# 14 Valvular Heart Disease: Anatomic Abnormalities

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**Key Points**

- Floppy mitral valve is due to myxomatous degeneration and can occur as an isolated entity or as a component of Marfan's syndrome or other connective tissue dyscrasias.
- Endocrine and metabolic conditions producing valvular dysfunction include carcinoid heart disease, cardiac amyloidosis, ochronosis, mucopolysaccharidoses, lipid storage diseases, hyperlipidemias, and gout.
- Collagen vascular diseases that produce valvular heart disease include rheumatic valvulitis, rheumatoid valvulitis, lupus erythematosus valvulitis, and other related conditions. Postinflammatory valvular disease is manifested by fibrosis and commissural fusion leading to incompetence and stenosis.
- The most common congenital malformation of heart valves is the bicuspid aortic valve; these valves are prone to progressive fibrosis, calcification, and stenosis.
- Infective endocarditis can develop on previously diseased or normal valves and produce valvular incompetence and embolization of infected thrombi.
- Complications of prosthetic heart valves include thrombosis of mechanical valves and degeneration and calcification of bioprostheses.

## Floppy Valve (Myxomatous Degeneration) and Connective Tissue Dyscrasias

Although myxomatous degeneration has been described in tricuspid, aortic, and pulmonary valves, the mitral valve is most commonly involved, and the posterior leaflet is affected more often and more severely than is the anterior leaflet. Grossly, the most outstanding feature is marked increase in surface area of the affected leaflets (Fig. 14.1), which are voluminous, hooded, and white; however, they transilluminate with ease, especially before fixation. On sectioning, the myxomatous consistency of the center of the leaflet is often apparent on gross examination. Small foci of ulceration with occasional superimposed thrombi may be noted on the atrial surface of the affected mitral leaflet.[1] The chordae tendineae often are elongated and thin; however, some localized thickening may be present at their insertions into the valve leaflets (Fig. 14.2). Rupture of the chordae tendineae is common in myxomatous degeneration of the mitral valve: less frequently, myxomatous degeneration may result in aneurysmal dilatation and rupture of a mitral leaflet. Commissural fusion is not a feature of the floppy valve. Because these valves are predisposed to infective endocarditis, gross evidence of this complication must be sought by the surgical pathologist, so that appropriate sections can be obtained for culture before fixation of the valve.

Microscopically, the spongiosa contains stellate cells embedded in a matrix rich in proteoglycans. Characteristically, there is focal to extensive replacement of the normal dense, homogeneous collagen of the fibrosa by this myxomatous tissue. This histologic pattern is in contrast to that seen in most valvular heart diseases, in which the spongiosa of the leaflets is partially or completely replaced by dense fibrous tissue. The collagen in the chordae tendineae may show changes similar to those in the fibrosa. The atrialis of the leaflet generally contains a variable degree of fibroelastic proliferation, and superficial ulceration with microscopic fibrin deposition is not uncommon. Unless there is superimposed infective endocarditis, there is no evidence of inflammation or vascularization. Ultrastructurally, there is focal loss of the normal orderly cross-banding of collagen fibers. Microscopically, small areas of myxomatous degeneration may be found near the free edges of normal or diseased valves and should not be confused with the diffuse findings in floppy valves.

†Posthumously, Dr. Ferrans remains an author of this chapter. Dr. Ferrans died in October 2001.

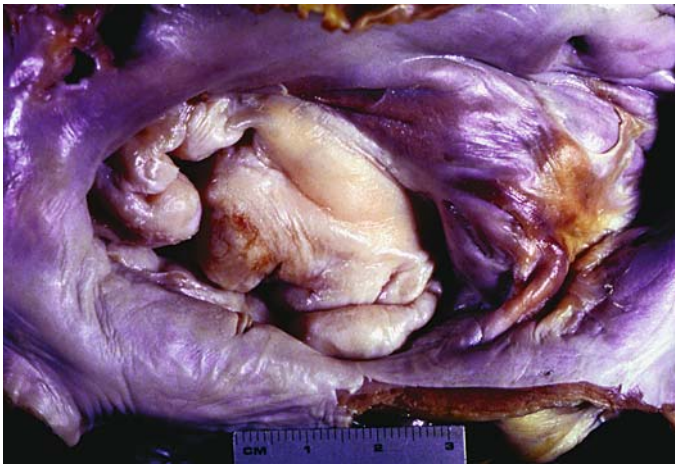

**FIGURE 14.1.** Floppy mitral valve. The most outstanding feature is a marked increase in the surface area of the leaflets. They are voluminous, hooded, and white; however, they transilluminate with ease. Commissural fusion is not a feature of the floppy valve.

Myxomatous degeneration of the cardiac valves, with resulting insufficiency, often occurs in connective tissue dyscrasias such as Marfan's syndrome, osteogenesis imperfecta, cutis laxa, and relapsing polychondritis. This group of diseases may also be associated with cystic medial degeneration of the aorta. Adults with Marfan's syndrome most commonly have myxomatous degeneration of the aortic valve; in children, however, the mitral valve is more commonly involved.[2] The affected mitral and aortic leaflets contain an accumulation of myxoid material mainly in the spongiosa. Recent studies have shown the importance of matrix metalloproteinases in the pathogenesis of these lesions in the Marfan syndrome.[3] The Ehlers-Danlos syndrome is a heterogeneous group of several genetically distinct disorders of connective tissue synthesis, which differ in major clinical features, inheritance patterns, and biochemical defects. Cardiovascular lesions have been described in types I to IV; however, myxomatous degeneration and prolapse of the mitral valve appear to be more common in type III, the benign hypermobile form.[2] The most common valvular lesion in osteogenesis imperfecta is aortic regurgitation; mitral regurgitation and combined aortic and mitral regurgitation are less common. The aortic regurgitation results from dilatation of the aortic root and deformity of the valvular leaflets, which become abnormally translucent, weak, and elongated. Aneurysms of the sinuses of Valsalva also occur. The mitral annulus is dilated, the mitral leaflets are attenuated and redundant and tend to prolapse, and the chordae tendineae may rupture.[2] In cutis laxa, the most common cardiac lesions involve the aorta, pulmonary artery, and pulmonary veins; less commonly, there may be myxomatous degeneration of the aortic or mitral valves.[2] The aortic and mitral valves are the cardiac valves most commonly involved in relapsing polychondritis. Lesions may be microscopically identical to those in the other connective tissue dyscrasias.[1]

**FIGURE 14.2.** Floppy mitral valve. The chordae tendineae are often elongated and thin; however, some localized thickening may be present at their insertion into the valve leaflets.

## Endocrine and Metabolic Valvular Diseases

In carcinoid heart disease, there is either focal or diffuse plaque-like thickening of valvular and mural endocardium and, occasionally, of the intima of the great veins, coronary sinus, pulmonary trunk, and main pulmonary arteries. The fibrous tissue is atypical and limited in the majority of instances to the right side of the heart. When the pulmonary valve is involved, deposition is almost exclusively on the arterial aspect of the valve cusps (Fig. 14.3). When the tricuspid valve is involved, however, the fibrous tissue is located predominantly on the ventricular aspect, often causing the leaflets to adhere to the adjacent ventricular wall.[4] Similar lesions may be observed in the mitral and aortic valves in patients with a patent foramen ovale or a functioning bronchial carcinoid tumor.[5] In some patients with predominant right-side carcinoid heart disease, the mitral and aortic valves also may be involved to a lesser degree. Microscopically, these lesions contain fibroblasts, myofibroblasts, and smooth muscle cells embedded in a distinctive stroma, which is rich in collagen and proteoglycans but lacking in elastic fibers. Blood vessels, often thick-walled, may be immediately adjacent to the valve leaflets. Lymphocytes and plasma cells are frequently located adjacent to these blood vessels.

Histologically, similar valvular and endocardial lesions have been described in patients taking methysergide[6] and ergot[7]; however, the mitral and aortic valves are most commonly involved in these cases. Similar valvular lesions have been described in patients taking fenfluramine and phentermine for appetite suppression.[8]

The heart valves are involved in 50% of patients with cardiac amyloidosis. Valvular involvement is usually minimal, but discrete nodules measuring from 1 to 4 mm in diameter are occasionally present on the valves either in the cusps or in the annulus.[2] Rarely, valvular involvement is diffuse, resulting in thick, rigid cusps and stenotic or regurgitant orifices (Fig. 14.4). The four cardiac valves are affected with almost equal frequency.

All heart valves and valvular annuli, especially the mitral and aortic valves, are sites of heavy pigment deposition in patients with ochronosis.[2] Although the pigment deposition

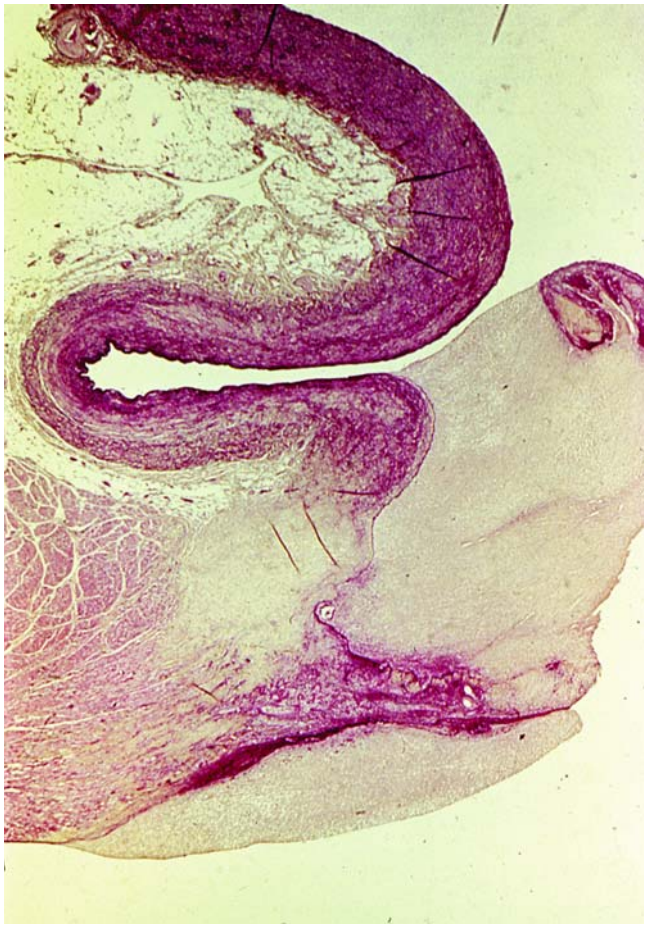

**FIGURE 14.3.** Carcinoid heart disease, pulmonic valve. Heavy deposition of collagen, lacking in elastic fibers, occurs almost exclusively on the arterial aspect of the valve cusps, resulting in pulmonic stenosis (Movat pentachrome, ×25).

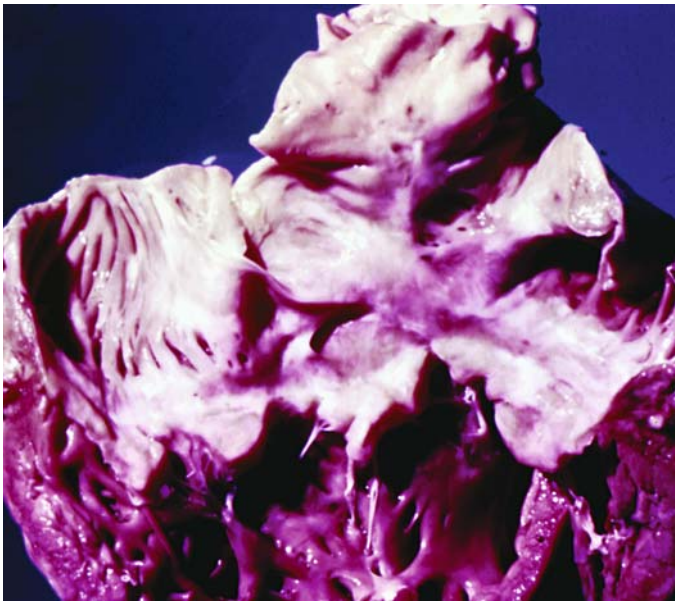

**FIGURE 14.4.** Amyloid valve disease. Valvular involvement is usually minimal; however, diffuse involvement, as illustrated in this heart, can occur, resulting in thick, rigid cusps and stenotic or regurgitant orifices.

is most prominent at the bases of the mitral and aortic valves and annulus fibrosus, the edges of the cusps may be roughened and fused for 1 to 2 mm at their bases; the cusps may be focally calcified. The ochronotic pigment appears blue-black on gross examination and yellow-tan in histologic sections. Infective endocarditis may occasionally be superimposed, especially when the valves are heavily calcified.

The cardiac valves may be involved in any of the mucopolysaccharidoses, most frequently in Hurler's syndrome (mucopolysaccharidosis I).[2] The valves are considerably thickened, particularly the mitral valve; right-sided cardiac valves are less severely affected than those in the left side of the heart (Fig. 14.5). The valvular thickening is most pronounced at the free margins, which have an irregular, nodular appearance. The commissures are not fused. The chordae tendineae of the atrioventricular valves are moderately shortened and thickened. Calcific deposits occur in the angle just beneath the basal attachment of the posterior mitral leaflet (mitral annular calcification), in the mitral leaflets, and in the aortic aspect of the aortic valve cusps. The valves contain large, oval or rounded connective tissue cells (Hurler cells) filled with numerous clear vacuoles, which are the sites of deposition of acid mucopolysaccharide.[2] This material is extremely soluble and difficult to preserve. In addition, small granular cells are present, which contain membrane-limited electron-dense material associated with fragments of collagen fibrils. The valve thickening is due to the presence of the cells and to an increase in the amount of fibrous connective tissue.

In Fabry's disease, the glycosphingolipid is deposited within the cardiac valves, occasionally resulting in valvular dysfunction.[2] The mitral and aortic valves are the two valves that most commonly present clinical problems. There may


**FIGURE 14.5.** Hurler's syndrome, mitral valve. The valvular thickening is most pronounced at the free margins, which have an irregular, nodular appearance. The commissures are not fused. The chordae tendineae are moderately shortened and thickened.

be thickening of the valves with interchordal hooding, or there may be attenuation of the chordae with thickening and ballooning of the mitral valve. Commissural fusion is not a feature of Fabry's disease.

Type II hyperlipoproteinemia (familial hypercholesterolemia) exists in homozygous and heterozygous forms, which differ in the severity and age of onset of clinical symptoms. Aortic valvular disease is frequent in homozygous patients but does not usually occur in heterozygous patients. The aortic valve may be markedly stenosed by fibrous tissue, deposits of foam cells, and cholesterol crystals in the cusps. Thickening of the mitral valve, which results in both stenosis and regurgitation, and thickening of the pulmonary valve and endocardium by foam cells also occur.[2]

Patients with gout most commonly develop dysfunction due to hypertension secondary to renal damage; however, tophi occasionally may be present in the heart, most commonly in the mitral valve and the endocardium of the left ventricle and, less frequently, in the mitral annulus and aortic and tricuspid valve leaflets.[2,9] To establish the diagnosis histologically, appreciable amounts of uric acid must be identified in the tophi to distinguish them from small amounts of uric acid that my be deposited on previously existing fibrocalcific lesions. Urate deposits are histochemically identifiable by fixation in absolute ethanol, followed by staining by the De Galantha method.

## Collagen Vascular Diseases

### Rheumatic Valvulitis

Acute rheumatic fever produces a pancarditis; however, valvular involvement is responsible for the most important long-term consequences. In the acute phase of rheumatic valvulitis, the most conspicuous lesions are minute, translucent nodules (verrucae) along the lines of closure of the valve cusps (Fig. 14.6). These are most frequently observed in the mitral and aortic valves, less often in the tricuspid, and rarely in the pulmonary valve. They vary in diameter from less than 1 mm to 3 mm and are located on the atrial surface of the atrioventricular valves and on the ventricular surface of the semilunar valves.[4] Occasionally, a few verrucae may be distributed elsewhere over the cusps. They are also characteristically present on the chordae tendineae, especially those of the mitral valve, and not infrequently, they extend over the posterior leaflet of the mitral valve onto the endocardium of the left atrium. The verrucae tend to conglomerate on the corpora arantii of the aortic valve and extend in a row along the semilunar cusps. Diffuse thickening of the valves, except the pulmonary, is a less conspicuous but frequent gross alteration.

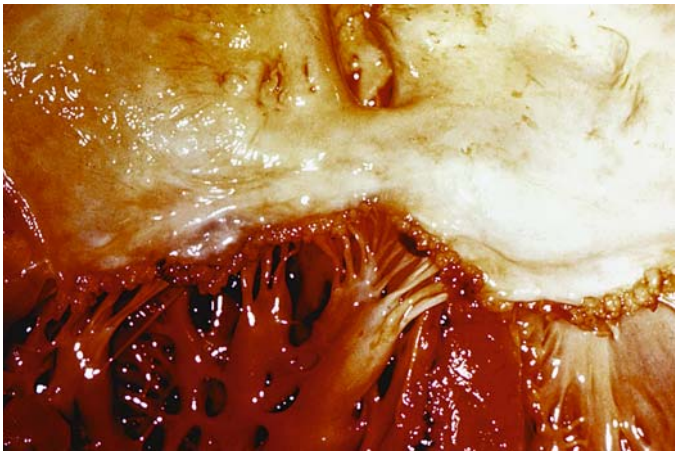

**FIGURE 14.6.** Acute rheumatic valvulitis, mitral valve. Fibrinoid necrosis is represented by minute, translucent nodules (verrucae), 1 to 3 mm in diameter, along the lines of closure.

Microscopically, the verrucae may have the appearance of either thrombi, formed by the deposition of platelets and fibrin on the surface of the valve, or extruded collagen that has undergone fibrinoid degeneration. The region immediately adjacent to the vegetation shows marked proliferation of fibroblasts, as well as edema and numerous lymphocytes.[4] The inflammatory process is observed most frequently in the auricularis layer of the atrioventricular valves and the ventricularis layer of the semilunar valves. A nonspecific inflammatory process, which may involve the entire valve and ring, consists of edema, increased numbers of capillaries, and a variety of inflammatory cells (mainly lymphocytes; occasionally polymorphonuclear leukocytes predominate). Plasma cells, fibroblasts, and other mononuclear cells are often present in variable numbers. Usually the valve also contains Anitschkow and Aschoff cells, which may be arranged in nodules or in rows and often surround foci of eosinophilic fragmented collagen, fibrinoid, or both. Aschoff cells may be multinucleated.[10] These lesions are typically accompanied by characteristic Aschoff nodules in the myocardium.[4,10,11]

Gross alterations of the cardiac valves become more pronounced as a result of recurrent rheumatic valvulitis. Thickening, irregularity of the surfaces, and gross vascularization are usually present. This thickening is usually most pronounced in the distal third of the valve leaflets.[4] The chordae tendineae become thicker and shorter, with especially prominent thickening at their insertions into the valve leaflets. Verrucae in various stages of activity and healing may be observed. In addition to being thickened, the aortic cusps may be considerably shortened, with their free margins rolled and inverted toward the sinus pocket. Fibrous adhesions are commonly present at the commissures, and verrucae in various stages of activity may extend across the commissures of aortic cusps. In recurrent valvulitis, there is a higher incidence of verrucae on the valves of the right side of the heart, and microscopic observation reveals considerable fibrosis, an apparent increase in elastic tissue, and inflammatory changes in various stages of activity.[4,11] The fibrosis and inflammation involve the rings as well as the leaflets. This histologic pattern differs from that of acute valvulitis, in which the thickening of the valves is the result only of edema and inflammation. Also in contrast to the appearance of acute valvulitis are numerous arteries with thick muscular walls in the ring and proximal portion of the valve.

In chronic rheumatic valvulitis, the alterations described in recurrent valvulitis are most advanced. Usually, the diffuse thickening and fibrosis of the valves have resulted in loss of elasticity and in narrowing of the orifice (Fig. 14.7). Thickening, fusion, and shortening of the chordae tendineae

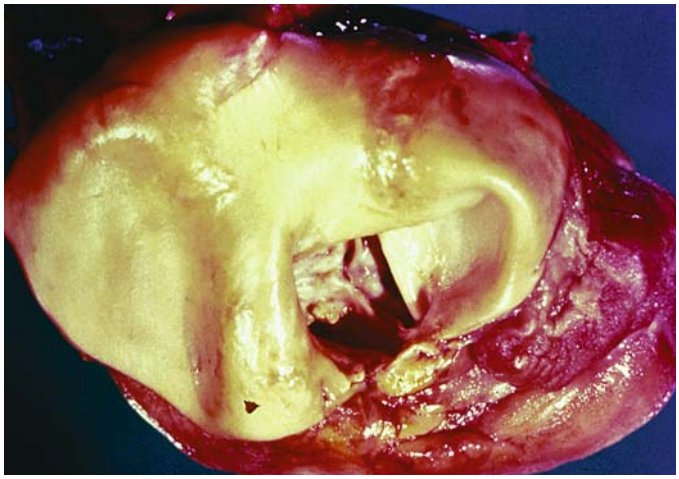

**FIGURE 14.7.** Chronic rheumatic aortic stenosis. Diffuse thickening and fibrosis of the valves with commissural fusion resulting in marked aortic stenosis. Also note the extensive poststenotic dilatation of the ascending aorta.

of the mitral valve are usually pronounced (Fig. 14.8). In addition, focal deposits of calcium salts may be present. These deposits may be extensive and may project to the atrial and ventricular surfaces, causing further distortion. Ossification, complete with hematopoiesis, may occur, causing further distortion.[11] Verrucae are less frequent in chronic valvulitis than in recurrent valvulitis and are broad and flat. Active inflammation is less pronounced in chronic than in recurrent valvulitis and usually consists of scattered foci of perivascular cuffing with lymphocytes. The grossly apparent thickening is due to an increase in fibrous and elastic tissue throughout the entire leaflet including the rings and the tips of the valves. The fibrous connective tissue is usually homogeneous and hyaline. These valves are vascularized by capillaries and thick-walled vessels, which are most numerous in the superficial layers. The verrucae no longer consist of material showing fibrinoid necrosis, but are organized and contain fibroblasts and collagen fibers. As chronicity progresses, the number of fibroblasts decreases, and the verrucae become dense, hyalinized scars.

## Rheumatoid Valvulitis

Rheumatoid granulomas may occur in any of the cardiac valves but are most common in the mitral and aortic valves.[12] Involvement may be focal or diffuse and is usually most prominent in the midportion or base of the valve (Fig. 14.9). The chordae tendineae are usually uninvolved, but occasionally, they may be fibrotic and shortened. Commissural fusion is rare. Rheumatoid nodules are most commonly located within the valve leaflets and are enclosed by fibrous tissue; rarely, a rheumatoid nodule may erode the surface of the valve, so that the necrotic center of the nodule communicates with a cardiac cavity (Fig. 14.10). In these unusual occurrences, there may be superimposed thrombus or infective endocarditis. Verrucae of fibrinoid necrosis, common in rheumatic valvulitis and systemic lupus erythematosus, are not a feature of pure rheumatoid valvulitis.

## Lupus Erythematosus Valvulitis

Lupus erythematosus valvulitis (atypical verrucous endocarditis of Libman and Sacks) is recognized as a specific valvular abnormality occurring in systemic lupus erythematosus. Any valve may be involved, but the mitral and tricuspid valves are most often affected (Fig. 14.11). The verrucae may be located on either side of a valve cusp but most frequently are present on the ventricular surface of the posterior mitral leaflet or in the valve ring; involvement of the anterior mitral leaflet is infrequent. The lesions have no special tendency to occur along the free edge of the valves and may be scattered on the chordae tendineae and atrial or ventricular mural endocardium. The lesions are small, usually ranging in size from 1 to 4 mm in diameter, but rarely may reach a diameter of 8 to 10 mm. They are sterile, dry, granular pink vegetations that may be single or multiple in conglomerates.[4] Histologically, the verrucae consist of a finely granular, eosinophilic,

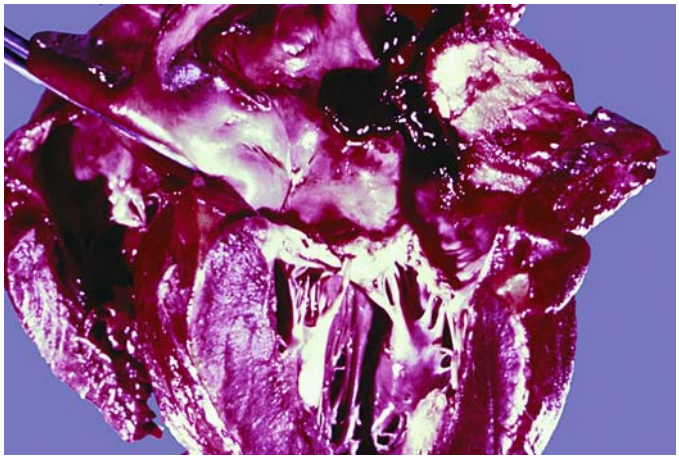

**FIGURE 14.8.** Chronic rheumatic mitral stenosis. Note the thickening, fusion, and shortening of the chordae tendineae, as well as diffuse thickening and fibrosis of the valves, with commissural fusion. The left atrium is enlarged and contains a mural thrombus.

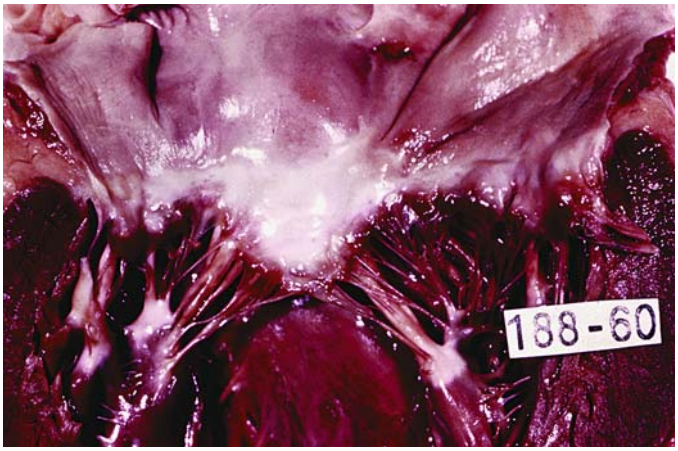


**FIGURE 14.9.** Rheumatoid valve disease, mitral valve. Involvement may be focal or diffuse, as in this case, and is usually most prominent in the midportion of the base of the valve. The chordae tendineae are usually uninvolved, and commissural fusion is rare.

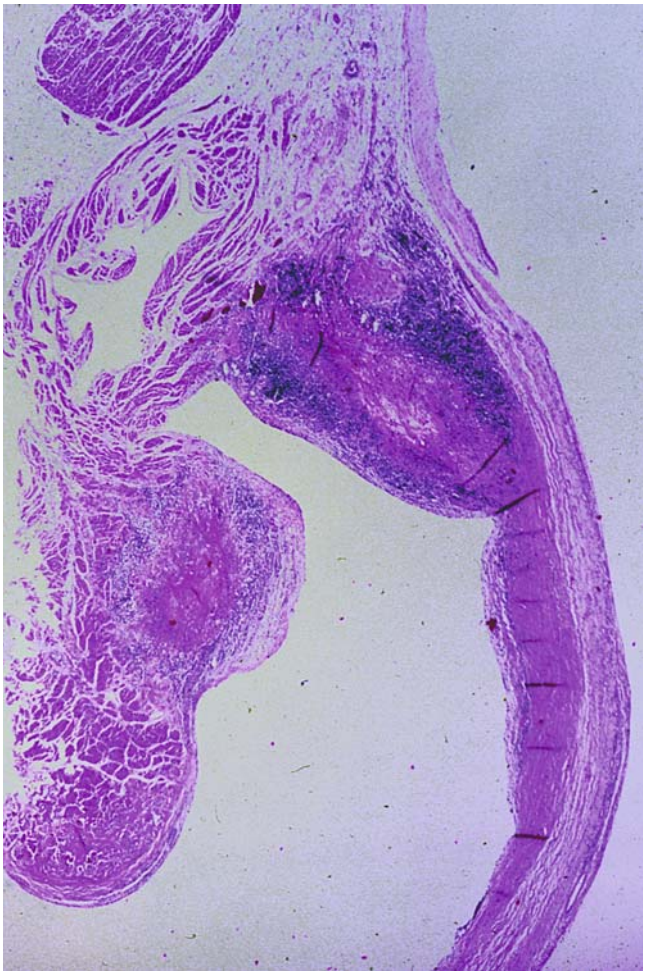

**FIGURE 14.10.** Rheumatoid valve disease, mitral valve. Rheumatoid granulomas with extensive contiguous fibrosis involve the base and midportion of a mitral valve. Another rheumatoid granuloma is present in the adjacent subvalvular myocardium (Hematoxylin and eosin, ×75).

fibrinoid material, which may contain hematoxylin bodies. In a general sense, these hematoxylin bodies are the tissue equivalent of the lupus erythematosus cell of the blood and bone marrow.[4] The verrucous endocardial lesions result from degenerative and inflammatory processes of the endocardium and deeper layers of the valves. An intense valvulitis is present, which is characterized by fibrinoid necrosis of the valve substance and is often contiguous with the vegetations. Exudative and proliferative cellular reactions are present in the deeper layers of the valve. Healing of these lesions may produce foci of granulation tissue, which develop into focal fibrous thickening in the valves or in the mural endocardium. Rarely, bacterial endocarditis may be superimposed on the Libman-Sacks lesions.[12]

## Other Collagen Vascular and Related Diseases

Valvular lesions in scleroderma are distinctly rare; the most common lesion is nonbacterial thrombotic endocarditis. In patients with thrombotic thrombocytopenic purpura, nonbacterial thrombotic endocarditis frequently is present. In both diseases, the cardiac valves most commonly involved are the mitral and the aortic.[12] Valvulitis is most unusual in Wegener's granulomatosis. The mitral valve is most commonly involved by the inflammatory process, which may result in subsequent fibrosis with commissural fusion resembling rheumatic mitral stenosis.[13] Primary valvulitis is not a feature of dermatomyositis. Diseases that may result in valvulitis but are manifested most commonly by aortitis include syphilis, ankylosing spondylitis, psoriatic arthritis, Reiter's syndrome, and granulomatous aortitis.

## Lesions Resembling Collagen Vascular Disease Valvulitis

Although not collagen vascular diseases, three entities that may result in fibrous thickening of the cardiac valves and thickening and fusion of chordae tendineae are Whipple's disease, endomyocardial fibrosis with eosinophilia, and radiation-induced disease. In Whipple's disease, the valve most commonly involved is the mitral, and then the tricuspid and the aortic valves.[14] The gross deformity closely resembles that seen in chronic rheumatic heart disease, with diffuse thickening and fibrosis of the valve leaflets and chordae tendineae and rolling of the free edges of the leaflets (Fig. 14.12). Microscopically, the valve substance contains large macrophages filled with granules that are positive for the periodic acid-Schiff reaction; these granules are identical to those found in the epithelial cells of the small intestine in patients with this disease. Proliferating fibrous tissue and chronic inflammatory cells are commonly associated with the periodic acid-Schiff–positive macrophages. Scattered rod-shaped bodies, measuring 1.5 to 2.0 μm in length and 0.2 to 0.4 μm in diameter, are present intracellularly and extracellularly. These bodies, as well as membrane-bound masses of fibrillar material within the macrophages, are identical to those described in jejunal biopsies of patients with Whipple's disease[14] and are thought to represent bacteria (*Tropheryma*

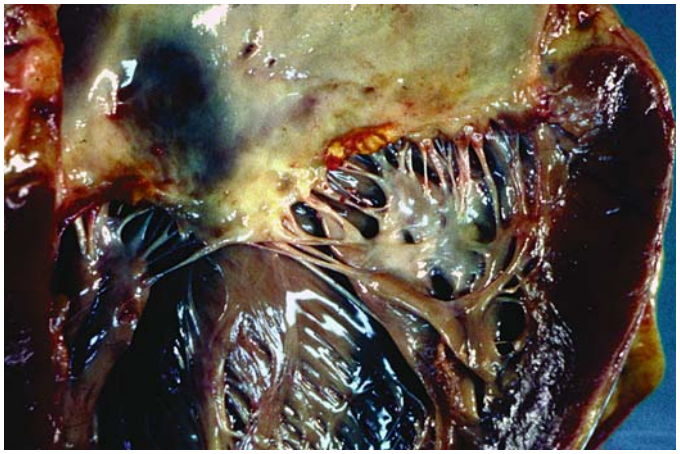

**FIGURE 14.11.** Lupus erythematosus valvulitis (atypical verrucous endocarditis of Libman and Sacks), mitral valve. The lesions represent fibrinoid necrosis as sterile, dry, granular vegetations that may be single or multiple in conglomerates. They have no special tendency to occur along the free edge of the valves and may be scattered on the chordae tendineae and atrial or ventricular mural endocardium.

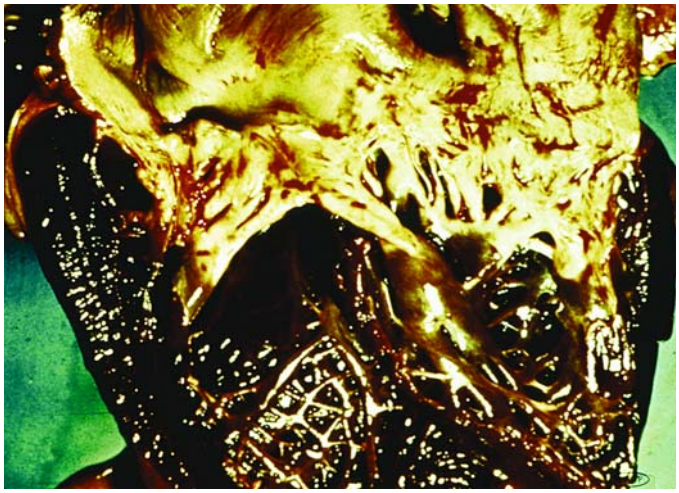

**FIGURE 14.12.** Whipple's disease, mitral valve. The gross deformity closely resembles that seen in chronic rheumatic valve disease, with diffuse thickening and fibrosis of the valve leaflets and chordae tendineae and rolling of the free edges of the leaflets.

*whippelii*), which are known to be associated with this disease.[15] In endomyocardial fibrosis with eosinophilia, the valves most commonly involved are the mitral and the tricuspid, with a lesser incidence of aortic valve involvement. There is fibrous thickening of endocardium, with superimposed fibrin thrombus beneath either the posterior mitral leaflet or the posterior or septal tricuspid leaflet. These leaflets become adherent to the underlying mural endocardium, which results in regurgitation.[16] The aortic valve cusps are occasionally thickened by vascularized fibrous tissue, which is superimposed on the ventricular aspects of the cusps. The commissures of the aortic valve may become fused by fibrous tissue with superimposed fibrin thrombus. Eosinophilic leukocytes in varying numbers are usually present at the periphery of the fibrous lesions.

Rarely, patients receiving mediastinal irradiation may develop lesions of the cardiac valves.[17,18] The valves most commonly involved are the tricuspid and the mitral, followed by the aortic and the pulmonary. The fibrous valvular thickenings are focal, and the anterior tricuspid leaflet and the anterior mitral leaflet are usually more markedly involved than are the posterior leaflets. The chordae tendineae also may be focally thickened by fibrous tissue.

## Congenital Valvular Heart Disease

The most common congenital malformation of heart valves is the bicuspid aortic valve. Unless it is the site of associated dysplasia, this valve is not inherently stenotic, although it frequently becomes stenotic in later life. Stenosis is secondary to fibrosis and calcification of the cusps and usually not to fusion of the commissures, as is seen in rheumatic aortic stenosis.[19] Classically, the calcific deposits form nodules at the base of the cusps in the sinuses of Valsalva and extend to, but frequently do not involve, the free edge of the valve cusps (Fig. 14.13). In addition, there are foci of calcification and extensive fibrosis within the substance of the cusps. Commissural fusion is usually minimal, involves only one commissure, and is only rarely extensive.[17,20] Another common reason for surgical excision of a bicuspid aortic valve is infective endocarditis. The moderately high incidence of infective endocarditis in patients with bicuspid aortic valves is well known. Therefore, each of these valves must be examined closely by the surgical pathologist for superimposed infective endocarditis, and if suspicious lesions are noted, sections must be taken for microbiologic culture before fixation.

The quadricuspid aortic valve is far less common than the bicuspid valve. The most frequent indication for surgical excision of these valves is aortic insufficiency. Most commonly, one of the cusps is rudimentary; however, the gross and microscopic appearance of the valves is usually otherwise normal.[21] Quadricuspid pulmonary valves rarely cause cardiac dysfunction unless there is associated dysplasia of the valve or a coexisting congenital cardiac defect. As in quadricuspid aortic valves, the fourth cusp is usually small and rudimentary, with the remaining cusps appearing morphologically normal.[21]

Valve dysplasia may affect any of the cardiac valves, most frequently the aortic valve; however, 25% of patients have multiple valve involvement.[22] The dysplastic changes may be severe and extensive, so that the entire valve is distorted, or mild and focal, so that valve function is not impaired. A dysplastic stenotic pulmonary valve is frequently present in patients with Noonan's syndrome. The dysplastic semilunar valve may be unicuspid, bicuspid, or tricuspid; failure of development of the commissures also may occur, resulting in a dome-shaped valve. Stenosis is secondary to the marked thickening of the individual valve cusps. The spongiosa of the dysplastic valve is quite cellular and composed primarily of small spindle cells resembling fibroblasts, set in an acid mucopolysaccharide matrix and haphazardly arranged bundles of collagen.[1] This loose connective tissue encroaches on and often replaces the ventricularis and fibrosa of the valve cusps. The majority of involved cusps consist entirely of this loose connective tissue; however, remnants of the ventricularis and fibrosa, interrupted by accumulations of

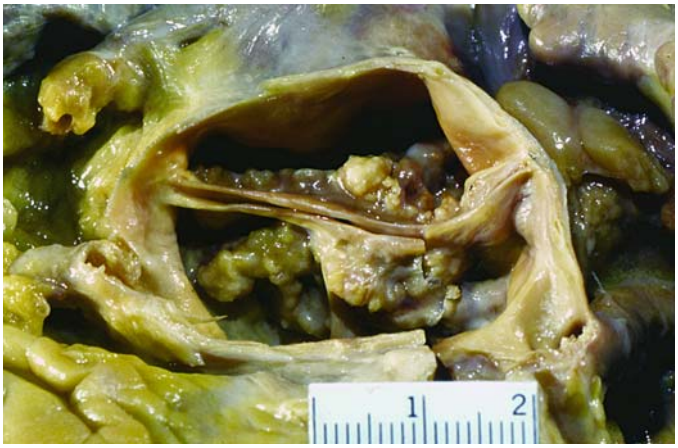


**FIGURE 14.13.** Bicuspid aortic valve. Stenosis is secondary to fibrosis and calcification of the midportion and hinge of the cusps and usually not to fusion of the commissures, as is seen in rheumatic aortic stenosis.

abnormal loose connective tissue, are often found at the base of the cusps. Inflammation and calcification are not features of the dysplastic valve. The abnormal valve tissue of the dysplastic or incompletely differentiated valve resembles the embryonic connective tissue of the cardiac valves in 8- to 12-week-old fetuses.[22]

## Infective Endocarditis

The relative frequency of involvement of the cardiac valves is similar for infective endocarditis and rheumatic heart disease: mitral, aortic, aortic and mitral, combined tricuspid, and pulmonary valves, in decreasing order of frequency. The tricuspid and pulmonary valves are not commonly involved, with the notable exception of intravenous drug abusers. In many cases of combined aortic and mitral involvement, the anterior leaflet of the mitral valve appears to be infected by regurgitation-induced deposition of organisms from the aortic vegetation. Lesions usually originate on the atrial surface of the atrioventricular valves and the ventricular surface of the semilunar valves and vary from tiny granular or flat vegetations to large polypoid masses. They may be single or multiple and may be firm or soft, but are usually friable. Grossly, they may appear yellow-white to red or brown.[23] The affected valve exhibits destruction and loss of tissue. Valvular ulceration, perforation, or formation of aneurysm of the valve may occur. Rupture of chordae tendineae is common. Infection may spread into the contiguous structures, resulting in annular or myocardial abscesses or aneurysms of the sinuses of Valsalva. Microscopically, the vegetations are composed of masses of necrotic tissue, fibrin, platelets, erythrocytes, leukocytes, and organisms. Classically, there is a superficial zone of fibrin, organisms, and leukocytes; an intermediate zone of amorphous necrotic material; and a basal zone of granulation tissue extending from the substance of the valve. Small foci of calcification are common.

Bicuspid aortic valves or valves with acquired deformities are most frequently involved in infective endocarditis; however, the disease may develop in previously normal valves, including the pulmonary and tricuspid valves, especially in patients over 60 years of age. In previously normal valves, the lesions tend to be larger, and tissue destruction is more extensive. Staphylococci and gram-negative organisms are more likely to be the etiologic agents than in the case of infection of deformed valves, in which *Streptococcus viridans* is the most common organism encountered. Infected but previously normal valves often show marked necrosis and inflammation, which are less common findings in infected, previously scarred valves.

Although streptococci and staphylococci are the most common microorganisms responsible for infection, a wide variety of bacteria and fungi have been recovered from patients with infective endocarditis. *Candida* species in particular are recovered from addicts and patients with prosthetic heart valves. Gram-negative bacilli account for only a small percentage of infections, despite the relative frequency of gram-negative bacteremia, and are more likely to be encountered in addicts or in patients with prosthetic heart valves. Rarely, infections are due to other organisms, such as meningococci, pneumococci, gonococci, *Brucella, Haemophilus, Corynebacterium*, mycobacteria, rickettsiae, and *Aspergillus* and other fungal species.[24] Fungal vegetations, in particular, tend to be large and friable, with a tendency to produce embolization. Because fungal endocarditis is frequently indolent clinically, it is important for the surgical pathologist to obtain appropriate special stains on any thromboembolus removed from a systemic artery. Any valve removed surgically that has gross lesions suggestive of infective endocarditis should have sections taken for microbiologic culture before fixation. Merely taking a swab of the surface of the valve for culture is not adequate. Indeed, even if the valve appears grossly normal, patients in whom the clinical history or physical findings suggest the possibility of infective endocarditis should have sections of the valve taken for culture.

Healing of vegetations may occur as a result of therapy or spontaneously, without antimicrobial therapy.[23] These healed vegetations often result in multiple, calcified, polypoid lesions on the surface of the valve. Contracture of scar tissue may further reduce the surface area of the valve. The healed vegetations in the heart valves or chordae tendineae are similar in gross appearance to those with active infection.[23] Occasionally, well-circumscribed defects with smooth edges remain in the heart valve after the healing of perforations that resulted from infective endocarditis. Usually, the etiology of these morphologic abnormalities cannot be identified, especially if there is no known antecedent infection. Histologic study rarely helps to resolve these issues because the alterations resulting from the healing of the inflammatory process tend to be similar in their end-state appearance.[23]

## Prosthetic Heart Valves

### Types

Prosthetic heart valves in current use can be classified into two major groups: rigid-framed (mechanical) valves and tissue valves (bioprosthesis). Rigid-framed valves are of three types: (1) valves with a centrally placed occluder (ball or disk), which moves up and down in a metal cage and allows only lateral blood flow; (2) valves with a tilting disk, which permits semicentral flow; and (3) valves with two hinged, semicircular plates (St. Jude type), which allow central flow. Tissue valves include (1) fresh and variously treated homografts, (2) human dura mater or fascia lata valves, (3) bovine pericardial valves, and (4) porcine aortic valves. The metal and plastic mounting frames and the preimplantation chemical treatments vary from one type of tissue valve to another. Tissue valves without supporting frames (unstented porcine and human homograft valves) also are being used clinically. Knowledge of the frames and treatments is necessary to interpret morphologic findings in tissue valves. Radiographs may be useful in the identification and evaluation of explanted valves.[25–27] Essential for the evaluation of any prosthetic valve is knowledge of the length of time the valve was in place and the specific reason for its removal.

## Complications

Certain complications are common to all types of prosthetic heart valves. Among these are thrombosis, embolization, infection, dehiscence of the valvular ring, paravalvular leak, disproportion, turbulent flow, and hemolysis. Complications limited to rigid-framed prostheses[28,29] are related to wear and fracture of mechanical components, resulting in interference with proper motion of the occluder (and sometimes also in embolic phenomena), whereas complications peculiar to tissue valves[28,29] are related to calcification or breakdown of the prosthetic tissue leaflets. Degenerative changes also develop in homograft human tissue valves.[30,31]

### Complications Common to All Types of Prosthetic Valves

Thrombus formation in mechanical prostheses is most common at the base of the struts forming the cage. From this area, thrombi can spread and interfere with motion of the occluder, with seating of the occluder on the orifice, or with blood flow. These thrombi can undergo organization, become infected, or be sources of emboli. Ball valves with cloth-covered cage struts are less likely to form thrombi than are those with uncovered struts. Tissue valves are least likely to form large thrombi, although aggregates of platelets do develop on their surfaces. Thrombi can splint the cusps of bioprostheses and render them stenotic.[32,33] Thrombi removed from prosthetic heart valves must be examined (by histology and by culture) for evidence of infection.[11] Dehiscence of a valvular ring must be regarded as due to infection until proved otherwise. Paravalvular leaks most frequently result from a prosthesis having been sutured to a ring that is heavily calcified or weakened (as occurs in patients with Marfan's syndrome or other connective tissue disorder). Anemia and renal hemosiderosis are typical findings in hemolysis produced by prosthetic heart valves.

Disproportion is caused by prosthetic heart valves that are too large for the chambers in which they are placed. This can result in interference with movement of the poppet, as in the case of large ball valves placed in a small ascending aorta (particularly in patients with combined mitral and aortic valve disease in whom the aortic root is usually not dilated) or in a small left ventricle (as in patients with combined mitral and aortic stenosis in whom the left ventricle is hypertrophied but not dilated). If a porcine bioprosthesis is improperly placed in the mitral orifice, one of its struts may obstruct the left ventricular outflow tract. In the case of the double valve replacement, the prosthetic mitral valve may be inadvertently placed in such a way as to interfere with proper seating of the poppet of the prosthetic aortic valve. Disproportion also may result from normal growth of the heart of a child in whom a small prosthetic valve was implanted at an early age.

### Complications Limited to Rigid-Framed (Mechanical) Prosthetic Valves

Turbulent blood flow produced by caged-ball prostheses may lead to diffuse endocardial fibroelastotic thickening and to intimal proliferation in the ascending aorta, sometimes with extension of the thickening into the coronary arterial ostia. Degeneration (variance) of the silicone rubber poppet was common in the caged-ball prostheses implanted before 1967. This complication, which resulted from surface abrasion and lipid infiltration, has not been reported in the metallic hollow poppet. Wear of a caged disk, causing "grooving" and disk cocking, has been described in most caged-disk prostheses. Disk cocking remains a potential problem with all caged-disk valves, and it may be totally unrecognized as a cause of fatalities. Wear of the cloth covering on the struts and the orifice occurred in some of the older models of completely cloth-covered caged-ball prostheses, but strut cloth wear has not been reported in the newer Starr-Edwards model with metal tracts. Dislodgment of caged disks and poppets has been reported in association with wear of these components or with fracture of struts.

### Complications Limited to Bioprosthetic (Tissue) Valves

The various types of bioprosthetic heart valves developed since the 1970s have the following characteristics in common: collagen is their major structural component; they are mounted (except for some of the homografts) on metal and plastic stents; the incidence of clinical episodes of thromboembolism is lower with these valves than with rigid-framed valves; and they have problems of long-term durability because they can become stenotic as a result of calcification or regurgitant due to alterations in collagen.[34]

## Porcine Aortic Valves

Porcine aortic valves treated with a low (<1%) concentration of glutaraldehyde (to crosslink tissue protein, to sterilize the tissue, and to eliminate problems of antigenicity) and mounted on flexible stents have become a widely used type of valvular bioprosthesis. During the first 5 years after implantation, these values usually have excellent function, although they can de velop extensive anatomic changes. After the first 5 years, appreciable incidences of calcification and cuspal damage become evident. Calcific deposits develop more frequently and earlier in children and young adults than in older individuals and also are more frequent in patients with chronic renal disease.[22,32] Cuspal perforations have no relation to patient age.

A bioprosthetic heart valve removed because of dysfunction should be first examined for evidence of infection, perforation, or calcification, and cultures should be taken as indicated by clinical or anatomic findings; then it should be radiographed and photographed before the cusps are detached from the frame for histologic sectioning. These valves are fragile and should be handled only by the mounting frame to avoid producing artifactual damage to the cusps. Connective tissue stains and stains for calcium are useful in evaluating these valves. Transmission electron microscopy provides the best method for studying the collagen, and scanning electron microscopy is the method of choice for examining the surfaces.

Histologically, porcine aortic valves are composed of the following three layers, which also are recognizable in the

bioprosthesis even after having been in place for long periods of time: (1) the ventricularis, which faces the ventricular cavity when the valve is in its anatomic position and which contains collagen and abundant elastic fibers; (2) the spongiosa, which is the proteoglycan-rich middle layer, and (3) the fibrosa, which contains densely packed collagen but only small, scanty elastic fibers and which faces the aortic wall. Proteoglycans are lost from the spongiosa during commercial processing and soon after implantation of the bioprosthesis, leaving empty spaces that gradually are filled with deposits of plasma proteins. The surfaces of porcine valvular bioprostheses usually do not become endothelialized, although they may be covered by macrophages, multinucleated giant cells, platelet aggregates, and small fibrin deposits. Polymorphonuclear leukocytes are very scanty or absent unless infection is present. Macrophages show little tendency to invade the bioprosthetic tissue, and there is no evidence that immunologic rejection plays a role in its deterioration.

Calcific deposits usually develop in association with collagen in foci of loss of proteoglycans and with surface thrombi, especially in the region near the commissures; they form yellow, plaque-like or raised lesions.[35] Calcific deposits also develop in the aortic wall just adjacent to the cusps and in cardiac muscle cells in a muscular shelf extending from the ventricular septum into the base of the right coronary cusp of the porcine aortic valve. This cusp is larger than the others, and its base is less translucent. Calcific deposits can also be associated with perforations, perhaps because collagen adjacent to those deposits undergoes severe mechanical stresses.[35] The collagen in bioprostheses undergoes a time-dependent process of degeneration, which may be related to material fatigue and many result in perforation of the cusps. Perforations in porcine valves occur most frequently near the basal attachment of the cusps. In pericardial valves, particularly those implanted in the mitral position, cuspal tears are likely to involve the free edge near the attachment to the post. It has been suggested that such tears begin at the attachment suture. Infection of porcine valvular bioprostheses differs from that of rigid-framed valves; it is likely to involve the cusps (rather than the sewing ring), is less likely to result in formation of a ring abscess, and usually extends into the collagen in the cusps.[34] The incidence of infection in the two types of valves appears to be similar.

### Other Bioprosthetic Valves

Fresh, antibiotic-sterilized, freeze-dried, and chemically treated aortic valve homografts (allografts) have been used infrequently in the United States. However, cryopreserved aortic valve allografts have been used more extensively in recent years.[30,31] In contrast to glutaraldehyde-treated bioprostheses, allografts tend to become covered with a fibrous sheath of host origin. These valves become completely acellular, and apoptosis has been shown to play an important role in the loss of the valvular cells.[36] Complications of allograft valves include calcification, cuspal rupture, and fibrous retraction of the edges of the cusps. Autologous fascia lata valves implanted without any chemical treatment have had a very poor record of durability and a high incidence of degeneration, thrombosis, calcification, and fibrous contraction of the cusps. Their use has been completely discontinued. Human dura mater valves preserved by glycerol treatment have been used extensively in Latin America. Bioprostheses made of glutaraldehyde-treated bovine pericardium have also been used as substitute cardiac valves. Both dura mater and pericardium consist of dense collagenous sheets with sparse elastic fibers. Their layered structure is easily distinguishable histologically from that of porcine aortic valves. Complications of pericardial and dura mater valves are similar to those of porcine valves, consisting mainly of calcification and cuspal dehiscence.[28]

## Conduits

Conduits composed of various synthetic materials have been used to correct hypoplasia or atresia of the pulmonary artery. Valveless conduits were first used; subsequently, conduits containing mechanical (Björk-Shiley) valves were employed but were found to be prone to valvular thrombosis. More recently, extensive use has been made of pulmonic conduits with bioprosthetic (porcine or pericardial) valves; in addition, left ventricular apical-aortic conduits have had limited use for correction of tunnel aortic stenosis.[28] The most frequent complication of conduits is obstruction, which can result from one or more of the following causes: (1) muscular compression of the proximal end of the conduit during ventricular systole, (2) accumulation of thrombotic or fibrous material (fibrous peel) in the wall of the conduit, (3) compression of the conduit by the sternum, (4) calcific or thrombotic stenosis of the bioprosthesis, and (5) stenosis at the distal end (the most common cause of obstruction) because of the small size of the artery at the anastomotic site.

## Summary

Valvular heart disease can result from a spectrum of degenerative and inflammatory conditions. Floppy mitral valve due to myxomatous degeneration occurs as an isolated entity or as a component of Marfan's syndrome or other connective tissue dyscrasias. Several endocrine and metabolic conditions can produce valvular diseases, including carcinoid heart disease and cardiac amyloidosis. Collagen vascular diseases commonly produce valvular heart disease, and these include rheumatic valvulitis, rheumatoid valvulitis, lupus erythematosus valvulitis, and other related conditions. The bicuspid aortic valve is the most common form of congenital valvular heart disease. Infective endocarditis can develop on previously diseased or normal valves. Prosthetic heart valves include mechanical valves and bioprostheses. Characteristic pathologic changes influence the suitability of the different prostheses for individual patients.

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