentlessly to frank congestive heart failure, and 75% of patients die within 5 years of symptom onset. Although supportive treatment is useful, cardiac transplantation or use of a ventricular assist device eventually becomes the only option.

Secondary Dilated Cardiomyopathy Has Many Causes

Almost 100 distinct myocardial diseases can result in the clinical features of DCM. Thus, secondary DCM is best viewed as a final common pathway for the effects of virtually any toxic, metabolic, or infectious disorder that directly injures cardiac myocytes. In this context, alcohol abuse, hypertension, pregnancy, and viral myocarditis predispose to
secondary DCM. Diabetes mellitus and cigarette smoking are also associated with increased incidence of this disorder.

**Toxic Cardiomyopathy**

Numerous chemicals and drugs cause myocardial injury. Several of the more important substances are discussed here.

**ETHANOL:** *Alcoholic cardiomyopathy is the single most common identifiable cause of DCM in the United States and Europe.* Ethanol abuse can lead to chronic, progressive cardiac dysfunction, which may be fatal. The typical patient is between 30 and 55 years of age and has been drinking heavily for at least 10 years. Although the short-term action of alcohol on cardiac myocytes is reversible, the cumulative injury eventually becomes irreversible.

**CATECHOLAMINES:** In high concentrations, catecholamines can cause focal myocyte necrosis. Toxic myocarditis may occur in patients with pheochromocytomas, those who require high doses of inotropic drugs to maintain blood pressure, and in accident victims who sustain massive head trauma.

**ANTHRACYCLINES:** Doxorubicin (Adriamycin; Pharmacia and Upjohn Company, Peapack, NJ) and other anthracycline drugs are potent chemotherapeutic agents, and their usefulness is limited by cumulative, dose-dependent, cardiac toxicity. The clinical major effect is poor myocyte contractility due to chronic, irreversible degeneration of cardiac myocytes. The histopathology of this disorder includes vacuolization and loss of myofibrils. Once severe degeneration occurs, intractable congestive heart failure develops.

**COCAINE:** Cocaine use is frequently associated with chest pain and palpitations. True DCM is an unusual complication of cocaine abuse, but myocarditis, focal necrosis, and thickening of intramyocardial coronary arteries have been reported. Sudden death due to spontaneous ventricular tachyarrhythmias is well documented. Mechanisms underlying the arrhythmogenic effects of cocaine include vasoconstriction, sympathomimetic activity, hypersensitivity responses, and direct toxicity.

**Cardiomyopathy of Pregnancy**

A unique form of DCM develops in the last trimester of pregnancy or the first 6 months after delivery. The disorder is relatively uncommon in the United States, but in some regions of Africa, it is encountered in as many as 1% of pregnant women. The risk of cardiomyopathy of pregnancy is greatest in black, multiparous women, older than 30 years of age. The cause of this form of DCM is unknown. Some patients exhibit inflammatory cells in heart biopsies taken during the symptomatic phase of the illness, consistent with the hypothesis that disordered immunity may underlie the development of DCM in this setting.

**In HCM, Cardiac Hypertrophy Is Out of Proportion to the Hemodynamic Load**

HCM that develops for no apparent physiologic reason is probably genetically determined in most patients and is identified as an autosomal dominant trait in half of patients. HCM is now known to be far more common than previously appreciated: its prevalence in the United States is about 1 in 500.

**PATHOGENESIS:** The clinical picture of HCM is caused by more than 100 mutations in at least nine genes encoding proteins of the sarcomere. The mutated genes most commonly involved encode (1) β-myosin heavy chain (35%), (2) myosin-binding protein C (20%), and (3) troponin T (15%). This proposed mechanism has led to the hypothesis that HCM is related to defects in force generation owing to altered sarcomeric function.

**PATHOLOGY:** The heart in HCM is always enlarged, but the degree of hypertrophy varies in different genetic forms. The left ventricle wall is thick, and its cavity is small, sometimes reduced to a slit. Papillary muscles and trabeculae carneae are prominent and encroach on the ventricular lumen. More than half of cases exhibit asymmetric hypertrophy of the interventricular septum, with a ratio of the septum thickness to that of the left ventricular free wall greater than 1.5 (Fig. 11-25A).

The most notable histologic feature of HCM is myofiber disarray, which is most extensive in the interventricular septum. Instead of the usual parallel arrangement of myocytes into muscle bundles, myofiber disarray is characterized by an oblique and often perpendicular orientation of adjacent hypertrophic myocytes (see Fig. 11-25B).

**CLINICAL FEATURES:** Most patients with HCM have few if any symptoms, and the diagnosis is commonly made during screening of the family with an affected member. Despite a lack of symptoms, such persons may be at risk for sudden death, particularly during severe exertion. In fact, unsuspected HCM is commonly found at autopsy in young competitive athletes who die suddenly. Clinical recognition of HCM can occur at any age, often in the third, fourth, or fifth decade of life, but the disorder is also encountered in the elderly. Some patients with HCM become incapacitated by cardiac symptoms, of which dyspnea, angina pectoris, and syncope are most common. The clinical course tends to remain stable for many years, although eventually, the disease can progress to congestive heart failure.
Restrictive Cardiomyopathy Impairs Diastolic Function

Restrictive cardiomyopathy describes a group of diseases in which myocardial or endocardial abnormalities limit diastolic filling, while contractile function remains normal. It is the least common category of cardiomyopathy in Western countries, although in some less-developed regions (e.g., parts of equatorial Africa, South America, and Asia), endomyocardial disease related to parasitic infections leads to many cases of restrictive cardiomyopathy.

PATHOGENESIS AND PATHOLOGY: Restrictive cardiomyopathy is caused by (1) interstitial infiltration of amyloid, metastatic carcinoma, or sarcoid granulomas; (2) endomyocardial disease characterized by marked fibrotic thickening of the endocardium; (3) storage diseases, including hemochromatosis; and (4) markedly increased interstitial fibrous tissue. Many cases of restrictive cardiomyopathy are classified as idiopathic, with interstitial fibrosis as the only histologic abnormality. The disease almost invariably progresses to congestive heart failure, and only 10% of the patients survive for 10 years.

Amyloidosis

The heart is affected in most forms of generalized amyloidosis (see Chapter 23). In fact, restrictive cardiomyopathy is the most common cause of death in AL amyloidosis of plasma cell dyscrasias.

PATHOLOGY: Amyloid infiltration of the heart results in cardiac enlargement without ventricular dilation, and the gross appearance of the heart may resemble that of HCM. Ventricular walls are typically thickened, firm, and rubbery. Microscopically, amyloid accumulation is most prominent in interstitial, perivascular, and endocardial regions. Endocardial involvement is common in the atria, where nodular endocardial deposits often impart a granular appearance and gritty texture to the endocardial surface. Amyloid deposits can also cause thickening of cardiac valves.

CLINICAL FEATURES: Cardiac amyloidosis is most often a restrictive cardiomyopathy, with symptoms mainly referable to right-sided heart failure. Infiltration of the conduction system can result in arrhythmias, and sudden cardiac death is not unusual. Cardiomegaly is characteristically prominent. The prognosis is grim; most patients survive less than 1 year once the disease becomes symptomatic.
SENILE CARDIAC AMYLOIDOSIS: Senile cardiac amyloidosis refers to the deposition of a protein closely related to prealbumin (transthyretin) in the hearts of elderly persons (see Chapter 23). The disorder may be present to some extent in up to 25% of patients who are 80 years old or older. The functional significance of senile cardiac amyloidosis is often minimal, and it is usually an incidental finding at autopsy.

Endomyocardial Disease

Endomyocardial disease comprises two geographically separate disorders.

ENDOMYOCARDIAL FIBROSIS: This condition is particularly common in equatorial Africa, where it accounts for 10% to 20% of all deaths from heart disease. The malady is also occasionally seen in other tropical and subtropical regions of the world. It is most common in children and young adults but has been reported to occur in persons up to 70 years of age. Endomyocardial fibrosis leads to progressive myocardial failure and has a poor prognosis, although survival for as long as 12 years has been reported.

EOSINOPHILIC ENDOCARDIAL DISEASE (LÖFFLER ENDOCARDITIS): This is a cardiac disorder of temperate regions characterized by hypereosinophilia (as high as 50,000/μL). It is usually encountered in men in the fifth decade and is often accompanied by a rash. Löffler endocarditis typically progresses to congestive heart failure and death, although corticosteroids may improve survival.

PATHOGENESIS: Endomyocardial fibrosis and Löffler endocarditis were once considered distinct entities, but there is a growing consensus that they represent variants of the same underlying disease. Endomyocardial disease is suspected to result from myocardial injury produced by eosinophils, possibly mediated by cardiotoxic granule components. In the tropics, transient high blood eosinophil counts often result from parasitic infestations; in temperate climates, idiopathic hypereosinophilia is usually persistent.

PATHOLOGY: At autopsy, a grayish-white layer of thickened endocardium extends from the apex of the left ventricle over the posterior papillary muscle to the posterior leaflet of the mitral valve and for a short distance into the left outflow tract. On cut section of the ventricle, endocardial fibrosis spreads into the inner one-third to one-half of the wall. Mural thrombi in various stages of organization may be present. When the right ventricle is involved, the entire cavity may exhibit endocardial thickening, which may penetrate as far as the epicardium. Microscopically, the fibrotic endocardium contains only a few elastic fibers. Myofibers trapped within the collagenous tissue display nonspecific degenerative changes.

Storage Diseases

The various lysosomal storage diseases are discussed in detail in Chapter 6. Only the cardiac manifestations are reviewed here.

GLYCOGEN STORAGE DISEASES: Of the various forms of glycogen storage disease, types II (Pompe disease), III (Cori disease), and IV (Andersen disease) affect the heart. The most common and severe involvement is with Pompe disease. In infants with this condition, the heart is markedly enlarged (up to seven times normal), and endocardial fibroelastosis is seen in 20% of patients. The myocytes are vacuolated as a result of the large amounts of stored glycogen. The functional changes are those of a restrictive type of cardiomyopathy, and the usual cause of death is cardiac failure.

MUCOPOLYSACCHARIDOSES: Several of the mucopolysaccharidoses involve the heart. Cardiac disease results from lysosomal accumulation of mucopolysaccharides (glycosaminoglycans) in various cells. In general, pseudohypertrophy of the ventricles develops, and contractility gradually diminishes. The coronary arteries may be narrowed by thickening of the intima and media, and in Hurler and Hunter syndromes, myocardial infarction is common.

SPHINGOLIPIDOSES: Fabry disease may result in the accumulation of glycosphingolipids in the heart, with functional and pathologic changes similar to those that complicate the mucopolysaccharidoses.

HEMOCHROMATOSIS: This multiorgan disease is associated with excessive iron deposition in many tissues (see Chapter 14). The degree of iron deposition in the heart varies and only roughly correlates with that in other organs. Cardiac involvement has features of both dilated and restrictive cardiomyopathy, with systolic and diastolic impairment. Congestive heart failure occurs in as many as one third of patients with hemochromatosis. At autopsy, the heart is dilated, and ventricular walls are thickened. The brown color seen on gross examination correlates with iron deposition in cardiac myocytes. The severity of myocardial dysfunction seems to be proportional to the quantity of iron deposited.

CARDIAC TUMORS

Primary cardiac tumors are rare but can result in serious problems when they occur.
Cardiac Myxoma Is the Most Common Primary Tumor of the Heart

Cardiac myxoma accounts for about 50% of all primary cardiac tumors. It is usually sporadic, but it is occasionally associated with familial autosomal dominant syndromes.

**PATHOLOGY:** Most myxomas (75%) arise in the left atrium, although they can occur in any cardiac chamber or on a valve. The tumor appears as a glistening, gelatinous, polypoid mass, usually 5 to 6 cm in diameter, with a short stalk (Fig. 11-26). It may be sufficiently mobile to obstruct the mitral valve orifice. Microscopically, cardiac myxoma has a loose myxoid stroma containing abundant proteoglycans. Polygonal stellate cells are found within the matrix, occurring singly or in small clusters.

**CLINICAL FEATURES:** More than half of patients with left atrial myxoma have clinical evidence of mitral valve dysfunction. Although the tumor does not metastasize in the usual sense, it often embolizes. One third of patients with myxomas of the left atrium or left ventricle die from tumor embolization to the brain. Surgical removal of the tumor is successful in most cases.

Rhabdomyoma Is a Childhood Tumor

*Rhabdomyoma* is the most common primary cardiac tumor in infants and children and forms nodular masses in the myocardium. It may actually be a hamartoma rather than a true neoplasm, although the issue is still debated. Almost all are multiple and involve both ventricles and, in one third of cases, the atria as well. In half of cases, the tumor projects into a cardiac chamber and obstructs the lumen or valve orifices.

**PATHOLOGY:** On gross examination, cardiac rhabdomyomas are pale masses, from 1 mm to several centimeters in diameter. Microscopically, tumor cells show small central nuclei and abundant glycogen-rich clear cytoplasm, in which fibrillar processes containing sarcomeres radiate to the margin of the cell (“spider cell”). Rhabdomyomas often occur in association with tuberous sclerosis (one third to one half of cases). A few cardiac rhabdomyomas have been successfully excised.

Metastatic Tumors to the Heart May Manifest as Restrictive Cardiomyopathy

Metastatic tumors to the heart are seen most frequently in patients with the most prevalent forms of carcinomas—those of the lung, breast, and gastrointestinal tract. Still, only a minority of patients with these tumors will show cardiac metastases. Lymphomas and leukemia may also involve the heart. Of all tumors, the one most likely to metastasize to the heart is malignant melanoma. Metastatic cancer of the myocardium can result in clinical manifestations of restrictive cardiomyopathy, particularly if the cardiac tumors are associated with extensive fibrosis.

Pericardial Effusion Can Cause Cardiac Tamponade

*Pericardial effusion* is the accumulation of excess fluid within the pericardial cavity, either as a transudate or an exudate. The pericardial sac normally contains no more than 50 mL of lubricating fluid. If the pericardium is slowly distended, it can accommodate up to 2 L of fluid without notable hemodynamic consequences. However, rapid accumulation of as little as 150 to 200 mL of pericardial fluid or blood may significantly increase intrapericardial pressure and restrict diastolic filling, especially of the right ventricle. *Cardiac tamponade* is the syndrome produced by the rapid accumulation of pericardial fluid, which restricts the filling of the heart.

- **Serous pericardial effusion** is often a complication of an increase in extracellular fluid volume, as occurs in congestive heart failure or the nephrotic syndrome. The fluid has a low protein content and few cellular elements.
- **Chylous effusion** (fluid containing chylomicrons) results from a communication of the thoracic duct with the pericardial space secondary to lymphatic obstruction by tumor or infection.
- **Hemopericardium** is bleeding directly into the pericardial cavity. The most common cause is ventricular free wall rupture at a myocardial infarct. Less frequent causes are penetrating cardiac trauma, rupture of a dissecting aneurysm of the aorta, infiltration of a vessel by tumor, or a bleeding diathesis.

The hemodynamic consequences range from a minimally symptomatic condition to abrupt cardiovascular collapse and death. As the pericardial pressure increases, it reaches and then exceeds central venous pressure, thereby limiting return of blood to the heart. Acute cardiac tamponade is almost invariably fatal unless the pressure is relieved by removing pericardial fluid, by either needle pericardiocentesis or surgical procedures.

**Acute Pericarditis May Follow Viral Infections**

 порядок по абзацам

Pericarditis refers to inflammation of the visceral or parietal pericardium.

**PATHOGENESIS:** The causes of pericarditis are similar to those for myocarditis (see Table 11-5). In most cases, the cause of acute pericarditis is obscure and (as in myocarditis) is attributed to an undiagnosed viral infection. Bacterial pericarditis is distinctly unusual in the antibiotic era. Metastatic tumors, most commonly breast and lung carcinomas, may involve the pericardium and cause a malignant pericardial effusion. Pericarditis associated with myocardial infarction and rheumatic fever is discussed above.

**PATHOLOGY:** Acute pericarditis can be classified as fibrinous, purulent, or hemorrhagic, depending on the gross and microscopic characteristics of the pericardial surfaces and fluid. The most common form is fibrinous pericarditis, in which the normal smooth, glistening appearance of the pericardial surfaces becomes replaced by a dull, granular fibrin-rich exudate (Fig. 11-27). The rough texture of the inflamed pericardial surfaces produces the characteristic friction rub heard by auscultation. The effusion fluid in fibrinous pericarditis is usually rich in protein, and the pericardium contains primarily mononuclear inflammatory cells.

**CLINICAL FEATURES:** The initial manifestation of acute pericarditis is sudden, severe, substernal chest pain, sometimes referred to the back, shoulder, or neck. A characteristic pericardial friction rub is easily heard. Idiopathic or viral pericarditis is a self-limited disorder, although it may infrequently lead to constrictive pericarditis. Corticosteroids are the treatment of choice. The therapy for other specific forms of acute pericarditis varies with the cause.
Constrictive Pericarditis May Mimic Right Heart Failure

Constrictive pericarditis is a chronic fibrosing disease of the pericardium that compresses the heart and restricts inflow.

**PATHOGENESIS AND PATHOLOGY:** Constrictive pericarditis results from an exuberant healing response after acute pericardial injury, in which the pericardial space becomes obliterated and visceral, and parietal layers become fused in a dense, rigid mass of fibrous tissue. The scarred pericardium may be so thick (up to 3 cm) that it narrows the orifices of the venae cavae (Fig. 11-28).

The fibrous envelope may contain calcium deposits. The condition is infrequent today and, in developed countries, is predominantly idiopathic. Constrictive pericarditis may follow tuberculous infection and is still the major cause in underdeveloped regions.

**CLINICAL FEATURES:** Patients with constrictive pericarditis have a small, quiet heart in which venous inflow is restricted, and the rigid pericardium determines the diastolic volume of the heart. These patients have high venous pressure, low cardiac output, small pulse pressure, and fluid retention with ascites and peripheral edema. Total pericardiectomy is the treatment of choice.
AUTHOR QUERIES

AQ1: Author: Please confirm all cross-referencing in the chapter (cross-referenced chapters and figures).