fused commissure that produces a conjoined cusp that is generally twice the size of the nonconjoined cusp. BAVs may also become incompetent as a result of aortic dilation, cusp prolapse, or infective endocarditis. The mitral valve is generally normal in patients with a congenitally bicuspid aortic valve.

Although BAV is usually asymptomatic early in life, late complications include aortic stenosis or regurgitation, infective endocarditis, and aortic dilation and/or dissection. In particular, BAVs are predisposed to progressive calcification, similar to that occurring in aortic valves with initially normal anatomy (Fig. 12-21*B*); calcified BAV comprise approximately 50% of cases of aortic stenosis in adults. Structural abnormalities of the aortic wall also commonly accompany BAV, even when the valve is hemodynamically normal, and this may potentiate aortic dilation or aortic dissection (see later).

Mitral Annular Calcification

As opposed to the predominantly cuspal involvement in aortic valve calcification, degenerative calcific deposits in the mitral valve typically develop in the fibrous annulus. Grossly, these appear as irregular, stony hard, occasionally ulcerated nodules (2 to 5 mm in thickness) at the base of the leaflets (Fig. 12-21*C, D*). Mitral annular calcification usually does not affect valvular function. However, in exceptional cases it can lead to:

- Regurgitation by interfering with physiologic contraction of the valve ring
- Stenosis by impairing opening of the mitral leaflets
- Arrhythmias and occasionally sudden death by penetration of calcium deposits to a depth sufficient to impinge on the atrioventricular conduction system.

Because calcific nodules may also provide a site for thrombus formation, patients with mitral annular calcification have an increased risk of embolic stroke, and the calcific nodules can become a nidus for infective endocarditis. Heavy calcific deposits are sometimes visualized on echocardiography or seen as distinctive, ringlike opacities on chest radiographs. Mitral annular calcification is most common in women older than age 60 and individuals with mitral valve prolapse (see later).

Mitral Valve Prolapse (Myxomatous Degeneration of the Mitral Valve)

In mitral valve prolapse (MVP), one or both mitral valve leaflets are "floppy" and *prolapse*, or balloon back, into the left atrium during systole. MVP affects approximately 2-3% of adults in the United States with an approximate 7:1 female-to-male ratio; it is most often an incidental finding on physical examination, but in a small minority of affected individuals may lead to serious complications.

Pathogenesis. The etiologic basis for the changes that weaken the valve leaflets and associated structures is unknown in most cases. Uncommonly, MVP is associated with heritable disorders of connective tissue including Marfan syndrome, caused by fibrillin-1 (*FBN-1*) mutations (Chapter 5). Fibrillin-1 defects alter cell-matrix interactions and dysregulate TGF-β signaling. Interestingly, mice with mutated *FBN-1* develop a form of mitral valve prolapse that is prevented by TGF-β inhibitors, indicating that excess TGF-β activity can cause the characteristic structural laxity and myxomatous changes. Whether similar mechanisms contribute to sporadic MVP is unknown. Genetic linkage analyses have also mapped inherited forms of MVP to loci involved in the remodeling of valvular extracellular matrix and cell:cell adhesion.

MORPHOLOGY

The characteristic anatomic change in MVP is interchordal ballooning (hooding) of the mitral leaflets or portions thereof (Fig. 12-22*A-C*). The affected leaflets are often enlarged, redundant, thick, and rubbery. The associated tendinous cords may be elongated, thinned, or even ruptured, and the annulus may be dilated. The tricuspid, aortic, or pulmonary valves may also be affected. The key histologic change in the tissue is marked thickening of the spongiosa layer with deposition of mucoid (myxomatous) material, called **myxomatous degeneration**; there is also attenuation of the collagenous fibrosa layer of the valve, on which the structural integrity of the leaflet depends (Fig. 12-22*E*). Secondary changes reflect the stresses and tissue injury incident to the billowing leaflets: (1) fibrous thickening of the valve leaflets, particularly where they rub against each other; (2) linear fibrous thickening of the left ventricular endocardial surface where the abnormally long cords snap or rub against it; (3) thickening of the mural endocardium of the left ventricle or atrium as a consequence of friction-induced injury induced by the prolapsing, hypermobile leaflets; (4) thrombi on the atrial surfaces of the leaflets or the atrial walls (Fig. 12-22*B*); and (5) focal calcifications at the base of the posterior mitral leaflet (Fig. 12-22*C*). Notably, mitral valve myxomatous degeneration can also occur as a secondary consequence of regurgitation of other etiologies (e.g., ischemic dysfunction).

Clinical Features. Most individuals diagnosed with MVP are asymptomatic; in such cases, the condition is discovered incidentally by auscultation of mid-systolic clicks, sometimes followed by a mid to late systolic murmur. The diagnosis is confirmed by echocardiography. A minority of patients have chest pain mimicking angina (although not exertional in nature), and a subset has dyspnea, presumably related to valvular insufficiency. Although the great majority of persons with MVP have no untoward effects, approximately 3% develop one of four serious complications: (1) infective endocarditis; (2) mitral insufficiency, sometimes with chordal rupture; (3) stroke or other systemic infarct, resulting from embolism of leaflet thrombi; or (4) arrhythmias, both ventricular and atrial. Rarely, MVP is the only finding in sudden cardiac death.

The risk of serious complications is very low in MVP discovered incidentally in young asymptomatic patients; the risk is higher for men, older patients, and those with arrhythmias or mitral regurgitation. Valve repair or replacement surgery can be done for symptomatic patients or those with increased risk for significant complications; indeed, in the United States, MVP is the most common cause for mitral valve surgery.