predispose to thrombus formation. The risk of such complications necessitates long-term anticoagulation in all individuals with mechanical valves, with the attendant risk of hemorrhagic stroke or other forms of serious bleeding.

- *Structural deterioration* rarely causes failure of any of the mechanical valves in current use. However, virtually all bioprostheses eventually become incompetent due to calcification and/or tearing (see Fig. 12.27B).
- *Infective endocarditis* is a potentially serious complication of any valve replacement. The vegetations of prosthetic valve endocarditis are usually located at the prosthesis-tissue interface, and they often cause the formation of a ring abscess, which can eventually lead to a paravalvular regurgitant blood leak. In addition, vegetations may directly involve the tissue of bioprosthetic valvular cusps.
- *Other complications* include paravalvular leak due to inadequate healing, obstruction due to overgrowth of fibrous tissue during healing, valve-orifice disproportion—where the effective valve area is too small for the needs of the patient, leading to a relative stenosis—or intravascular hemolysis due to high shear forces.

### KEY CONCEPTS

#### VALVULAR HEART DISEASE

- Valve pathology can lead to occlusion (stenosis) and/or regurgitation (insufficiency); acquired aortic and mitral valve stenoses account for approximately two-thirds of all valve disease; much of the remainder is mitral regurgitation.
- Valve calcification is a degenerative process that typically results in stenosis.
- Abnormal matrix synthesis and turnover result in myxomatous degeneration and insufficiency.
- Inflammatory valve diseases lead to postinflammatory scarring. RHD results from anti-streptococcal antibodies and T cells that cross-react with cardiac tissues; it most commonly affects the mitral valve and is responsible for 99% of acquired mitral stenoses.
- IE can be aggressive and rapidly destroy normal valves (acute IE), or can be indolent and minimally destructive of previously abnormal valves (subacute IE). Systemic embolization can produce septic infarcts.
- NBTE occurs on previously normal valves due to hypercoagulable states; embolization is an important complication.
- Mechanical prosthetic valves have thrombotic or hemorrhagic complications related to the nonlaminar flow of blood and the need for chronic anticoagulation. Bioprosthetic valves are nonviable and are therefore susceptible to long-term calcification and/or degeneration with tearing. Both types of valves have an increased risk of developing endocarditis relative to native valves.

## CARDIOMYOPATHIES

The term cardiomyopathy (literally, heart muscle disease) has been historically applied to any cardiac dysfunction. Technically, that is not incorrect; the major heart disease categories already discussed—ischemic, valvular, hypertensive, or congenital—do cause "heart muscle disease." However, these major categories of cardiac diseases cause heart failure as predictable secondary consequences of other forms of cardiac dysfunctions—e.g., loss of pump function due to MI, or volume-pressure overloads due to an incompetent valve; in Table 12.11 these are referred to as secondary myocardial dysfunction. To distinguish these forms of "heart disease" from those associated with innate "primary" myocardial dysfunction, a more nuanced definition of cardiomyopathy has emerged. Thus, stimulated by the recognition of new phenotypes and the advent of more sophisticated molecular characterization—an expert panel has suggested: "Cardiomyopathies are a heterogeneous group of diseases of the myocardium associated with mechanical and/or electrical dysfunction that usually (but not invariably) exhibit inappropriate ventricular hypertrophy or dilatation and are due to a variety of causes that frequently are genetic. Cardiomyopathies either are confined to the heart or are part of generalized systemic disorders, often leading to cardiovascular death or progressive heart failure-related disability."

There are two major groups of cardiomyopathies:

- *Primary cardiomyopathies* involve predominantly the heart. They may be genetic or acquired (e.g., viral myocarditis, anthracycline cardiotoxic).
- *Secondary cardiomyopathies* have myocardial involvement as a component of a systemic or multiorgan disorder (e.g. hemochromatosis, amyloidosis).

**Table 12.11 Cardiomyopathies: Functional Patterns and Causes**

| Functional Pattern | Left Ventricular Ejection Fraction[a] | Mechanisms of Heart Failure | Causes | Secondary Myocardial Dysfunction (Mimicking Cardiomyopathy) |
|---|---|---|---|---|
| Dilated | <40% | Impairment of contractility (systolic dysfunction) | Genetic; alcohol; peripartum; myocarditis; hemochromatosis; chronic anemia; anthracycline medications; sarcoidosis; idiopathic | Ischemic heart disease; valvular heart disease; hypertensive heart disease; congenital heart disease |
| Hypertrophic | 50%–80% | Impairment of compliance (diastolic dysfunction) | Genetic; Friedreich ataxia; storage diseases; infants of diabetic mothers | Hypertensive heart disease; aortic stenosis |
| Restrictive | 45%–90% | Impairment of compliance (diastolic dysfunction) | Amyloidosis; radiation-induced fibrosis; idiopathic | Pericardial constriction |

[a]Range of normal values is approximately 50% to 65%.

A major advance in our understanding of the pathogenesis of cardiomyopathies stems from the accelerating identification of underlying genetic causes, including mutations in myocardial proteins involved in energy generation, contraction, cell-to-cell contacts, or connecting cytoskeleton to the extracellular matrix. These, in turn, lead to abnormal contraction or relaxation, or to dysregulated ion transport that can cause arrhythmias.

Cardiomyopathies can be classified according to a variety of criteria, including the underlying genetic basis of dysfunction; we have already discussed a number of the arrhythmia-inducing channelopathies. Here, we will confine our discussion to disorders that produce anatomic abnormalities falling into one of three distinct pathologic patterns (Fig. 12.28 and Table 12.11):

- *Dilated cardiomyopathy (DCM)* (including arrhythmogenic cardiomyopathy)
- *Hypertrophic cardiomyopathy*
- *Restrictive cardiomyopathy*

Among the three major patterns, DCM is most common (90% of cases), and restrictive cardiomyopathy is the least frequent. Within each pattern, there is a spectrum of clinical severity, and in some cases clinical features overlap among the groups. In addition, each of these patterns is associated with a specific identifiable cause or idiopathic; although many cases of DCM were previously labeled "idiopathic," the majority of these can now be assigned a genetic, toxic, or infectious etiology (Tables 12.11 and 12.12).

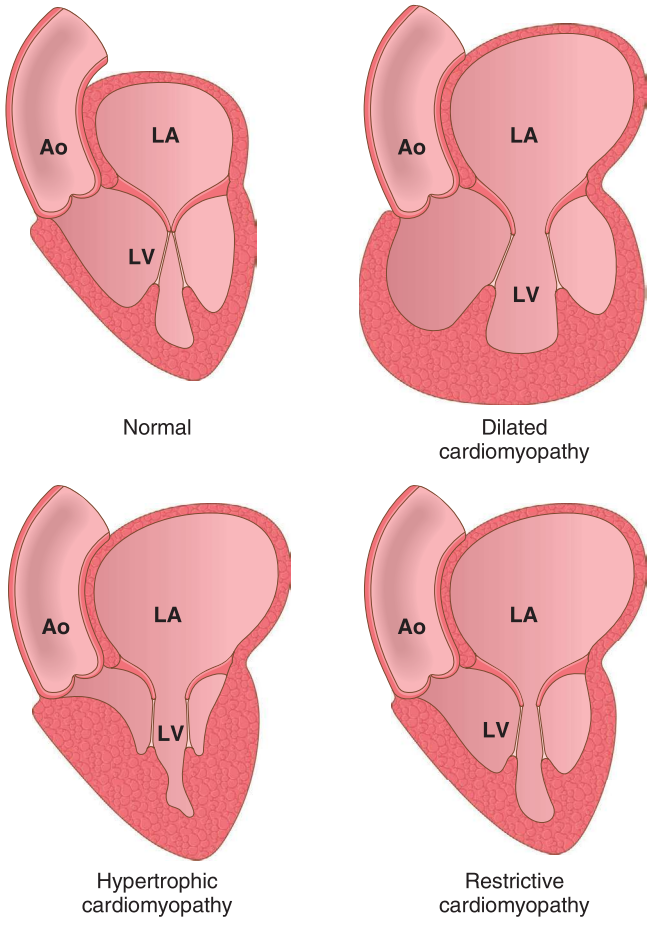


**Figure 12.28** The three major morphologic patterns of cardiomyopathy. Dilated cardiomyopathy leads primarily to systolic dysfunction, whereas restrictive and hypertrophic cardiomyopathies result in diastolic dysfunction. Note the changes in atrial and/or ventricular wall thickness. *Ao*, Aorta; *LA*, left atrium; *LV*, left ventricle.

**Table 12.12 Conditions Associated With Heart Muscle Diseases**

| |
|---|
| **Cardiac Infections** |
| Viruses |
| Chlamydia |
| Rickettsia |
| Bacteria |
| Fungi |
| Protozoa |
| **Toxins** |
| Alcohol |
| Cobalt |
| Catecholamines |
| Carbon monoxide |
| Lithium |
| Hydrocarbons |
| Arsenic |
| Cyclophosphamide |
| Doxorubicin (Adriamycin) and daunorubicin |
| **Metabolic** |
| Hyperthyroidism |
| Hypothyroidism |
| Hyperkalemia |
| Hypokalemia |
| Nutritional deficiency (protein, thiamine, other avitaminoses) |
| Hemochromatosis |
| **Neuromuscular Disease** |
| Friedreich ataxia |
| Muscular dystrophy |
| Congenital atrophies |
| **Storage Disorders and Other Depositions** |
| Hunter-Hurler syndrome |
| Glycogen storage disease |
| Fabry disease |
| Amyloidosis |
| **Infiltrative** |
| Leukemia |
| Carcinomatosis |
| Sarcoidosis |
| Radiation-induced fibrosis |
| **Immunologic** |
| Myocarditis (several forms) |
| Posttransplant rejection |

## Dilated Cardiomyopathy (DCM)

**DCM is characterized morphologically and functionally by progressive cardiac dilation and contractile (systolic) dysfunction, usually with concomitant hypertrophy.** Many cases are familial, but the DCM phenotype can result from diverse causes, both primary and secondary.

### Pathogenesis

Several different pathways can lead to DCM (Fig. 12.29). Identifying which may be causal in any given case is often

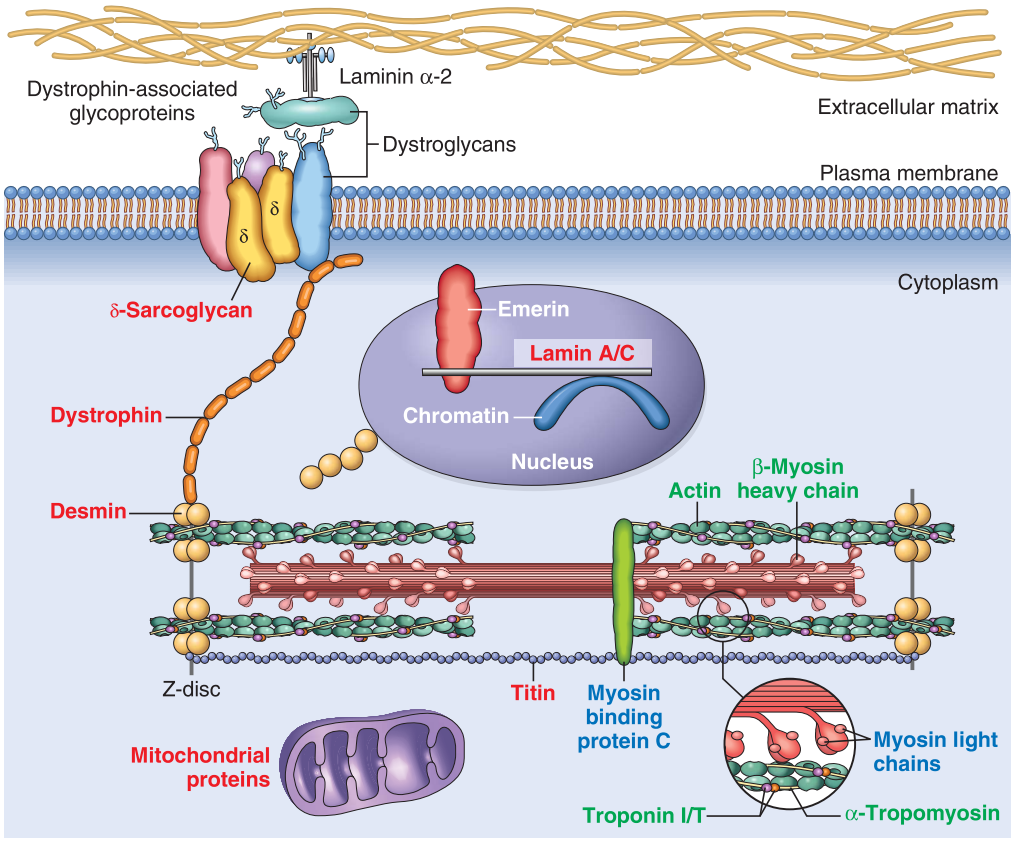


**Figure 12.29** Schematic of a myocyte, showing key proteins mutated in dilated cardiomyopathy *(red labels)*, hypertrophic cardiomyopathy *(blue labels)*, or both *(green labels)*. Mutations in titin (the largest known human protein at approximately 30,000 amino acids) account for approximately 20% of all dilated cardiomyopathy. Titin spans the sarcomere and connects the Z and M bands, thereby limiting the passive range of motion of the sarcomere as it is stretched. Titin also functions like a molecular spring, with domains that unfold when the protein is stretched and refold when the tension is removed, thereby affecting the passive elasticity of striated muscle.

frustrating, because diagnosis is only made after the patient has developed end-stage heart failure; very simply, the heart is nonspecifically dilated and poorly contractile. The clinical evaluation at that point is done to exclude ischemic, valvular, hypertensive, or congenital causes; once they have been ruled out, a diagnosis of primary dilated cardiomyopathy can be suggested. Although an exhaustive evaluation may not be able to pinpoint a specific etiology ("idiopathic DCM"), familial (genetic) forms of DCM are increasingly recognized, and the final pathology can also result from a host of myocardial insults:

- *Genetic Influences.* DCM is probably familial in up to 50% of cases, caused by mutations in a diverse group of more than 20 genes encoding proteins involved in the cytoskeleton, sarcolemma, and nuclear envelope (e.g., lamin A/C). In particular, truncation mutations in *TTN*, a gene that encodes titin (so-called because it is the largest protein expressed in humans), may account for approximately 10% to 20% of all cases of DCM (Fig. 12.30). In the genetic forms of DCM, autosomal dominant inheritance is the predominant pattern, although there is often variable penetrance even within the same families, suggesting that the progression to DCM can be multifactorial.

  X-linked, autosomal recessive, and mitochondrial inheritance of DCM are less common. In some families, mitochondrial gene deletions affect oxidative phosphorylation; in others, there are mutations in genes encoding enzymes involved in fatty acid β-oxidation. Mitochondrial defects typically manifest in the pediatric population, whereas X-linked DCM typically presents after puberty and into early adulthood. X-linked cardiomyopathy can also be associated with mutations affecting the membrane-associated dystrophin protein that couples cytoskeleton to the extracellular matrix (recall that dystrophin is mutated in the most common skeletal myopathies, Duchenne and Becker muscular dystrophies; Chapter 27); some dystrophin gene mutations have DCM as the primary clinical feature. Interestingly, and probably resulting from the common developmental origin of contractile myocytes and conduction elements, congenital abnormalities of conduction may also be associated with DCM.
- *Myocarditis.* Sequential endomyocardial biopsies have documented progression from myocarditis to DCM. In other studies, the detection of the genetic fingerprints of coxsackie B and other viruses within myocardium of patients with DCM suggests that viral myocarditis can be causal (see later discussion).
- *Alcohol and other toxins.* Alcohol abuse is strongly associated with the development of DCM, raising the possibility that ethanol toxicity (Chapter 9) or a secondary nutritional disturbance can underlie myocardial injury. Alcohol or its metabolites (especially acetaldehyde) have a direct toxic effect on the myocardium. Moreover, chronic alcoholism may be associated with thiamine deficiency,

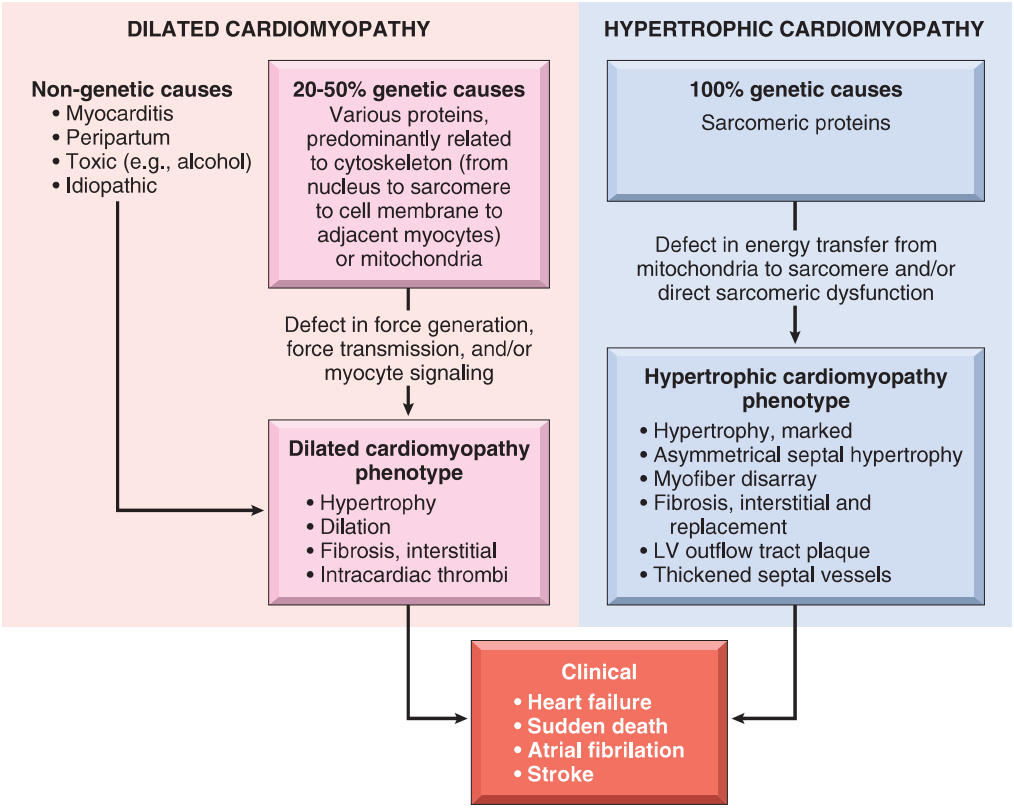


**Figure 12.30** Causes and consequences of dilated and hypertrophic cardiomyopathy. Some dilated cardiomyopathies and virtually all hypertrophic cardiomyopathies are genetic in origin. The genetic causes of dilated cardiomyopathy involve mutations in any of a wide range of genes. They encode proteins predominantly of the cytoskeleton, but also the sarcomere, mitochondria, and nuclear envelope. In contrast, all of the mutated genes that cause hypertrophic cardiomyopathy encode proteins of the sarcomere. Although these two forms of cardiomyopathy differ greatly in subcellular basis and morphologic phenotypes, they share a common set of clinical complications. *LV,* left ventricle.

which can lead to beriberi heart disease (a form of DCM). Nevertheless, no morphologic features serve to distinguish alcoholic cardiomyopathy from DCM of other causes. Cobalt is an example of a heavy metal with cardiotoxicity and has caused DCM in the setting of inadvertent tainting (e.g., in beer production). Cardiotoxic drugs used for chemotherapy (discussed later) are also important causes of DCM.

- *Childbirth.* Peripartum cardiomyopathy can occur late in pregnancy or up to 5 months postpartum; the mechanism is probably multifactorial, including contributions from genetic susceptibility, pregnancy-associated hypertension, volume overload, nutritional deficiency, and/or other subtle metabolic derangements. In mouse models, DCM can also be induced by increased levels of circulating antiangiogenic mediators including vascular endothelial growth factor inhibitors (e.g., sFLT1, as occurs with preeclampsia) or antiangiogenic cleavage products of the hormone prolactin (which rises late in pregnancy). Thus, in pregnant women with a particular genetic predisposition, elevated antiangiogenic molecules can potentially lead to a microvascular angiogenic imbalance (microvascular loss in excess of angiogenesis), ultimately resulting in functional ischemic injury.
- *Iron overload* in the heart can result from either hereditary hemochromatosis (Chapter 18) or from multiple transfusions. DCM is the most common manifestation of such iron excess, and it may be caused by interference with metal-dependent enzyme systems or by injury from iron-mediated production of reactive oxygen species.
- *Supraphysiologic stress* can also result in DCM. This can happen with persistent tachycardia, hyperthyroidism, or even during development, as in the fetuses of insulin-dependent diabetic mothers. Excess catecholamines, in particular, cause multifocal myocardial contraction band necrosis that can eventually progress to DCM. This can happen in individuals with pheochromocytomas, tumors that elaborate epinephrine (Chapter 24); use of cocaine or vasopressor agents such as dopamine can have similar consequences. Such "catecholamine effect" also occurs in the setting of intense autonomic stimulation, for example, secondary to intracranial lesions or emotional duress. *Takotsubo cardiomyopathy* is an entity characterized by left ventricular contractile dysfunction after extreme psychological stress (thus also called broken heart syndrome); affected myocardium may be stunned or show contraction band necrosis. For unclear reasons, the left ventricular apex is most often affected, leading to "apical ballooning" that resembles a *takotsubo,* Japanese for "fishing pot for trapping octopus" (hence, the name). The mechanism of catecholamine cardiotoxicity is uncertain but likely relates either to direct myocyte toxicity due to calcium overload or to focal vasoconstriction in the coronary arterial macro- or microcirculation in the face of an increased heart rate.

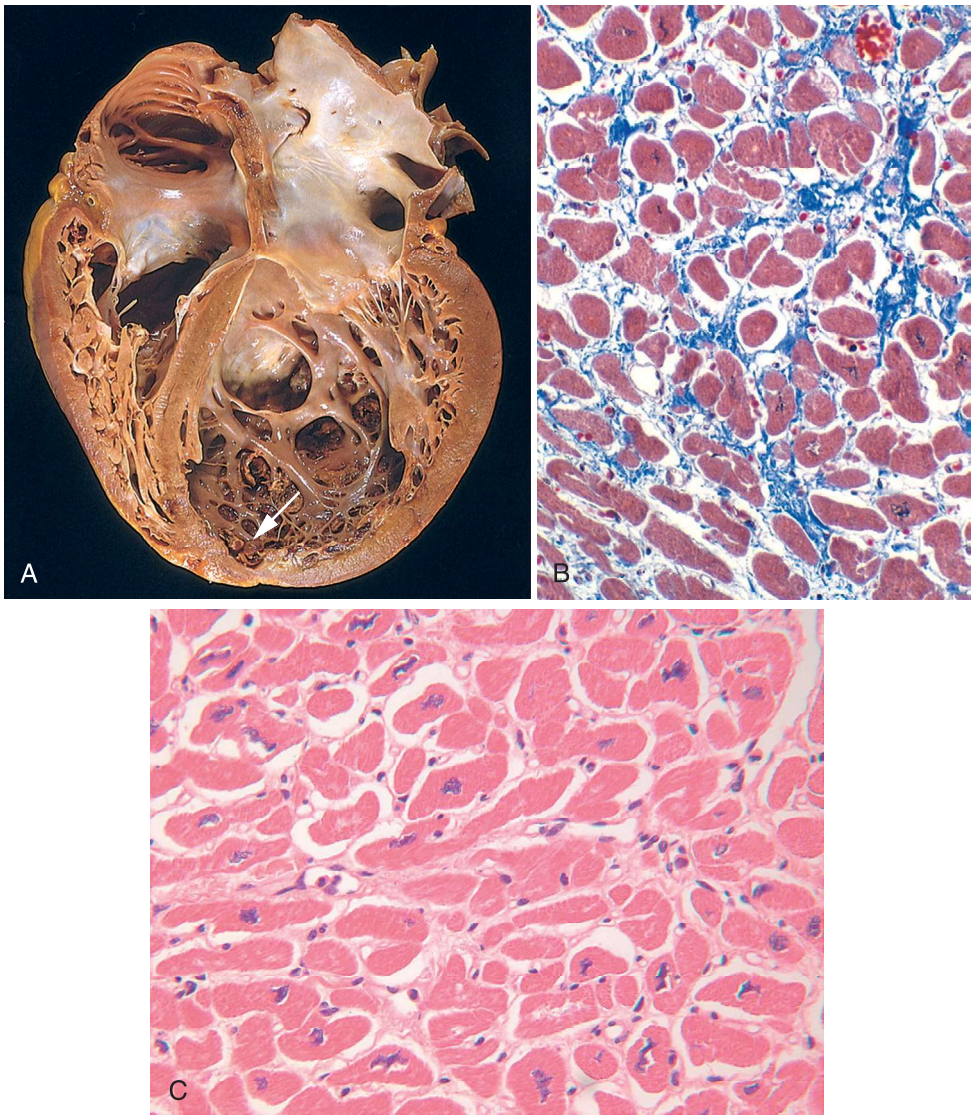


**Figure 12.31** Dilated cardiomyopathy. (A) Four-chamber dilatation and hypertrophy are evident. There is a mural thrombus *(arrow)* at the apex of the left ventricle (seen on the right in this apical four-chamber view). The coronary arteries were patent. (B) Histologic section demonstrating variable myocyte hypertrophy and interstitial fibrosis (collagen is highlighted as blue in this Masson trichrome stain). (C) Histologic appearance of the enlarged, bizarre, hyperchromatic nuclei (likened to "Ninja stars") that are seen in greater numbers in patients with dilated cardiomyopathy caused by titin-truncating mutations.

## MORPHOLOGY

In the DCM phenotype, the heart is typically enlarged, heavy (often weighing two to three times normal), and flabby, due to dilation of all chambers (Fig. 12.31). Mural thrombi can result from relative stasis of the blood in poorly contractile chambers and may be a source of thromboemboli. To be considered DCM, the heart should have no primary valvular alterations; if mitral (or tricuspid) regurgitation is present, it results from left (or right) ventricular chamber dilation (functional regurgitation). Either the coronary arteries are free from significant narrowing or the obstructions present are insufficient to explain the degree of cardiac dysfunction.

**The histologic abnormalities in DCM are nonspecific and usually do not point to a specific etiology** (see Fig. 12.31B). Moreover, the severity of morphologic changes may not reflect either the degree of dysfunction or the patient's prognosis.

Interstitial and endocardial fibrosis of variable degree is present, and small subendocardial scars may replace individual cells or groups of cells, probably reflecting healing of previous ischemic necrosis of myocytes caused by hypertrophy-induced imbalance between perfusion and demand. Most muscle cells are hypertrophied with enlarged nuclei, but some are attenuated, stretched, and irregular. In DCM caused by truncating mutations in the titin gene, myocytes may exhibit hyperchromatic, highly distorted "Ninja star"-like nuclei (see Fig. 12.31C); although these can be a nonspecific finding, identifying them in greater than or equal to 5% of myocytes is highly suggestive of a titin-truncation mutation.

### Clinical Features

The fundamental defect in DCM is ineffective contraction. Thus, in end-stage DCM, the cardiac ejection fraction typically is less than 25% (normal is 50% to 65%). DCM can

occur at any age, including in childhood, but it most commonly affects individuals between 20 and 50 years of age. It presents with slowly progressive signs and symptoms of CHF including dyspnea, easy fatigability, and poor exertional capacity. Secondary mitral regurgitation and abnormal cardiac rhythms are common, and embolism from intracardiac thrombi can occur. Death usually results from progressive cardiac failure or arrhythmia, and it can occur suddenly. Although the annual mortality is high (10% to 50%), some severely affected patients respond well to pharmacologic or electrical resynchronization (biventricular pacing) therapies. Cardiac transplantation is also increasingly performed, and long-term ventricular assist can be beneficial. Interestingly, in some patients, relatively short-term mechanical cardiac support can induce durable improvement of cardiac function.

## Arrhythmogenic Cardiomyopathy

**Arrhythmogenic right ventricular cardiomyopathy is an autosomal dominant disorder that classically manifests with right-sided heart failure and rhythm disturbances, which can cause sudden cardiac death.** Left-sided involvement with left-sided heart failure can also occur. Classically, the right ventricular wall is severely attenuated due to loss of myocytes, accompanied by massive fatty infiltration and focal fibrosis (Fig. 12.32). Although mononuclear inflammation may be present around degenerating cardiomyocytes, arrhythmogenic cardiomyopathy is not considered an inflammatory cardiomyopathy. Classical arrhythmogenic cardiomyopathy has an autosomal dominant inheritance with a variable penetrance; many of the causal mutations involve genes encoding desmosomal junctional proteins at the intercalated disk (e.g., plakoglobin) as well as proteins that interact with the desmosome (e.g., the intermediate filament desmin). Naxos syndrome is a disorder characterized by arrhythmogenic cardiomyopathy and hyperkeratosis of plantar and palmar skin surfaces, and is also associated with plakoglobin mutations.

## Hypertrophic Cardiomyopathy

**Hypertrophic cardiomyopathy (HCM) is a common (1 in 500 prevalence), clinically heterogeneous, genetic disorder characterized by myocardial hypertrophy, poorly compliant left ventricular myocardium leading to abnormal diastolic filling, and (in about one-third of cases) intermittent ventricular outflow obstruction.** It is the leading cause of left ventricular hypertrophy unexplained by other clinical or pathologic causes. The heart is thick-walled, heavy, and hypercontracting, in striking contrast to the flabby, hypocontracting heart of DCM. HCM causes primarily diastolic dysfunction; systolic function is usually preserved. The two most common diseases that must be distinguished clinically from HCM are deposition diseases (e.g., amyloidosis, Fabry disease) and hypertensive heart disease coupled with age-related subaortic septal hypertrophy (see earlier discussion under Hypertensive Heart Disease in this chapter). Occasionally, valvular or congenital subvalvular aortic stenosis can also mimic HCM.

### Pathogenesis

In most cases, the pattern of transmission is autosomal dominant with variable penetrance. **HCM is most commonly caused by mutations in any one of several genes that encode sarcomeric proteins;** there are more than 400 different known mutations in nine different genes, most being missense mutations. Mutations causing HCM are found most commonly in the genes encoding myosin-binding protein C *(MYBP-C)* or β-myosin heavy chain *(β-MHC/MYH7),* followed by the genes coding for cardiac TnI, TnT, and α-tropomyosin; overall, these account for 70% to 80% of all cases. Different affected families can have distinct mutations involving the same protein; thus, over 50 different *β-MHC* mutations can cause HCM. The prognosis of HCM varies widely and correlates strongly with specific mutations.

As mentioned earlier, HCM is a disease caused by mutations in proteins of the sarcomere. Although the precise mechanism by which these mutations cause HCM is unclear,

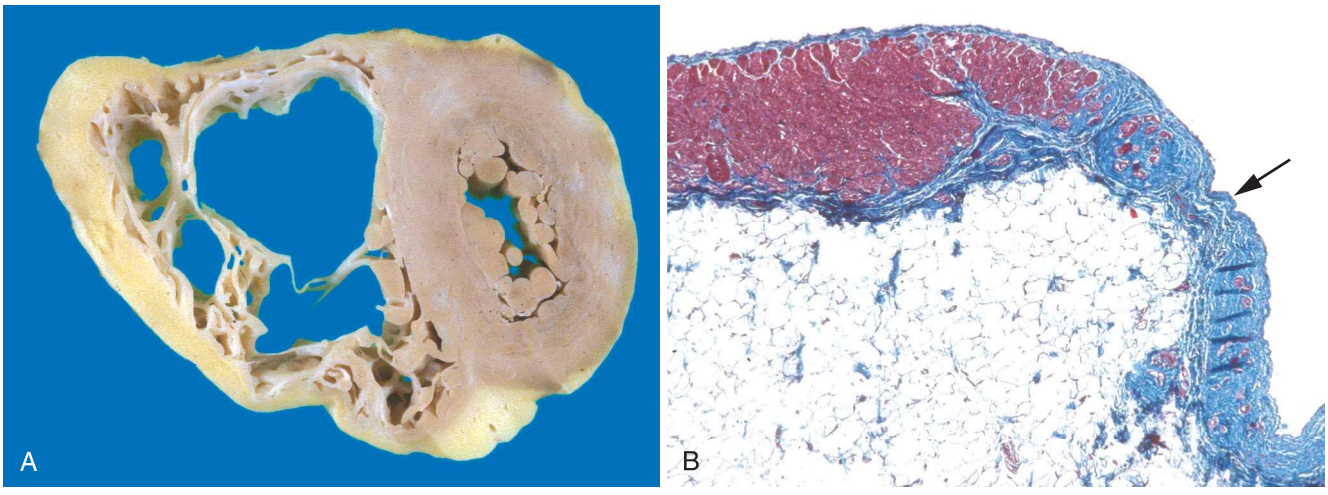


**Figure 12.32** Arrhythmogenic cardiomyopathy. (A) Gross photograph, showing dilation of the right ventricle and near-transmural replacement of the right ventricular free-wall by fat and fibrosis. The left ventricle has a virtually normal configuration in this case, but can also be involved by the disease process. (B) Histologic section of the right ventricular free wall, demonstrating replacement of myocardium *(red)* by fibrosis *(blue, arrow)* and fat (Masson trichrome stain).

current evidence suggests that it arises from defective energy transfer from its source of generation (mitochondria) to its site of use (sarcomeres). In contrast, DCM is mostly associated with abnormalities of cytoskeletal proteins (see Fig. 12.30) and can be conceptualized as a disease of abnormal force generation, force transmission, or myocyte signaling. To complicate matters, mutations in certain genes (highlighted in Fig. 12.30) can give rise to either HCM or DCM, depending on the site and nature of the mutation. Genetic testing in cardiomyopathies is still hindered by the large number of genetic "variants of unknown significance," so genetic screening of family members of affected probands must be interpreted within the clinical context.

## MORPHOLOGY

The essential feature of HCM is **massive myocardial hypertrophy, usually without ventricular dilation** (Fig. 12.33). The classic pattern involves disproportionate thickening of the ventricular septum relative to the left ventricle free wall, termed **asymmetric septal hypertrophy.** In about 10% of cases, the hypertrophy is concentric and symmetrical. On longitudinal sectioning, the normally round-to-ovoid left ventricular cavity may be compressed into a "banana-like" configuration by bulging of the ventricular septum into the lumen (see Fig. 12.33A). Although marked hypertrophy can involve the entire septum, it is usually most prominent in the subaortic region; the left ventricular outflow tract often exhibits a fibrous endocardial plaque and thickening of the anterior mitral leaflet. Both findings result from contact of the anterior mitral leaflet with the septum during ventricular systole; they correlate with the echocardiographic "systolic anterior motion" of the anterior leaflet, with functional left ventricular outflow tract obstruction during systole.

The most important histologic features of HCM myocardium are (1) massive myocyte hypertrophy, with transverse myocyte diameters frequently greater than 40 μm (normal is approximately 15 μm); (2) haphazard disarray of bundles of myocytes, individual myocytes, and contractile elements in sarcomeres within cells (termed ***myofiber disarray***); (3) fibrotic narrowing of small intramural arteries; and (4) interstitial and replacement fibrosis (see Fig. 12.33B).

## Clinical Features

HCM is characterized by reduced stroke volume due to impaired diastolic filling—a consequence of a reduced chamber size, as well as the reduced compliance of the massively hypertrophied left ventricle. In addition, approximately 25% of patients with HCM have dynamic obstruction to the left ventricular outflow as the anterior mitral leaflet moves toward the ventricular septum during systole. The compromised cardiac output in conjunction with a secondary increase in pulmonary venous pressure explains the exertional dyspnea seen in these patients. Auscultation discloses a harsh systolic ejection murmur caused by the ventricular outflow obstruction. Because of the massive hypertrophy, high left ventricular chamber pressure, and frequently thick-walled intramural arteries, focal myocardial ischemia commonly results, even in the absence of concomitant epicardial CAD. Major clinical problems in HCM are atrial fibrillation, mural thrombus formation leading to embolization and possible stroke, intractable cardiac failure, ventricular arrhythmias, and, not infrequently, sudden death, especially with certain mutations. Indeed, HCM is one of the most common causes of sudden, otherwise unexplained death in young athletes.

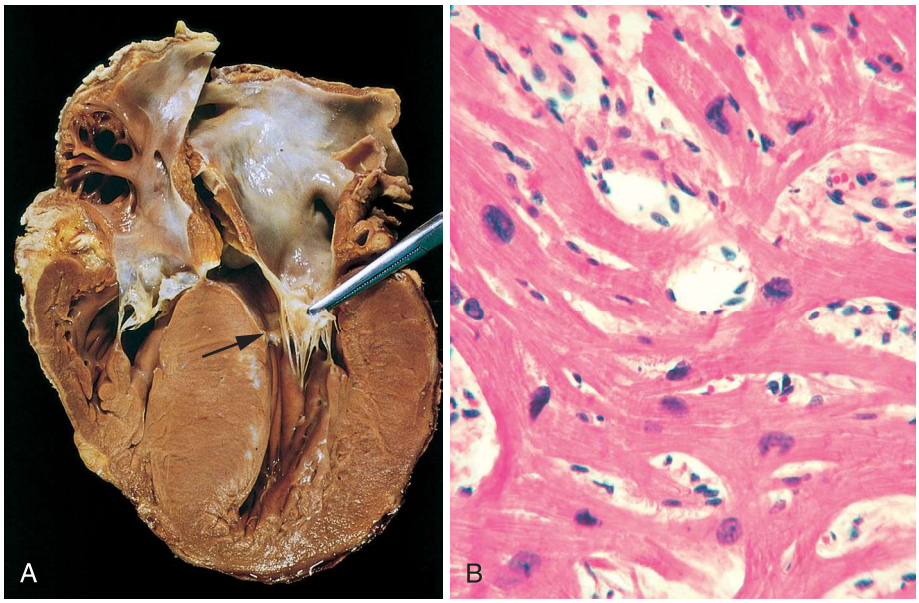


**Figure 12.33** Hypertrophic cardiomyopathy with asymmetric septal hypertrophy. (A) The septal muscle bulges into the left ventricular outflow tract, and the left atrium is enlarged. The anterior mitral leaflet has been reflected away from the septum to reveal a fibrous endocardial plaque *(arrow)* (see text). (B) Histologic appearance demonstrating myocyte disarray, extreme hypertrophy, and exaggerated myocyte branching, as well as the characteristic interstitial fibrosis.

The natural history of HCM is highly variable. Most patients can be helped by pharmacologic intervention (e.g., β-adrenergic blockade) to decrease heart rate and contractility. Implantable cardioverter defibrillators are warranted for HCM patients at risk for ventricular arrhythmias. Some benefit can also be gained by reducing the septal myocardial mass, thus relieving the outflow tract obstruction. This can be achieved either by surgical excision of muscle or by carefully controlled septal infarction through a catheter-based infusion of alcohol.

## Restrictive Cardiomyopathy

**Restrictive cardiomyopathy is characterized by a primary decrease in ventricular compliance, resulting in impaired ventricular diastolic filling.** Because the contractile (systolic) function of the left ventricle is usually unaffected, the functional abnormality can be confused with that of constrictive pericarditis or HCM. Restrictive cardiomyopathy can be idiopathic or associated with distinct disorders that affect the myocardium, principally amyloidosis (described later), sarcoidosis, radiation-induced fibrosis, metastatic tumors, or the accumulation of metabolites from inborn errors of metabolism.

The gross morphologic features are somewhat nonspecific; although bi-atrial dilation is commonly observed due to restricted ventricular filling and pressure overloads, the ventricles are of approximately normal size (or slightly enlarged), the cavities are not dilated, and the myocardium is largely unremarkable. Microscopically, there can be patchy or diffuse interstitial fibrosis, varying from minimal to extensive. Cardiac imaging is increasingly used to characterize myocardial "infiltrates," and endomyocardial biopsy can occasionally suggest a specific etiology.

Three other restrictive conditions merit brief mention.

- *Endomyocardial fibrosis* is principally a disease of children and young adults in Africa and other tropical areas, characterized by fibrosis of the ventricular endocardium and subendocardium that extends from the apex upward, often eventually involving the tricuspid and mitral valves. The fibrous tissue markedly diminishes the volume and compliance of affected chambers and so causes a restrictive functional defect. Ventricular mural thrombi sometimes develop, and indeed much of the endocardial fibrosis may result from thrombus organization. Endomyocardial fibrosis is linked to nutritional deficiencies and/or inflammation related to parasitic infections (e.g., hypereosinophilia); worldwide, it is the most common form of restrictive cardiomyopathy.
- *Loeffler endomyocarditis* also results in endomyocardial fibrosis, typically with large mural thrombi, and an overall morphology similar to the tropical disease. However, in addition to the cardiac changes, there is often a peripheral eosinophilia and eosinophilic infiltrates in multiple organs, including the heart. The release of toxic products of eosinophils, especially major basic protein, probably causes endomyocardial necrosis, followed by scarring of the necrotic area, layering of the endocardium by thrombus, and finally organization of the thrombus. Many patients with Loeffler endomyocarditis have a myeloproliferative disorder associated with chromosomal rearrangements involving either the platelet-derived growth factor receptor *(PDGFR)-α* or *-β* genes (Chapter 13). These rearrangements produce fusion genes that encode constitutively active PDGFR tyrosine kinases. Treatment of such patients with tyrosine kinase inhibitors has resulted in hematologic remissions and resolution of the endomyocardial lesions.
- *Endocardial fibroelastosis* is an uncommon heart disease characterized by fibroelastic thickening that typically involves the left ventricular endocardium. It is most common in the first 2 years of life; in one-third of cases, it is accompanied by aortic valve obstruction or other congenital cardiac anomalies. Endocardial fibroelastosis may actually represent a common morphologic end-point of several different insults including viral infections (e.g., intrauterine exposure to mumps) or mutations in the gene for tafazzin, which affects mitochondrial inner membrane integrity. Diffuse involvement may be responsible for rapid and progressive cardiac decompensation and death.

### *Amyloidosis*

Amyloidosis is an important form of restrictive cardiomyopathy resulting from the extracellular accumulation of protein fibrils that form insoluble β-pleated sheets (Chapter 6). Cardiac amyloidosis can appear as a consequence of systemic amyloidosis (e.g., due to myeloma or inflammation-associated amyloid) or can be restricted to the heart, particularly in the aged (senile cardiac amyloidosis). Cardiac amyloidosis characteristically occurs in individuals 70 years of age and older, and it has a far better prognosis than systemic amyloidosis; the amyloid deposits are largely composed of transthyretin, a normal serum protein synthesized in the liver that transports thyroxine and retinol-binding protein. Mutant forms of transthyretin can accelerate the cardiac amyloid deposition; 4% of African Americans have a transthyretin mutation substituting isoleucine for valine at position 122 that produces a particularly amyloidogenic protein that is responsible for autosomal dominant familial transthyretin amyloidosis.

Cardiac amyloidosis most frequently produces a restrictive cardiomyopathy, but it can also be asymptomatic, manifest as dilation or arrhythmias, or mimic ischemic or valvular disease. The varied presentations depend on the predominant location of the deposits, for example, interstitium, conduction system, coronary vasculature, or valves.

#### MORPHOLOGY

In cardiac amyloidosis, the heart varies in consistency from normal to firm and rubbery. The chambers are usually of normal size but can be dilated and have thickened walls. Small, semitranslucent nodules resembling drips of wax may be seen on the atrial endocardial surface, particularly on the left. Histologically, hyaline eosinophilic deposits of amyloid may be found in the interstitium, conduction tissue, valves, endocardium, pericardium, and small intramural coronary arteries (Fig. 12.34). Amyloid accumulations can be distinguished from other deposits by special stains such as Congo red or sulfated Alcian blue; the former produces classic apple-green birefringence when viewed under polarized light (see Fig. 12.34B). Intramural arteries and arterioles may have sufficient amyloid in their walls to compress and occlude their lumens, inducing myocardial ischemia ("small-vessel disease").

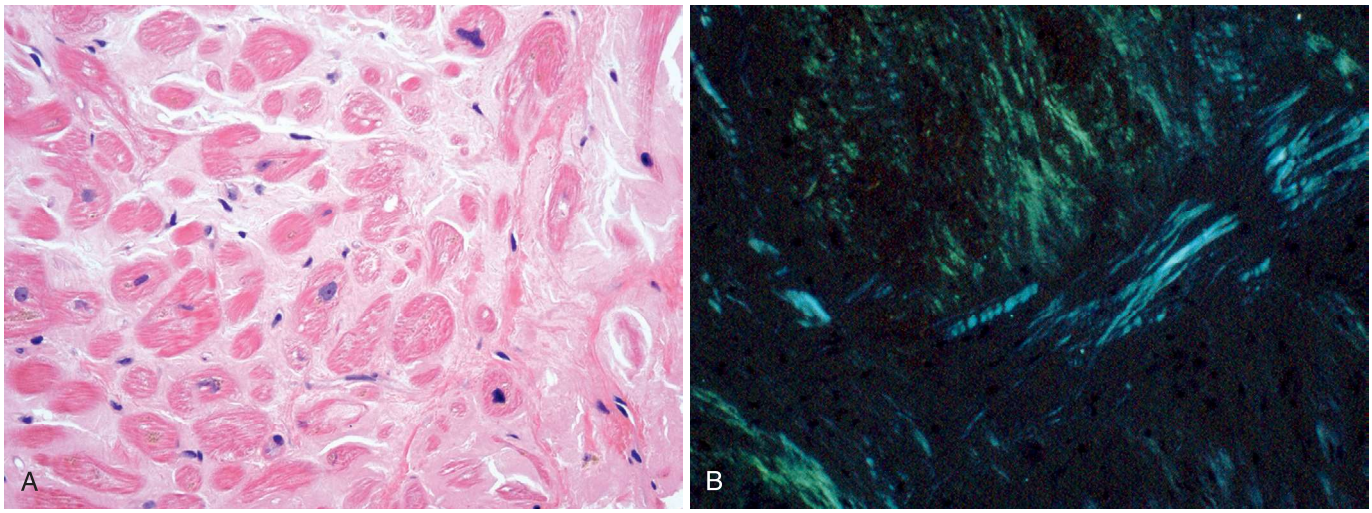


**Figure 12.34** Cardiac amyloidosis. (A) Hematoxylin and eosin stain, showing amyloid appearing as amorphous pink material around myocytes. (B) Congo red stain viewed under polarized light, in which amyloid shows characteristic apple-green birefringence (compared with collagen, pale blue).

## Myocarditis

**Myocarditis is a diverse group of pathologic entities in which infectious microorganisms and/or a primary inflammatory process cause myocardial injury.** Myocarditis should be distinguished from conditions such as IHD, in which myocardial inflammation is secondary to other causes.

### Pathogenesis

In the United States, viral infections are the most common cause of myocarditis. Coxsackie viruses A and B and other enteroviruses probably account for most of the cases. Other less common etiologic agents include cytomegalovirus, HIV, and influenza (Table 12.13). In some (but not all) cases, the offending agent can be implicated by serologic studies or by identifying viral nucleic acid sequences in myocardial biopsies. Depending on the pathogen and the host, viruses can potentially cause myocardial injury either as a direct cytopathic effect, or by eliciting a destructive immune response. Inflammatory cytokines produced in response to myocardial injury can also cause myocardial dysfunction that is out of proportion to the degree of actual myocyte damage.

Nonviral agents are also important causes of infectious myocarditis, particularly the protozoan *Trypanosoma cruzi,* the agent of Chagas disease. Chagas disease is endemic in some regions of South America, with myocardial involvement in most infected individuals. About 10% of patients die during an acute attack; others develop a chronic immune-mediated myocarditis that may progress to cardiac insufficiency in 10 to 20 years. Trichinosis *(Trichinella spiralis)* is the most common helminthic disease associated with myocarditis. Parasitic diseases, including toxoplasmosis, and bacterial infections such as Lyme disease and diphtheria, can also cause myocarditis. In the case of diphtheritic myocarditis, the myocardial injury is a consequence of diphtheria toxin release by *Corynebacterium diphtheriae* (Chapter 8). Myocarditis occurs in approximately 5% of patients with Lyme disease, a systemic illness caused by the bacterial spirochete *Borrelia burgdorferi* (Chapter 8); it manifests primarily as a self-limited conduction system disorder that may require a temporary pacemaker. AIDS-associated myocarditis may reflect inflammation and myocyte damage without a clear etiologic agent, or a myocarditis attributable directly to HIV or to an opportunistic pathogen.

There are also noninfectious causes of myocarditis. Broadly speaking they are either immunologically mediated (hypersensitivity myocarditis) or idiopathic conditions with distinctive morphology (giant cell myocarditis) suspected to be of immunologic origin (see Table 12.13). More recently, immune checkpoint inhibitors administered for treatment of cancer have occasionally led to an (often fatal) lymphocytic myocarditis.

**Table 12.13 Major Causes of Myocarditis**

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| **Infections** |
| Viruses (e.g., coxsackievirus, echovirus, influenza, HIV, cytomegalovirus) |
| Chlamydiae (e.g., *Chlamydophila psittaci*) |
| Rickettsiae (e.g., *Rickettsia typhi*, typhus fever) |
| Bacteria (e.g., *Corynebacterium diphtheriae*, *Neisseria meningococcus*, *Borrelia* (Lyme disease) |
| Fungi (e.g., *Candida*) |
| Protozoa (e.g., *Trypanosoma cruzi* [Chagas disease], toxoplasmosis) |
| Helminths (e.g., trichinosis) |
| **Immune-Mediated Reactions** |
| Postviral |
| Poststreptococcal (rheumatic fever) |
| Systemic lupus erythematosus |
| Drug hypersensitivity (e.g., methyldopa, sulfonamides) |
| Transplant rejection |
| Immune checkpoint inhibitor therapies |
| **Unknown** |
| Sarcoidosis |
| Giant cell myocarditis |

*HIV,* Human immunodeficiency virus.