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 *hyper*contracting, in striking contrast to the flabby, *hypo*contracting 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). 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 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 gene encoding β-myosin heavy chain (β-MHC), followed by the genes coding for cardiac TnT, α-tropomyosin, and myosin-binding protein C (MYBP-C); overall, these account for 70% to 80% of all cases. Different affected families may have distinct mutations involving the same protein. For example, approximately 50 different mutations of β-MHC are known to cause HCM. The prognosis of HCM varies widely and correlates strongly with specific mutations. Although it is clear that these genetic defects are critical to the etiology of HCM, the sequence of events leading from mutations to disease is still poorly understood.

As discussed above, HCM is a disease caused by mutations in proteins of the sarcomere. Although such sarcomeric alterations have been thought to be pathologic on the basis of abnormal cardiac contraction causing a secondary compensatory hypertrophy, newer evidence suggests that HCM may instead arise from defective energy transfer from its source of generation (mitochondria) to its site of use (sarcomeres). In addition, the interstitial fibrosis in HCM probably occurs secondary to exaggerated responses of the myocardial fibroblasts to the primary myocardial dysfunction. In contrast, DCM is mostly associated with abnormalities of cytoskeletal proteins (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, depicted in Figure 12-30, can give rise to either HCM or DCM, depending on the site and nature of the mutation.

MORPHOLOGY

The essential feature of HCM is **massive myocardial hypertrophy, usually without ventricular dilation** (Fig. 12-34). The classic pattern involves disproportionate thickening of the ventricular septum relative to the left ventricle free wall (with a ratio of septum to free wall greater than 3:1), 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 (Fig. 12-34*A*). 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 associated with 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 mid-systole.

The most important histologic features of HCM myocardium are (1) massive myocyte hypertrophy, with transverse myocyte diameters frequently greater than 40 μm (normal, approximately 15 μm); (2) haphazard disarray of bundles of myocytes, individual myocytes, and contractile elements in sarcomeres within cells (termed **myofiber disarray**); and (3) interstitial and replacement fibrosis (Fig. 12-34*B*).

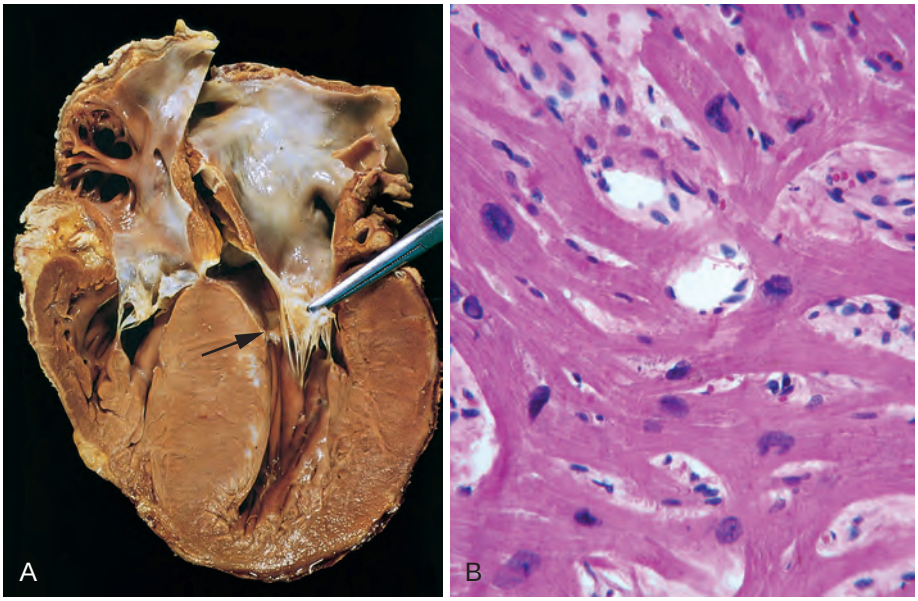

Figure 12-34 Hypertrophic cardiomyopathy with asymmetric septal hypertrophy. **A,** The septal muscle bulges into the left ventricular outflow tract, and the left atrium is enlarged. The anterior mitral leaflet has been reflected away from the septum to reveal a fibrous endocardial plaque *(arrow)* (see text). **B,** Histologic appearance demonstrating myocyte disarray, extreme hypertrophy, and exaggerated myocyte branching, as well as the characteristic interstitial fibrosis (collagen is blue in this Masson trichrome stain).