Other single gene mutations associated with congenital heart disease can alter structural proteins or affect signaling pathway molecules. Thus, mutations in genes encoding various components of the Notch pathway (Chapter 1) are associated with a variety of congenital heart defects, including bicuspid aortic valve (*NOTCH1*, discussed later) and tetralogy of Fallot (*JAG1* and *NOTCH2*). As described in Chapter 11, fibrillin mutations underlie Marfan syndrome—associated with valvular defects and aortic aneurysms. Although fibrillin is an important structural protein in the ECM, it is also an important negative regulator of TGF-β signaling, and hyperactive TGF-β signaling contributes to the cardiovascular abnormalities in Marfan syndrome and Loeys-Dietz syndrome.

A notable example of a small chromosomal lesion causing congenital heart disease is deletion of chromosome 22q11.2, occurring in up to 50% of patients with DiGeorge syndrome. In this syndrome, the fourth branchial arch and the derivatives of the third and fourth pharyngeal pouches (which contribute to the formation of the thymus, parathyroids, and heart) develop abnormally. The syndrome is therefore associated with multiple deficits (memorable through the mnemonic CATCH-22: *c*ardiac abnormality, *a*bnormal facies, *t*hymic aplasia, *c*left palate, and *h*ypocalcemia, all on chromosome 22). Of the 30 or so genes present on this chromosome segment, deletion specifically of the *TBX1* transcription factor gene is probably the culprit lesion. TBX1 regulates neural crest migration, as well as the expansion of cardiac progenitors in the second heart field. Interestingly, deletions in this region are also associated with mental illness, including schizophrenia.

Other important genetic causes of congenital heart disease include chromosomal aneuploidies, particularly Turner syndrome (monosomy X) and trisomies 13, 18, and 21. Indeed, *the most common genetic cause of congenital heart disease is trisomy 21 (Down syndrome)*; roughly 40% of patients with Down syndrome have one or more heart defects, most often affecting structures derived from the second heart field (e.g., the atrioventricular septae). The mechanisms by which aneuploidy causes congenital heart disease likely involve the dysregulated expression of multiple genes.

Despite these genetic advances, our understanding of the mechanisms underlying congenital heart disease remains rudimentary. Most affected patients have no identifiable genetic risk, and even in those that do, the nature and severity of the defect are highly variable. Thus, *environmental factors*, alone or in combination with genetic factors, are also increasingly implicated in congenital heart disease. Examples include congenital rubella infection, gestational diabetes, and teratogen exposure (including some therapeutic drugs). Nutritional factors may also influence risk. For instance, folate supplementation during early pregnancy may reduce congenital heart disease risk.

Clinical Features. Most of the various structural anomalies in congenital heart disease can be organized into three major categories:

- Malformations causing a *left-to-right shunt*
- Malformations causing a *right-to-left shunt*
- Malformations causing an *obstruction*

A *shunt* is an abnormal communication between chambers or blood vessels. Abnormal channels permit blood flow down pressure gradients from the left (systemic) side to the right (pulmonary) side of the circulation or vice versa. When blood from the right side of the circulation flows directly into the left side *(right-to-left shunt)*, hypoxemia and *cyanosis* (a dusky blueness of the skin and mucous membranes) result because the pulmonary circulation is bypassed and poorly oxygenated venous blood shunts directly into the systemic arterial supply. In addition, right-to-left shunts can allow emboli from the peripheral veins to bypass the lungs and directly enter the systemic circulation *(paradoxical embolism)*. Severe, long-standing cyanosis also causes a peculiar distal blunting and enlargement ("clubbing") of the tips of the fingers and toes (called *hypertrophic osteoarthropathy*), as well as *polycythemia*. The most important causes of right-to-left shunts are Tetralogy of Fallot, transposition of the great arteries, persistent truncus arteriosus, tricuspid atresia, and total anomalous pulmonary venous connection.

In contrast, *left-to-right shunts* (e.g., ASD, VSD, and patent ductus arteriosus [PDA]) increase pulmonary blood flow, but are not *initially* associated with cyanosis. However, left-to-right shunts chronically elevate both volume and pressure in the normally low-pressure, low-resistance pulmonary circulation. To maintain relatively normal distal pulmonary capillary and venous pressures, the muscular pulmonary arteries (<1 mm in diameter) initially respond by undergoing medial hypertrophy and vasoconstriction. However, prolonged pulmonary arterial vasoconstriction stimulates the development of irreversible obstructive intimal lesions analogous to the arteriolar changes seen in systemic hypertension; pulmonary arteries can even develop frank atherosclerotic lesions (Chapter 11). The right ventricle also responds to the pulmonary vascular changes by undergoing progressive right ventricular hypertrophy. Eventually, pulmonary vascular resistance approaches systemic levels, and the original left-to-right shunt becomes a right-to-left shunt that introduces poorly oxygenated blood into the systemic circulation *(Eisenmenger syndrome)*.

Once irreversible pulmonary hypertension develops, the structural defects of congenital heart disease are considered irreparable; subsequent right heart failure can lead to the patient's death. This provides the rationale for early intervention to close significant left-to-right shunts.

Obstructive congenital heart disease occurs when there is abnormal narrowing of chambers, valves, or blood vessels; these include coarctation of the aorta, aortic valvular stenosis, and pulmonary valvular stenosis. A complete obstruction is called an *atresia*. In some disorders (e.g., Tetralogy of Fallot [TOF]), an obstruction (pulmonary stenosis) and a shunt (right-to-left through a VSD) are both present.

The altered hemodynamics of congenital heart disease usually cause cardiac dilation or hypertrophy (or both). However, some defects induce a decrease in the volume and muscle mass of a cardiac chamber; this is called *hypoplasia* if it occurs before birth and *atrophy* if it develops postnatally.

Left-to-Right Shunts

Left-to-right shunts are the most common congenital heart disease; these include ASD, VSD, and PDA as shown in