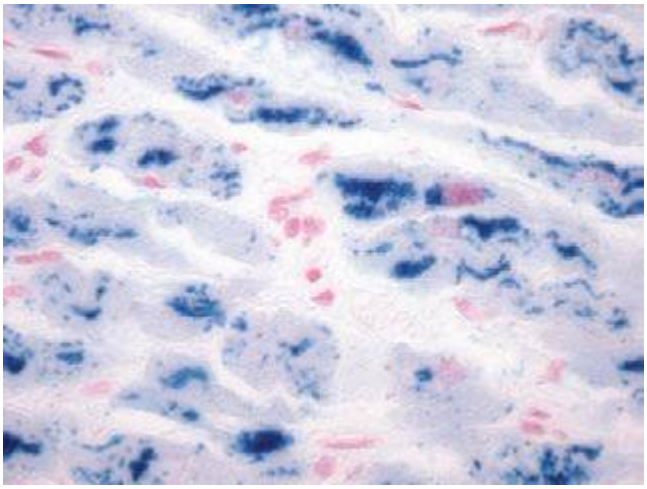


FIGURE 287-9 Hemochromatosis. Microscopic image of an endomyocardial biopsy showing extensive iron deposition within the cardiac myocytes with the Prussian blue stain (400× original magnification). *(Image courtesy of Robert Padera, MD, PhD, Department of Pathology, Brigham and Women's Hospital, Boston.)*

hypomagnesemia rarely becomes sufficiently profound to cause clinical cardiomyopathy.

Hemochromatosis is variably classified as a metabolic or storage disease (Chap. 428). It is included among the causes of restrictive cardiomyopathy, but the clinical presentation is often that of a dilated cardiomyopathy. The autosomal recessive form is related to the *HFE* gene. With up to 10% of the population heterozygous for one mutation, the clinical prevalence might be as high as 1 in 500. The lower observed rates highlight the limited penetrance of the disease, suggesting the role of additional genetic and environmental factors for clinical expression. Hemochromatosis can also be acquired from iron overload due to hemolytic anemia and transfusions. Excess iron is deposited in the perinuclear compartment of cardiomyocytes, with resulting disruption of intracellular architecture and mitochondrial function. Diagnosis is easily made from measurement of serum iron and transferrin saturation, with a threshold of >60% for men and >45–50% for women. MRI can help to quantitate iron stores in the liver and heart, and endomyocardial biopsy tissue can be stained for iron (Fig. 287-9), which is particularly important if the patient has another cause for cardiomyopathy. If diagnosed early, hemochromatosis can often be managed by repeated phlebotomy to remove iron. For more severe iron overload, iron chelation therapy with desferrioxamine (deferoxamine) or deferasirox can help to improve cardiac function if myocyte loss and replacement fibrosis are not too severe.

Inborn disorders of metabolism occasionally present with dilated cardiomyopathy, although they are most often associated with restrictive cardiomyopathy (Table 287-4).

FAMILIAL DILATED CARDIOMYOPATHY

The genetic basis for cardiomyopathy is discussed in the section, "Genetic Etiologies of Cardiomyopathy." The recognized frequency of familial involvement in dilated cardiomyopathy has increased to over 30%. Mutations in *TTN*, encoding the giant sarcomeric protein titin, are the most common cause of dilated cardiomyopathy, accounting for up to 25% of familial disease. On average, men with *TTN* mutations develop cardiomyopathy a decade before women, without distinctive clinical features. Mutations in thick and thin filament genes account for ~8% of dilated cardiomyopathy and may manifest in early childhood.

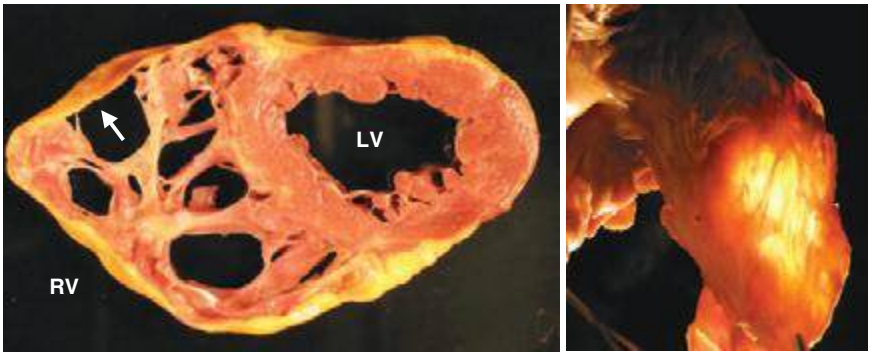
The most recognizable familial cardiomyopathy syndromes with extracardiac manifestations are the *muscular dystrophies*. Both Duchenne's and the milder Becker's dystrophy result from abnormalities in the X-linked dystrophin gene of the sarcolemmal membrane. Skeletal myopathy is present in multiple other genetic cardiomyopathies (Table 287-3), some of which are associated with creatine kinase elevations.

Families with a history of atrial arrhythmias, conduction system disease, and cardiomyopathy may have abnormalities of the nuclear membrane lamin proteins. While all dilated cardiomyopathies carry a risk of sudden death, a family history of cardiomyopathy with sudden death raises suspicion for a particularly arrhythmogenic mutation; affected family members may be considered for implantable defibrillators even before meeting the reduced ejection fraction threshold for primary prevention of sudden death.

A prominent family history of sudden death or ventricular tachycardia before clinical cardiomyopathy suggests genetic defects in the desmosomal proteins (Fig. 287-10). Originally described as affecting the right ventricle (arrhythmogenic right ventricular dysplasia [ARVD]), this disorder (arrhythmogenic ventricular dysplasia) can affect either or both ventricles. Patients often present first with ventricular tachycardia. Genetic defects in proteins of the desmosomal complex disrupt myocyte junctions and adhesions, leading to replacement of myocardium by deposits of fat. Thin ventricular walls may be recognized on echocardiography but are better visualized on MRI. Because desmosomes are also important for elasticity of hair and skin, some of the defective desmosomal proteins are associated with striking "woolly hair" and thickened skin on the palms and soles. Implantable defibrillators are usually indicated to prevent sudden death. There is variable progression to right, left, or biventricular failure.

Left ventricular noncompaction is a condition of unknown prevalence that is increasingly revealed with the refinement of imaging techniques. The diagnostic criteria include the presence of multiple trabeculations in the left ventricle distal to the papillary muscles, creating a "spongy" appearance of the apex. Noncompaction has been associated with multiple genetic variants in the sarcomeric and other genes, such as *TAZ* (encoding tafazzin). The diagnosis may be made incidentally or in patients previously diagnosed with cardiomyopathy, in whom the criteria for noncompaction may appear and resolve with changing left ventricular size and function. The three cardinal clinical features are ventricular arrhythmias, embolic events, and heart failure. Treatment generally includes anticoagulation and early consideration for an implantable defibrillator, in addition to neurohormonal antagonists as indicated by stage of disease.

Some families inherit a susceptibility to viral-induced myocarditis. This propensity may relate to abnormalities in cell surface receptors, such as the coxsackie-adenovirus receptor, that bind viral proteins.



A *B*

FIGURE 287-10 Arrhythmogenic right ventricular dysplasia. *A.* Cross-sectional slice of a pathology specimen removed at transplantation, showing severe dysplasia of the right ventricle (RV) with extensive fatty replacement of right ventricular myocardium. ***B.*** The remarkably thin right ventricular free wall is revealed by transillumination. LV, left ventricle. *(Images courtesy of Gayle Winters, MD, and Richard Mitchell, MD, PhD, Division of Pathology, Brigham and Women's Hospital, Boston.)*