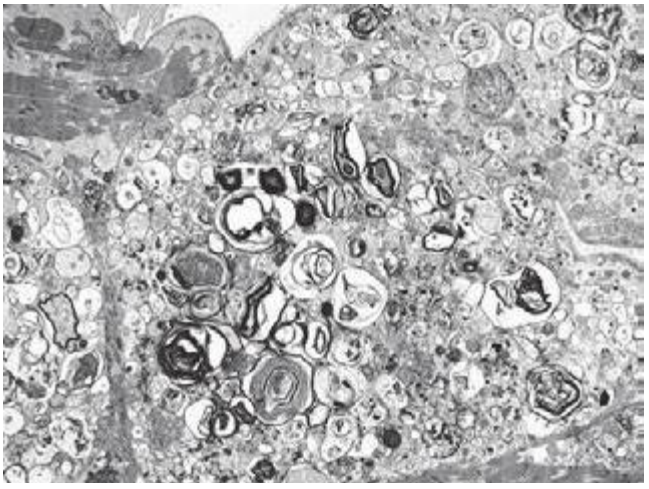

FIGURE 287-11 Fabry's disease. Transmission electron micrograph of a right ventricular endomyocardial biopsy specimen at high magnification showing the characteristic concentric lamellar inclusions of glycosphingolipids accumulating as a result of deficiency of the lysosomal enzyme alpha-galactosidase A. Image taken at 15,000× original magnification. *(Image courtesy of Robert Padera, MD, PhD, Department of Pathology, Brigham and Women's Hospital, Boston.)*

Two monogenic metabolic cardiomyopathies have recently been described as causes of increased ventricular wall thickness without an increase of muscle subunits or an increase in contractility. Mutations in the gamma-2 regulatory subunit of the adenosine monophosphate (AMP)-activated protein kinase important for glucose metabolism (*PRKAG2*) have been associated with a high prevalence of conduction abnormalities, such as AV block and ventricular preexcitation (Wolff-Parkinson-White syndrome). Several defects have been reported in an X-linked lysosome-associated membrane protein (*LAMP2*). This defect can be maternally transmitted or sporadic and has occasionally been isolated to the heart, although it often leads to a syndrome of skeletal myopathy, mental retardation, and hepatic dysfunction referred to as *Danon's disease.* Extreme left ventricular hypertrophy appears early, often in childhood, and can progress rapidly to end-stage heart failure with low ejection fraction. Electron microscopy of these metabolic disorders shows that the myocytes are enlarged by multiple intracellular vacuoles of metabolic by-products.

RESTRICTIVE CARDIOMYOPATHY

The least common of the physiologic triad of cardiomyopathies is restrictive cardiomyopathy, which is dominated by abnormal diastolic function, often with mildly decreased contractility and ejection fraction (usually >30–50%). Both atria are enlarged, sometimes massively. Modest left ventricular dilation can be present, usually with an end-diastolic dimension <6 cm. End-diastolic pressures are elevated in both ventricles, with preservation of cardiac output until late in the disease. Subtle exercise intolerance is usually the first symptom but is often not recognized until after clinical presentation with congestive symptoms. The restrictive diseases often present with relatively more right-sided symptoms, such as edema, abdominal discomfort, and ascites, although filling pressures are elevated in both ventricles. The cardiac impulse is less displaced than in dilated cardiomyopathy and less dynamic than in hypertrophic cardiomyopathy. A fourth heart sound is more common than a third heart sound in sinus rhythm, but atrial fibrillation is common. Jugular venous pressures often show rapid Y descents and may increase during inspiration (positive Kussmaul's sign). Most restrictive cardiomyopathies are due to infiltration of abnormal substances between myocytes, storage of abnormal metabolic products within myocytes, or fibrotic injury (Table 287-5). The differential diagnosis should include constrictive pericardial disease, which may also be dominated by right-sided heart failure.

INFILTRATIVE DISEASE

Amyloidosis is the major cause of restrictive cardiomyopathy **(Figs. 287-12, 287-13, and 287-14)**. Several proteins can self-assemble to form the beta-sheets of amyloid proteins, which deposit with different consequences depending on the type of protein. The systemic amyloidoses are discussed in **Chap. 137**. In addition to cardiac infiltration, neurologic involvement occurs commonly with primary amyloidosis (immunoglobulin light chains) and with familial amyloidosis (genetic abnormalities of transthyretin). There are over 100 identified mutations in transthyretin on chromosome 13, among which the V122I transthyretin mutation has been identified in about 4% of African Americans and in 10% of African Americans with heart failure and may contribute importantly to heart failure in general in the elderly African-American population. Organ dysfunction was previously attributed solely to physical disruption from the infiltrating amyloid fibrils, but newer information suggests additional direct toxicity from the immunoglobulin light chain and abnormal transthyretin protein aggregates themselves. In senile amyloidosis, there is abnormal accumulation of normal transthyretin or natriuretic peptide folding, detected in 10% of people over 80 years and half of those over 90 years but often without apparent clinical disease. Men show a greater burden of amyloid deposition and 20-fold greater likelihood of clinical disease with senile amyloidosis. The aging of the population will soon render senile amyloidosis the most common of the amyloidoses.

Cardiac amyloid is classically suspected from thickened ventricular walls with an ECG that shows low voltage. However, low voltage is not always present and is less common in familial or senile amyloidosis than in primary AL amyloidosis. A characteristic refractile brightness in the septum on echocardiography is suggestive of the diagnosis, but neither sensitive nor specific. Both atria are dilated, often dramatically, and diastolic dysfunction may be more obvious than in left ventricular hypertrophy from other causes. Amyloid infiltration can also be detected with gadolinium enhancement in MRI.

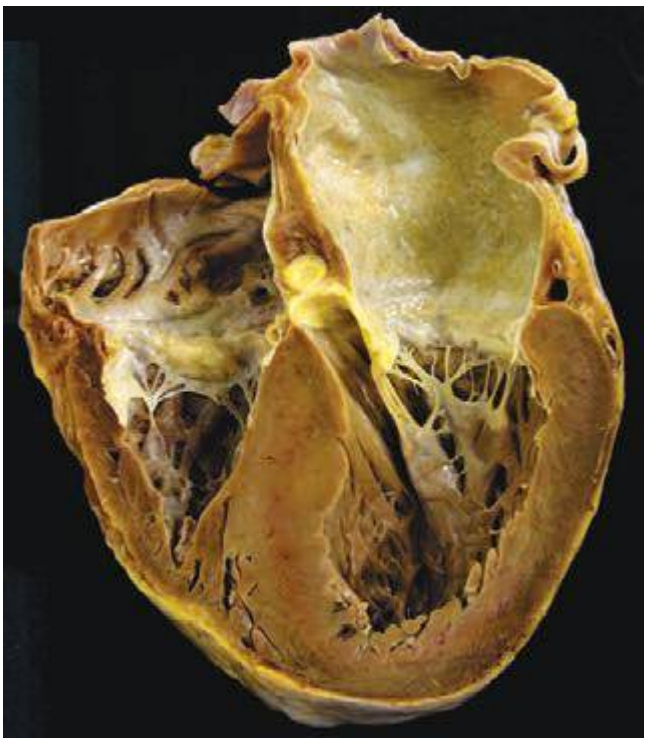

FIGURE 287-12 Restrictive cardiomyopathy—amyloidosis. Gross specimen of a heart with amyloidosis. The heart is firm and rubbery with a waxy cut surface. The atria are markedly dilated, and the left atrial endocardium, normally smooth, has yellow-brown amyloid deposits that give texture to the surface. *(Image courtesy of Robert Padera, MD, PhD, Department of Pathology, Brigham and Women's Hospital, Boston.)*