Some may have partial homology with viral proteins such that an autoimmune response is triggered against the myocardium.

Prognosis and therapy of familial dilated cardiomyopathy are dictated primarily by the stage of clinical disease and the risk for sudden death. In some cases, the familial etiology facilitates prognostic decisions, particularly regarding the likelihood of recovery after a new diagnosis, which is unlikely for familial disease. The rate of progression of disease, once manifest, is, to some extent, heritable, although marked variation can be seen. However, there have been cases of remarkable clinical remission after acute presentation, likely after a reversible additional insult, such as prolonged tachycardia or infective myocarditis.

TAKOTSUBO CARDIOMYOPATHY

The apical ballooning syndrome, or stress-induced cardiomyopathy, occurs typically in older women after sudden intense emotional or physical stress. The ventricle shows global ventricular dilation with basal contraction, forming the shape of the narrow-necked jar (*takotsubo*) used in Japan to trap octopi. Originally described in Japan, it is increasingly recognized elsewhere during emergency cardiac catheterization and intensive care unit admissions for noncardiac conditions. Presentations include pulmonary edema, hypotension, and chest pain with ECG changes mimicking an acute infarction. The left ventricular dysfunction extends beyond a specific coronary artery distribution and generally resolves within days to weeks. Animal models and ventricular biopsies suggest that this acute cardiomyopathy may result from intense sympathetic activation with heterogeneity of myocardial autonomic innervation, diffuse microvascular spasm, and/or direct catecholamine toxicity. Coronary angiography may be required to rule out acute coronary occlusion. No therapies have been proven beneficial, but reasonable strategies include nitrates for pulmonary edema, intraaortic balloon pump if needed for low output, combined alpha and beta blockers rather than selective beta blockade if hemodynamically stable, and magnesium for arrhythmias related to QT prolongation. Anticoagulation is generally withheld due to the occasional occurrence of ventricular rupture. While the prognosis is generally good, recurrences have been described in up to 10% of patients.

IDIOPATHIC DILATED CARDIOMYOPATHY

Idiopathic dilated cardiomyopathy is a diagnosis of exclusion, when all other known factors have been excluded. Approximately two-thirds of dilated cardiomyopathies are still labeled as idiopathic; however, a substantial proportion of these may reflect unrecognized genetic disease. Continued reconsideration of etiology during chronic heart failure management often reveals specific causes later in a patient's course.

OVERLAPPING TYPES OF CARDIOMYOPATHY

The limitations of our phenotypic classification are revealed through the multiple overlaps between the etiologies and presentations of the three types. Cardiomyopathy with reduced systolic function but without severe dilation can represent early dilated cardiomyopathy, "minimally dilated cardiomyopathy," or restrictive diseases without marked increases in ventricular wall thickness. For example, sarcoidosis and hemochromatosis can present as dilated or restrictive disease. Early stages of amyloidosis are often mistaken for hypertrophic cardiomyopathy. Progression of hypertrophic cardiomyopathy into a "burned-out" phase occurs occasionally, with decreased contractility and modest ventricular dilation. Overlaps are particularly common with the inherited metabolic disorders, which can present as any of the three major phenotypes (Fig. 287-4).

DISORDERS OF METABOLIC PATHWAYS

Multiple genetic disorders of metabolic pathways can cause myocardial disease, due to infiltration of abnormal products or cells containing them between the myocytes, and storage disease, due to their accumulation within cells (see HPIM 18e, Table 238-4, and 287-5). The restrictive phenotype is most common, but mildly dilated cardiomyopathy may occur. Hypertrophic cardiomyopathy may be mimicked by the myocardium thickened with these abnormal products causing "pseudohypertrophy." Most of these diseases are diagnosed during childhood.

TABLE 287-5 CAUSES OF RESTRICTIVE CARDIOMYOPATHIES

Infiltrative (Between Myocytes)
Amyloidosis
Primary (light chain amyloid)
Familial (abnormal transthyretin)[a]
Senile (normal transthyretin or atrial peptides)
Inherited metabolic defects[a]
Storage (Within Myocytes)
Hemochromatosis (iron)[a]
Inherited metabolic defects[a]
Fabry's disease
Glycogen storage disease (II, III)
Fibrotic
Radiation
Scleroderma
Endomyocardial
Possibly related fibrotic diseases
Tropical endomyocardial fibrosis
Hypereosinophilic syndrome (Löffler's endocarditis)
Carcinoid syndrome
Radiation
Drugs: e.g., serotonin, ergotamine
Overlap with Other Cardiomyopathies
Hypertrophic cardiomyopathy/"pseudohypertrophic"[a]
"Minimally dilated" cardiomyopathy
Early-stage dilated cardiomyopathy
Partial recovery from dilated cardiomyopathy
Sarcoidosis
Idiopathic[a]

[a]Can be familial.

Fabry's disease results from a deficiency of the lysosomal enzyme alpha-galactosidase A caused by one of more than 160 mutations. This disorder of glycosphingolipid metabolism is an X-linked recessive disorder that may also cause clinical disease in female carriers. Glycolipid accumulation may be limited to the cardiac tissues or may also involve the skin and kidney. Electron microscopy of endomyocardial biopsy tissue shows diagnostic vesicles containing concentric lamellar figures (Fig. 287-11). Diagnosis is crucial because enzyme replacement can reduce abnormal deposits and improve cardiac and clinical function. The magnitude of clinical impact has not been well-established for this therapy, which requires frequent infusions of the enzyme at a cost of over $100,000 a year. Enzyme replacement can also improve the course of Gaucher's disease, in which cerebroside-rich cells accumulate in multiple organs due to a deficiency of beta-glucosidase. Cerebroside-rich cells infiltrate the heart, which can also lead to a hemorrhagic pericardial effusion and valvular disease.

Glycogen storage diseases lead to accumulation of lysosomal storage products and intracellular glycogen accumulation, particularly with *glycogen storage disease type III,* due to a defective debranching enzyme. There are more than 10 types of *mucopolysaccharidoses,* in which autosomal dominant or X-linked deficiencies of lysosomal enzymes lead to the accumulation of glycosaminoglycans in the skeleton, nervous system, and occasionally the heart. With characteristic facies, short stature, and frequent cognitive impairment, most individuals are diagnosed early in childhood and die before adulthood.

Carnitine is an essential cofactor in long-chain fatty acid metabolism. Multiple defects have been described that lead to carnitine deficiency, causing intracellular lipid inclusions and restrictive or dilated cardiomyopathy, often presenting in children. Fatty acid oxidation requires many metabolic steps with specific enzymes that can be deficient, with complex interactions with carnitine. Depending on the defect, cardiac and skeletal myopathy can be ameliorated with replacement of fatty acid intermediates and carnitine.