mechanical stress than normal tricuspid valves, which may explain their accelerated stenosis. The chronic progressive injury leads to valvular degeneration and incites the deposition of hydroxyapatite (the same calcium salt found in bone). Although this model provides a good starting point for understanding calcific degeneration, it is increasingly clear that the valve injury of calcific aortic stenosis differs in some important respects from atherosclerosis. Most notably, the abnormal valves contain cells resembling osteoblasts that synthesize bone matrix proteins and promote the deposition of calcium salts. Moreover, interventions that improve atherosclerotic risk (e.g., statins), do not appear to significantly impact valvular calcific degeneration.

MORPHOLOGY

The gross morphologic hallmark of nonrheumatic, calcific aortic stenosis (involving either tricuspid or bicuspid valves) is mounded calcified masses within the aortic cusps that ultimately protrude through the outflow surfaces into the sinuses of Valsalva, and prevent cuspal opening. The free edges of the cusps are usually not involved (Fig. 12-21*A*). Microscopically, the layered architecture of the valve is largely preserved. The calcific process begins in the valvular fibrosa on the outflow surface of the valve, at the points of maximal cusp flexion (near the margins of attachment). Inflammation is variable, and metaplastic bone (and even bone marrow) may be seen. In aortic stenosis, the functional valve area is decreased by large nodular calcific deposits that can eventually cause measurable outflow obstruction; this subjects the left ventricular myocardium to progressively increasing pressure overload.

In contrast to rheumatic (and congenital) aortic stenosis (see Fig. 12-23*E*), commissural fusion is not usually seen. The mitral valve is generally normal, although some patients may have direct extension of aortic valve calcific deposits onto the anterior mitral leaflet. In contrast, virtually all patients with rheumatic aortic stenosis also have concomitant and characteristic structural abnormalities of the mitral valve (see later discussion).

Clinical Features. In calcific aortic stenosis (superimposed on a previously normal or bicuspid aortic valve), the obstruction to left ventricular outflow leads to gradual narrowing of the valve orifice (valve area approximately 0.5 to 1 cm^2 in severe aortic stenosis; normal approximately 4 cm^2) and an increasing pressure gradient across the calcified valve, reaching 75 to 100 mm Hg in severe cases. Left ventricular pressures rise to 200 mm Hg or more in such instances, producing concentric left ventricular (pressure overload) hypertrophy. The hypertrophied myocardium tends to be ischemic (as a result of diminished microcirculatory perfusion, often complicated by coronary atherosclerosis), and angina pectoris may occur. Both systolic and diastolic myocardial function may be impaired; eventually, cardiac decompensation and CHF can ensue. The onset of symptoms (angina, CHF, or syncope) in aortic stenosis heralds cardiac decompensation and carries an extremely poor prognosis. If untreated, most patients with aortic stenosis will die within 5 years of developing angina, within 3 years of developing syncope, and within 2 years of CHF onset. Treatment requires surgical valve replacement, as medical therapy is ineffective in severe symptomatic aortic stenosis.

Calcific Stenosis of Congenitally Bicuspid Aortic Valve

Bicuspid aortic valve (BAV) is a developmental abnormality with prevalence in the population of approximately 1%. Some cases of BAV show familial clustering, often with associated aorta or left ventricular outflow tract malformations. While the heritability of BAV is well-established, and three loci on chromosomes 18q, 5q, and 13q have been identified in kindred studies, the specific genes that are responsible for the disorder remain largely unknown. Thus far, only loss-of-function mutations in *NOTCH1* (mapping to chromosome 9q34.3) have been specifically associated with BAV in a few families; tantalizingly, modulation of Notch activity in animal models also impacts valvular calcification.

In a congenitally bicuspid aortic valve, there are only two functional cusps, usually of unequal size, with the larger cusp having a midline *raphe*, resulting from incomplete commissural separation during development; less frequently the cusps are of equal size and the raphe is absent. The raphe is frequently a major site of calcific deposits. Once stenosis is present, the clinical course is similar to that described earlier for calcific aortic stenosis. Valves that become bicuspid because of an acquired deformity (e.g., rheumatic valve disease) have a

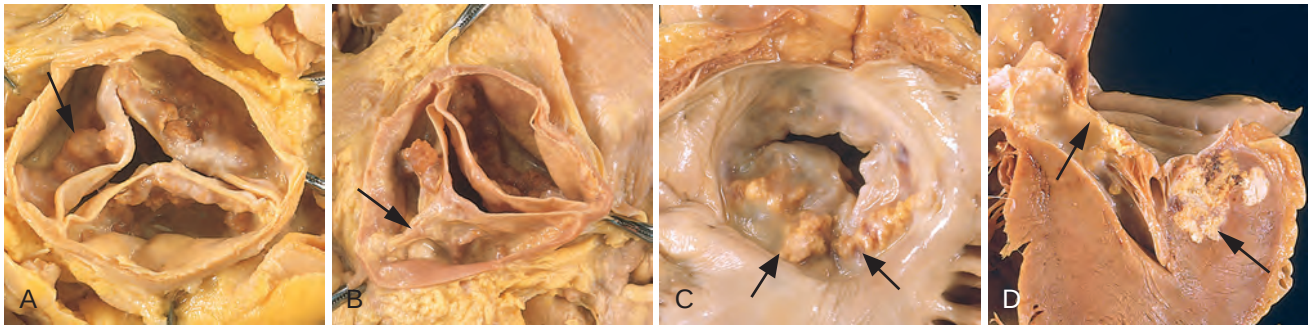

Figure 12-21 Calcific valvular degeneration. **A,** Calcific aortic stenosis of a previously normal valve (viewed from aortic aspect). Nodular masses of calcium are heaped up within the sinuses of Valsalva *(arrow).* Note that the commissures are not fused, as occurs with postrheumatic aortic valve stenosis (see Fig. 12-23*E*). **B,** Calcific aortic stenosis of a congenitally bicuspid valve. One cusp has a partial fusion at its center, called a *raphe (arrow)*. **C** and **D,** Mitral annular calcification, with calcific nodules at the base (attachment margin) of the anterior mitral leaflet *(arrows).* **C,** Left atrial view. **D,** Cut section of myocardium showing the lateral wall with dense calcification that extends into the underlying myocardium (*arrow*).