affect myocyte survival after injury, or affect contractility or electrical conduction in the face of biomechanical stressors. Indeed, the pathogenesis of many congenital heart defects involves an underlying genetic abnormality whose expression is modified by environmental factors (see later). Moreover, genes that control the development of the heart may also regulate the response to various forms of injury including aging. Subtle polymorphisms can significantly affect the risk of many forms of heart disease, and, as discussed later, a number of adult-onset heart disorders have a fundamentally genetic basis. Thus, cardiovascular genetics provides an important window on the pathogenesis of heart disease, and molecular diagnoses are increasingly a critical part of its classification.

HEART FAILURE

Heart failure, often called congestive heart failure (CHF), is a common, usually progressive condition with a poor prognosis. Each year in the United States, CHF affects more than 5 million individuals (approximately 2% of the population), necessitating more than 1 million hospitalizations, and contributing to the death of nearly 300,000 people. Roughly one-half of patients die within 5 years of receiving a diagnosis of CHF, and 1 in 9 deaths in the United States include heart failure as a contributory cause.

Heart failure is defined as the condition in which a heart cannot pump blood to adequately meet the metabolic demands of peripheral tissues, or can do so only at elevated filling pressures. It is the common end stage of many forms of chronic heart disease, often emerging insidiously from the cumulative effects of chronic work overload (e.g., in valve disease or hypertension) or IHD (e.g., after myocardial infarction [MI] with heart damage). However, acute hemodynamic stresses, such as fluid overload, abrupt valvular dysfunction, or myocardial infarction, can all precipitate sudden CHF.

When cardiac workload increases or cardiac function is compromised, several physiologic mechanisms swing into action, and can at least initially maintain arterial pressure and organ perfusion:

- *Frank-Starling mechanism:* Increased filling volumes dilate the heart, thereby increasing actin-myosin cross-bridge formation, and enhancing contractility and stroke volume.
- *Activation of neurohumoral systems:* These augment heart function and/or regulate filling volumes and pressures (and many of the therapies for CHF affect these systems when they become maladaptive).
  - *Release of norepinephrine* by adrenergic nerves of the autonomic nervous system, elevating heart rate, augmenting myocardial contractility and increasing vascular resistance
  - *Activation of the renin-angiotensin-aldosterone system,* promoting water and salt retention (augmenting circulatory volume) and increasing vascular tone
  - *Release of atrial natriuretic peptide,* counterbalancing the renin-angiotensin-aldosterone system through diuresis and vascular smooth muscle relaxation
- *Myocardial adaptations*: In many pathologic states, heart failure is preceded by cardiac hypertrophy, a compensatory response to increased mechanical work. Ventricular remodeling is the general term applied to the collective molecular, cellular, and structural changes that occur in response to injury or altered ventricular loading.

Although such adaptive mechanisms can potentially maintain adequate cardiac output in the face of acute perturbations, their capacity to do so may ultimately be overwhelmed. Heart failure can result from progressive deterioration of myocardial contractile function (systolic dysfunction)—reflected as a decrease in ejection fraction (EF, the percentage of blood volume ejected from the ventricle during systole; normal is approximately 45% to 65%). Reduction in EF can occur with ischemic injury, inadequate adaptation to pressure or volume overload due to hypertension or valvular disease, or ventricular dilation. Increasingly, heart failure is recognized as resulting from an inability of the heart chamber to expand and fill sufficiently during diastole (diastolic dysfunction), for example, due to left ventricular hypertrophy, myocardial fibrosis, constrictive pericarditis, or amyloid deposition.

Cardiac Hypertrophy: Pathophysiology and Progression to Heart Failure

Sustained increase in mechanical work of either ventricle due to pressure overload, volume overload, or trophic signals (e.g., those mediated through the activation of β-adrenergic receptors) causes myocytes to increase in size (cellular hypertrophy); cumulatively, this increases the size and weight of the heart (Fig. 12.1). Hypertrophy requires increased protein synthesis to form additional sarcomeres, as well as increasing the numbers of mitochondria. Hypertrophic myocytes also have multiple or enlarged nuclei, attributable to increased DNA ploidy resulting from DNA replication in the absence of cell division.

The pattern of hypertrophy reflects the nature of the stimulus.

- In *pressure-overload hypertrophy* (e.g., due to hypertension or aortic stenosis), new sarcomeres are predominantly assembled in parallel to the long axes of cells, expanding the cross-sectional area of myocytes in ventricles and causing a concentric increase in wall thickness.
- In contrast, *volume-overload hypertrophy* (e.g., due to valvular regurgitation) is characterized by new sarcomeres being assembled in series within existing sarcomeres, leading primarily to ventricular dilation. As a result, in dilation due to volume overload, or dilation that accompanies failure of a previously pressure overloaded heart, the wall thickness may be increased, normal, or less than normal. Consequently, heart weight, rather than wall thickness, is the best measure of hypertrophy in dilated hearts.

Heart disease can lead to dramatic levels of cardiac hypertrophy. Patients with systemic hypertension, IHD, aortic stenosis, mitral regurgitation, or dilated cardiomyopathy frequently have heart weights double or triple the average, and aortic regurgitation or hypertrophic cardiomyopathy can produce heart weights threefold to fourfold greater than normal.

Important changes at the tissue and cell level occur with cardiac hypertrophy. Significantly, myocyte hypertrophy

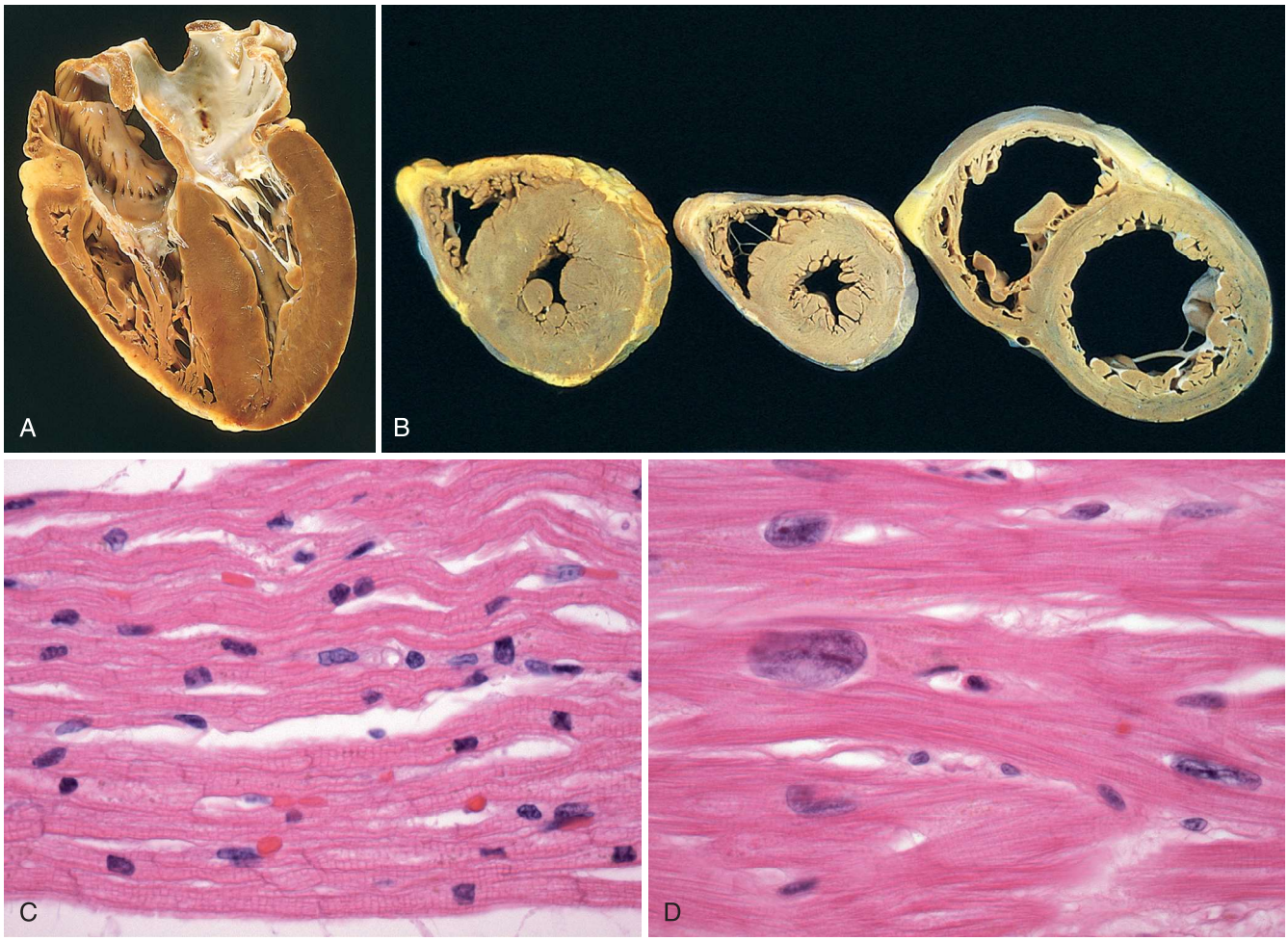

Figure 12.1 Left ventricular hypertrophy. (A) Pressure hypertrophy due to left ventricular outflow obstruction. The left ventricle is on the lower right in this apical four-chamber view of the heart. (B) Left ventricular hypertrophy with and without dilation, viewed in transverse heart sections. Compared with a normal heart *(center)*, the pressure-hypertrophied hearts *(left and in A)* have increased mass and a thick left ventricular wall, and the hypertrophied, dilated heart *(right)* has increased mass and an apparently normal wall thickness. (C) Normal myocardium. (D) Hypertrophied myocardium (C and D are photomicrographs at the same magnification). Note the increases in both cell size and nuclear size in the hypertrophied myocytes, and the interstitial cells remain small. (A and B, Reproduced with permission from Edwards WD: Cardiac anatomy and examination of cardiac specimens. In Emmanouilides GC, et al., editors: *Moss and Adams Heart Disease in Infants, Children, and Adolescents: Including the Fetus and Young Adults*, ed 5, Philadelphia, 1995, Williams & Wilkins, p 86.)

is not accompanied by a proportional increase in capillary numbers. As a result, the supply of oxygen and nutrients to the hypertrophied heart, particularly one undergoing pressure-overload hypertrophy, is more tenuous than in the normal heart. At the same time, cardiac hypertrophy is associated with heightened metabolic demands due to increases in mass, heart rate, and contractility (inotropic state, or force of contraction), all of which increase cardiac oxygen consumption. As a result of these changes, the hypertrophied heart is vulnerable to ischemia-related decompensation, which can evolve to cardiac failure. Adding insult to injury, hypertrophy is also typically accompanied by deposition of fibrous tissue (interstitial fibrosis), causing increased resistance to diastolic filling.

Molecular changes in hypertrophied cardiomyocytes include the expression of immediate-early genes (e.g., *FOS, JUN, MYC,* and *EGR1*) (Chapter 2) putatively driving cellular growth and altered protein expression; with prolonged hemodynamic overload, myocytes can even express genes usually only seen during fetal cardiac development (including fetal forms of myosin, natriuretic peptides, and collagen).

The proposed sequence of initially adaptive—and later harmful—events in response to increased cardiac work is summarized in Fig. 12.2. As illustrated, heart failure eventually supervenes. The degree of anatomic abnormality does not always reflect the severity of dysfunction; indeed, the gross appearance of the "failing heart" does not adequately convey the underlying structural, biochemical, and molecular basis for myocardial contractile failure. The hearts of patients with CHF are generally heavy and dilated, but can be relatively thin-walled, and histologically they exhibit variable degrees of myocyte hypertrophy. Loss of myocardial mass in the setting of infarction leads to work-related hypertrophy of the surrounding viable myocardium. In valvular heart disease, the increased pressure or volume overloads the myocardium globally. Increased heart mass owing to disease

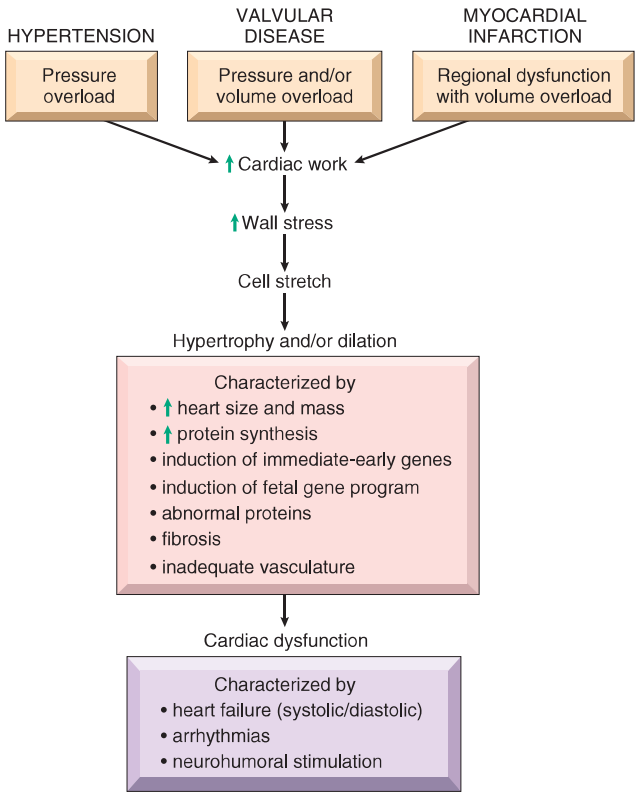

Figure 12.2 Schematic representation of the causes and consequences of cardiac hypertrophy.

is correlated with excess cardiac mortality and morbidity; indeed, cardiomegaly is an independent risk factor for sudden death.

In contrast to the pathologic hypertrophy associated with persistent mechanical stressors, regular exercise can promote potentially beneficial physiologic hypertrophy. Aerobic exercise (e.g., long-distance running) tends to be associated with volume-load hypertrophy accompanied by increases in capillary density (unlike other forms of hypertrophy); regular aerobic activity also decreases the resting heart rate and blood pressure—effects that are all beneficial. In comparison, purely static exercise (e.g., weight lifting) induces mild pressure hypertrophy (e.g., secondary to recurring Valsalva maneuvers) and less beneficial remodeling.

Whatever its basis, CHF is characterized by variable degrees of decreased cardiac output and tissue perfusion (forward failure), as well as pooling of blood in the venous capacitance system (backward failure); the latter may cause pulmonary edema, peripheral edema, or both. As a result, many of the significant clinical features and morphologic changes noted in CHF are actually secondary to disorders induced by hypoxia and congestion in noncardiac peripheral tissues.

The cardiovascular system is a closed circuit. Thus, although left-sided and right-sided failure can occur independently, failure of one side (particularly the left) often produces excessive strain on the other, terminating in global heart failure. Despite this interdependence, it is easiest to understand the pathology of heart failure by considering right- and left-sided heart failure separately.

Left-Sided Heart Failure

Left-sided heart failure is most often caused by the following:

- IHD
- Hypertension
- Aortic and mitral valvular diseases
- Primary myocardial diseases

The clinical and morphologic effects of left-sided CHF are a consequence of passive congestion (blood backing up in the pulmonary circulation), stasis of blood in the left-sided chambers, and inadequate perfusion of downstream tissues leading to organ dysfunction.

MORPHOLOGY

Heart. The findings depend on the disease process, ranging from myocardial infarcts, to stenotic or regurgitant valves, to intrinsic myocardial pathology. Except for failure caused by mitral valve stenosis or unusual restrictive cardiomyopathies (described later), the left ventricle is usually hypertrophied and often dilated, sometimes massively. Left ventricular diastolic dysfunction or dilation with mitral valve incompetence causes secondary dilation of the left atrium, increasing the risk of atrial fibrillation. This in turn results in stasis of blood, particularly in the atrial appendage, which is a common site of thrombus formation. The microscopic changes in the failing heart are nonspecific: variable degrees of myocyte hypertrophy and interstitial fibrosis.

Lungs. Pulmonary congestion and **edema** produce heavy, wet lungs, as described elsewhere (Chapters 4 and 15). Pulmonary changes—from mildest to most severe—include (1) perivascular and interstitial edema, particularly in the interlobular septa, (2) progressive edematous widening of alveolar septa, and (3) accumulation of edema fluid in the alveolar spaces. Extravasated red cells and plasma proteins in the alveoli are phagocytosed and digested by macrophages; the accumulated iron is stored as hemosiderin. These hemosiderin-laden macrophages (also known as **heart failure cells**) are telltale signs of previous episodes of pulmonary edema. Pleural effusions (typically serous) arise from elevated pleural capillary and lymphatic pressure and the resultant transudation of fluid into the pleural cavities.

Early left-sided heart failure symptoms are related to pulmonary congestion and edema. Initially, cough and dyspnea (breathlessness) may occur only with exertion. As CHF progresses, worsening pulmonary edema may cause orthopnea (dyspnea when supine, relieved by sitting or standing) or paroxysmal nocturnal dyspnea (dyspnea usually occurring at night that is so severe that it induces a feeling of suffocation). Dyspnea at rest may follow. The respiratory symptoms are characteristically associated with fine rales at the lung bases, caused when edematous pulmonary alveoli snap open during inspiration. Other manifestations of left ventricular failure include an enlarged heart (cardiomegaly, apparent on imaging), tachycardia, a third heart sound due to volume overload (S3), or a fourth heart sound (S4) due to increased myocardial stiffness. If heart failure is associated with progressive ventricular dilation, the papillary muscles are displaced outward, causing mitral regurgitation. Subsequent chronic dilation of the left atrium can cause atrial

fibrillation, and such uncoordinated, chaotic atrial contractions reduce the atrial contribution to ventricular filling, thus reducing the ventricular stroke volume.

In moderate CHF, a reduced ejection fraction leads to diminished renal perfusion, causing activation of the renin-angiotensin-aldosterone system as a compensatory mechanism to correct the "perceived" hypotension. This leads to salt and water retention, with expansion of the interstitial and intravascular fluid volumes (Chapters 4 and 11) exacerbating the ongoing pulmonary edema. If the hypoperfusion of the kidney becomes sufficiently severe, impaired excretion of nitrogenous products may cause azotemia (called prerenal azotemia; Chapter 20). In far-advanced CHF, cerebral hypoperfusion can give rise to hypoxic encephalopathy (Chapter 28), with irritability, loss of attention span, and restlessness that can progress to stupor and coma with ischemic cerebral injury.

Left-sided heart failure can be divided into systolic and diastolic failure:

- *Systolic failure* is defined by insufficient ejection fraction (pump failure) and can be caused by any of the many disorders that damage or derange the contractile function of the left ventricle.
- In *diastolic failure,* the left ventricle is abnormally stiff and cannot relax during diastole. Thus, although cardiac function is relatively preserved at rest, the heart is unable to increase its output in response to increases in the metabolic demands of peripheral tissues (e.g., during exercise). Moreover, because the left ventricle cannot expand normally, any increase in filling pressure is immediately transferred back into the pulmonary circulation, producing pulmonary edema. Hypertension is the most common underlying etiology; diabetes mellitus, obesity, and bilateral renal artery stenosis can also be causal. Reduced left ventricular relaxation may stem from myocardial fibrosis (e.g., in cardiomyopathies and IHD) or infiltrative disorders associated with restrictive cardiomyopathies (e.g., cardiac amyloidosis). Diastolic failure may appear in older patients without any known predisposing factors, possibly as an exaggeration of the normal stiffening of the heart with age. Constrictive pericarditis (discussed later) can also limit myocardial relaxation and therefore mimics primary diastolic dysfunction.

Right-Sided Heart Failure

Right-sided heart failure is most commonly caused by left-sided heart failure, as any increase in pressure in the pulmonary circulation from left-sided failure inevitably burdens the right side of the heart. Consequently, the causes of right-sided heart failure include all the etiologies for left-sided heart failure. Isolated right-sided heart failure is infrequent and typically occurs in patients with one of a variety of disorders affecting the lungs; hence it is often referred to as cor pulmonale. Besides parenchymal lung diseases, cor pulmonale can also arise secondary to disorders that affect the pulmonary vasculature, for example, primary pulmonary hypertension (Chapter 15), recurrent pulmonary thromboembolism (Chapter 4), or conditions that cause pulmonary vasoconstriction (obstructive sleep apnea, altitude sickness). The common feature of these disorders is pulmonary hypertension (discussed later), which results in hypertrophy and dilation of the right side of the heart. In extreme cases, leftward bulging of the interventricular septum can even cause left ventricular dysfunction. The major morphologic and clinical effects of primary right-sided heart failure differ from those of left-sided heart failure in that pulmonary congestion is minimal while engorgement of the systemic and portal venous systems is pronounced.

MORPHOLOGY

Heart. As in left-heart failure, the cardiac morphology varies with cause. Rarely, structural defects such as tricuspid or pulmonary valvular abnormalities or endocardial fibrosis (as in carcinoid heart disease) may be present. However, because isolated right heart failure is most often caused by lung disease, most cases exhibit only hypertrophy and dilation of the right atrium and ventricle.

Liver and Portal System. Congestion of the hepatic and portal vessels may produce pathologic changes in the liver, the spleen, and the gastrointestinal tract. The liver is usually increased in size and weight **(congestive hepatomegaly)** caused by **passive congestion,** greatest around the central veins (Chapter 4). Grossly, this is reflected as congested red-brown pericentral zones, with relatively normal-colored tan periportal regions, producing the characteristic "nutmeg liver" appearance (Chapter 4). In some instances, especially when left-sided heart failure with hypoperfusion is also present, severe centrilobular hypoxia produces **centrilobular necrosis.** With longstanding severe right-sided heart failure, the central areas can become fibrotic, eventually culminating in **cardiac cirrhosis** (Chapter 18). Portal venous hypertension also causes enlargement of the spleen with platelet sequestration **(congestive splenomegaly)** and can also contribute to chronic congestion and edema of the bowel wall. The latter may be sufficiently severe as to interfere with nutrient (and/or drug) absorption.

Pleural, Pericardial, and Peritoneal Spaces. Systemic venous congestion can lead to fluid accumulation **(effusions)** in the pleural, pericardial, or peritoneal spaces (a peritoneal effusion is also called **ascites**). Large pleural effusions can impact lung inflation, causing atelectasis, and substantial ascites can also limit diaphragmatic excursion, causing dyspnea on a purely mechanical basis.

Subcutaneous Tissues. Edema of the peripheral and dependent portions of the body, especially foot/ankle (pedal) and pretibial edema, is a hallmark of right-sided heart failure. In chronically bedridden patients, presacral edema may predominate. Generalized massive edema **(anasarca)** can also occur.

The kidney and the brain are also prominently affected in right-sided heart failure. Renal congestion is more marked with right-sided than with left-sided heart failure, leading to greater fluid retention and peripheral edema, and more pronounced azotemia. Venous congestion and hypoxia of the central nervous system can also produce deficits of mental function akin to those seen in left-sided heart failure with poor systemic perfusion.

Although we have discussed right and left heart failure separately, it is again worth emphasizing that in many cases of chronic cardiac decompensation, patients with biventricular CHF have symptoms reflecting both right-sided and left-sided heart failure. Besides a careful history and physical

examination, serum levels of B-type (or brain) natriuretic factor (BNP) have become a popular tool to quantitatively assess the extent of CHF. Recall that BNP is released by ventricular cardiomyocytes during increased wall stress; a low value has a high negative predictive value for CHF. Echocardiography is also an extremely valuable tool in following patients with CHF, providing a measure of ejection fraction, wall motion, valvular function, and possible mural thrombosis.

Treatment for CHF is initially focused on correcting any underlying cause, for example, a valvular defect or inadequate cardiac perfusion. Beyond that, the clinical approach includes salt restriction or pharmacologic agents that variously reduce volume overload (e.g., diuretics), increase myocardial contractility (so-called positive inotropes), or reduce afterload (via adrenergic blockade or inhibitors of angiotensin-converting enzymes [ACE]). Although many of these medications provide benefit through effects on neurohumoral pathways, ACE inhibitors also limit myocyte hypertrophy and cardiac remodeling. Although cardiac resynchronization therapy (exogenous pacing of both the right and left ventricles) and mechanical ventricular assist devices (VADs, discussed later) have also been added to the cardiologist's armamentarium, CHF remains a serious cause of human morbidity and mortality.

KEY CONCEPTS

HEART FAILURE

- Heart failure occurs when the heart is unable to provide adequate perfusion to meet the metabolic requirements of peripheral tissues; inadequate cardiac output is usually accompanied by increased congestion of the venous circulation.
- Left-sided heart failure is most commonly due to IHD, systemic hypertension, mitral or aortic valve disease, and primary diseases of the myocardium; symptoms are mainly a consequence of pulmonary congestion and edema, although systemic hypoperfusion can cause secondary renal and cerebral dysfunction.
- Right-sided heart failure is most often due to left heart failure, and less commonly to primary pulmonary disorders; symptoms are chiefly related to peripheral edema and visceral congestion.

CARDIAC DEVELOPMENT

The heart is a mechanical organ that generates pulsatile blood within just 3 weeks after fertilization. It is therefore likely that hemodynamic forces play an important role in cardiac development, just as they influence adaptations in the adult heart such as hypertrophy and dilation.

The diverse malformations seen in congenital heart disease (CHD) are caused by errors that occur during the complex migration and folding that constitutes cardiac morphogenesis. Derived from cells in the lateral mesoderm, the earliest cardiac precursors move to the midline in two migratory waves (called the first and second heart fields) within the first 15 days of fetal development. Although these are multipotent progenitor cells that can produce all of the major cell types of the heart (endocardium, myocardium, and smooth muscle cells), they rapidly assume distinct fates; cells in the first wave largely populate the developing left ventricle, whereas those in the second wave become the outflow tract, right ventricle, and most of the atria. Thus, defects in one or the other anlage can explain some of the CHDs involving discrete structures. By day 20 of development, the nascent heart has become a beating tube, which begins to form the basic heart chambers roughly 8 days later. At about the same time, (1) neural crest–derived cells migrate into the outflow tract, where they participate in the septation of the aortic and pulmonic outflow tracts and the formation of the aortic arch; and (2) interstitial connective tissue expands to become definitive endocardial cushions that will become the future atrioventricular canals and outflow tracts. By day 50, further septation of the ventricles, atria, and atrioventricular valves produces a four-chambered heart.

Proper orchestration of these remarkable transformations depends on a network of transcription factors that are regulated by a number of signaling pathways, particularly the Wnt, hedgehog, vascular endothelial growth factor (VEGF), bone morphogenetic protein, transforming growth factor-β (TGF-β), fibroblast growth factor, and Notch pathways (Chapter 1). It is not too surprising then that many of the inherited defects that affect heart development involve genes that encode transcription factors; these typically cause partial loss of function and are autosomal dominant (discussed later). In addition, specific micro-RNAs play critical roles in cardiac development by coordinating patterns and levels of transcription factor expression.

CONGENITAL HEART DISEASE

CHD refers to abnormalities of the heart or great vessels that are present at birth. Most CHD arises from faulty embryogenesis during gestational weeks 3 to 8, when major cardiovascular structures form and begin to function. The most severe anomalies preclude intrauterine survival, and significant heart malformations are common among stillborn infants. On the other hand, circumscribed defects affecting discrete regions of the heart or individual chambers can be compatible with live birth. In this latter category are the following:

- *Septal defects,* or "holes in the heart," including atrial septal defects (ASDs) or ventricular septal defects (VSDs)
- *Stenotic lesions,* either at the level of valves, or the entire cardiac chamber as in hypoplastic left heart syndrome
- *Outflow tract anomalies* including inappropriate routing of the great vessels from the ventricles, or anomalous coronary arteries

Such "tolerated" forms of CHD usually produce clinically important manifestations only after birth—uncovered by the transition from fetal to perinatal circulation; roughly one-half will be diagnosed in the first year of life, although some milder forms may not be discovered until adulthood (e.g., ASD).

Incidence

The incidence of CHD depends on what is counted as a defect. Thus, if echocardiography is performed routinely on neonates, small muscular VSDs or ASDs are detected in over 5% of live births. However, these typically close