Valvular Heart Disease

Valvular involvement by disease causes stenosis, insufficiency (regurgitation or incompetence), or both. **Stenosis is the failure of a valve to open completely, thereby impeding forward flow.** **Insufficiency, in contrast, results from failure of a valve to close completely, thereby allowing reversed flow.** These abnormalities can be either pure, when only stenosis or regurgitation is present, or mixed, when both stenosis and regurgitation coexist in the same valve, but one of these defects usually predominates. **Isolated disease** refers to disease affecting one valve, and **combined disease** implies that more than one valve may be dysfunctional. **Functional regurgitation** results when a valve becomes incompetent owing to either (1) dilation of the ventricle, which causes the right or left ventricular papillary muscles to be pulled down and outward, thereby preventing coaptation of otherwise intact mitral or tricuspid leaflets during systole, or (2) dilation of the aortic or pulmonary artery, pulling the valve commissures apart and preventing full closure of the aortic or pulmonary valve cusps. Abnormalities of flow often produce abnormal heart sounds known as murmurs.

Valvular dysfunction can vary in degree from slight and physiologically unimportant to severe and rapidly fatal. The clinical consequences depend on the valve involved, the degree of impairment, the rate of its development, and the rate and quality of compensatory mechanisms. For example, sudden destruction of an aortic valve cusp by infection (as in infective endocarditis; see later) may cause rapidly fatal cardiac failure owing to massive regurgitation. In contrast, rheumatic mitral stenosis usually develops over years and its clinical effects are remarkably well tolerated. Depending on degree, duration, and etiology, valvular stenosis or insufficiency often produces secondary changes in the heart, blood vessels, and other organs, both proximal and distal to the valvular lesion. Most important are the myocardial hypertrophy and the pulmonary and systemic changes discussed earlier. Moreover, a patch of endocardial thickening often occurs at the point where a jet lesion impinges, such as the focal endocardial fibrosis in the left atrium secondary to a regurgitant jet of mitral insufficiency.

Valvular abnormalities may be caused by congenital disorders (discussed earlier) or by a variety of acquired diseases. **Most frequent are acquired stenoses of the aortic and mitral valves, which account for approximately two-thirds of all valve disease.** Valvular stenosis almost always is due to a primary cuspal abnormality and is virtually always a chronic process. In contrast, valvular insufficiency may result from either intrinsic disease of the valve cusps or damage to or distortion of the supporting structures (e.g., the aorta, mitral annulus, tendinous cords, papillary muscles, ventricular free wall) without primary changes in the cusps. It may appear acutely, as with rupture of cords, or chronically with leaflet scarring and retraction.

The most important causes of acquired heart valve diseases are summarized in Table 12-7 and are discussed in the following sections. In contrast to the many potential causes of valvular insufficiency, only a relatively few mechanisms produce acquired valvular stenosis. The most frequent causes of the major functional valvular lesions are as follows:

- Aortic stenosis: calcification of anatomically normal and congenitally bicuspid aortic valves
- Aortic insufficiency: dilation of the ascending aorta, related to hypertension and aging.
Mitral stenosis: rheumatic heart disease
Mitral insufficiency: myxomatous degeneration (mitral valve prolapse)

Table 12-7 -- Major Etiologies of Acquired Heart Valve Disease

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<tr>
<th>Mitral Valve Disease</th>
<th>Aortic Valve Disease</th>
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<td><strong>Mitral Stenosis</strong></td>
<td><strong>Aortic Stenosis</strong></td>
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<td>Postinflammatory scarring (rheumatic heart disease)</td>
<td>Postinflammatory scarring (rheumatic heart disease)</td>
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<tr>
<td>Senile calcific aortic stenosis</td>
<td>Senile calcific aortic stenosis</td>
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<tr>
<td>Calcification of congenitally deformed valve</td>
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<td><strong>Mitral Regurgitation</strong></td>
<td><strong>Aortic Regurgitation</strong></td>
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<td><strong>Abnormalities of Leaflets and Commissures</strong></td>
<td><strong>Intrinsic Valvular Disease</strong></td>
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<td>Postinflammatory scarring</td>
<td>Postinflammatory scarring (rheumatic heart disease)</td>
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<td>Infective endocarditis</td>
<td>Infective endocarditis</td>
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<td>Mitral valve prolapse</td>
<td>Mitral valve prolapse</td>
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<td>Fen-phen-induced valvular fibrosis</td>
<td>Fen-phen-induced valvular fibrosis</td>
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<td><strong>Abnormalities of Tensor Apparatus</strong></td>
<td><strong>Aortic Disease</strong></td>
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<tr>
<td>Rupture of papillary muscle</td>
<td>Degenerative aortic dilation</td>
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<td>Papillary muscle dysfunction (fibrosis)</td>
<td>Syphilitic aortitis</td>
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<td>Rupture of chordae tendineae</td>
<td>Ankylosing spondylitis</td>
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<td>Rheumatoid arthritis</td>
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<td>Marfan syndrome</td>
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<td><strong>Abnormalities of Left Ventricular Cavity and/or Annulus</strong></td>
<td><strong>Aortic Disease</strong></td>
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<td>LV enlargement (myocarditis, dilated cardiomyopathy)</td>
<td>LV enlargement (myocarditis, dilated cardiomyopathy)</td>
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<td>Calcification of mitral ring</td>
<td>Calcification of mitral ring</td>
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<td>LV, Left ventricular.</td>
<td>LV, Left ventricular.</td>
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**VALVULAR DEGENERATION CAUSED BY CALCIFICATION**

The heart valves are subjected to high repetitive mechanical stresses, particularly at the hinge points of the cusps and leaflets owing to (1) 40 million or more cardiac cycles per year, (2)
substantial tissue deformations at each cycle, and (3) transvalvular pressure gradients in the
closed phase of approximately 120 mm for the mitral and 80 mm for the aortic valve. It is therefore
not surprising that these normally delicate structures suffer cumulative damage complicated by
formation of calcific deposits (composed of calcium phosphate mineral), which may lead to
clinically important disease (see Chapter 1). The most frequent calcific valvular diseases,
illustrated in Figure 12-22, are calcific aortic stenosis, calcification of a congenitally bicuspid aortic
valve, and mitral annular calcification. Each comprises primarily dystrophic calcification without
significant lipid deposition or cellular proliferation, a process distinct from but with some features of
atherosclerosis.

Figure 12-22  Calcific valvular degeneration. A, Calcific aortic stenosis of a previously normal
valve having three cusps (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
in postrheumatic aortic valve stenosis (see Fig. 12-24E). B, Calcific aortic stenosis occurring
on 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

Calcific Aortic Stenosis

Aortic stenosis is the most common of all valvular abnormalities. Acquired aortic stenosis is usually
the consequence of calcification owing to progressive and advanced age-associated "wear and
tear" of either previously anatomically normal aortic valves or congenitally bicuspid valves (with
which approximately 1% of the population is born, see later). The incidence of aortic stenosis is
increasing with the rising average age of the population. With the decline in the incidence of
rheumatic fever in North America, rheumatic aortic stenosis now accounts for less than 10% of
cases of acquired aortic stenosis. Aortic stenosis comes to clinical attention primarily in the sixth to
seventh decades of life with congenitally bicuspid valves but not until the eighth and ninth decades
with previously normal valves; hence the term senile calcific aortic stenosis is used to describe the
latter condition.

Morphology.

The morphologic hallmark of non-rheumatic, calcific aortic stenosis (with either tricuspid or bicuspid
valves) is heaped-up calcified masses within the aortic cusps that ultimately protrude through the
outflow surfaces into the sinuses of Valsalva, preventing the opening of the cusps. The calcific deposits distort the cuspal architecture, primarily at the bases; the free cuspal edges are usually not involved (see Fig. 12-22A). The calcific process begins in the valvular fibrosa, at the points of maximal cusp flexion (the margins of attachment), and the microscopic layered architecture is largely preserved. An earlier, hemodynamically inconsequential stage of the calcification process is called **aortic valve sclerosis**. In aortic stenosis, the functional valve area is decreased sufficiently to cause measurable obstruction to outflow; this subjects the left ventricular myocardium to progressively increasing pressure overload.

Notably, in contrast to rheumatic (and congenital) aortic stenosis (see Fig. 12-24E), commissural fusion is not a usual feature of degenerative aortic stenosis. By the time valves with aortic stenosis are seen at surgical resection or postmortem examination, however, the cusps may be secondarily fibrosed and thickened. The mitral valve is generally normal in patients with calcific aortic stenosis, although some patients may have direct extension of aortic valve calcific deposits onto the mitral anterior leaflet or independent calcification of the mitral annulus. In contrast, virtually all patients with rheumatic aortic stenosis have concomitant and characteristic structural abnormalities of the mitral valve (see later).

**Clinical Features.**

In calcific aortic stenosis (superimposed on a previously normal or bicuspid aortic valve), the obstruction to left ventricular outflow leads to a gradually increasing pressure gradient across the calcified valve, which may reach 75 to 100 mm Hg in severe cases. These pressures imply severe aortic stenosis with a valve area of approximately 0.5 to 1 cm$^2$ (normal, approximately 4 cm$^2$). Left ventricular pressure must consequently rise to 200 mm Hg or more in such instances, and cardiac output is maintained by the development of concentric left ventricular (pressure overload) hypertrophy. The hypertrophied myocardium tends to be ischemic (owing to decreased coronary blood flow reserve and impaired microcirculatory perfusion even in the presence of unobstructed coronary arteries), and angina pectoris may appear. There may be impairment of both systolic and diastolic myocardial function, with symptoms of CHF. Eventually, cardiac decompensation may ensue. The onset of symptoms (angina, CHF, or syncope, for which the pathophysiologic basis is poorly understood) in aortic stenosis heralds the exhaustion of compensatory cardiac hyperfunction and carries a poor prognosis (approximately 50% with angina will die within 5 years and 50% with CHF will die within 2 years) if not treated by surgery. Since medical therapy is ineffective in severe symptomatic aortic stenosis, such patients require prompt relief of the obstruction by surgical valve replacement. In contrast, most asymptomatic patients have an excellent prognosis. Thus, the presence or absence of symptoms is the crucial factor that determines management of aortic stenosis.

**Calcific Stenosis of Congenitally Bicuspid Aortic Valve**

Occurring with an estimated frequency of approximately 1.4% of live births, bicuspid aortic valves are generally neither stenotic nor symptomatic at birth or throughout early life. However, they are predisposed to progressive degenerative calcification, similar to that occurring in aortic valves with initially normal anatomy (see Fig. 12-22B). In a congenitally bicuspid aortic valve, there are only two functional cusps. The two cusps are usually of unequal size, with the larger cusp
having a midline raphe, resulting from incomplete separation during development; less frequently the cusps are of the same size and the raphe is absent.\(^{79}\) The raphe that represents the incomplete commissure is frequently a major site of calcific deposits. Once stenosis is present, the clinical course is similar to that described above for calcific aortic stenosis. Valves that become bicuspid owing to an acquired deformity (e.g., postinflammatory commissural fusion in rheumatic valve disease) have a conjoined cusp containing the fused commissure that is generally twice the size of the nonconjoined cusp. The mitral valve is normal in patients with a congenitally bicuspid aortic valve. Bicuspid aortic valves may also become incompetent as a result of aortic dilation, cusp prolapse, or infective endocarditis.

**Mitral Annular Calcification**

Degenerative calcific deposits can develop in the fibrous ring (annulus) of the mitral valve, visualized on gross inspection as irregular, stony hard, and occasionally ulcerated nodules (2–5 mm in thickness) that lie behind the leaflets (see Fig. 12-22C and D). The process generally does not affect valvular function. In unusual cases, however, it may lead either to regurgitation by interfering with systolic contraction of the mitral valve ring, to stenosis by impairing opening of the mitral leaflets, or to arrhythmias and occasionally sudden death by the calcium deposits penetrating sufficiently deeply to impinge on the atrioventricular conduction system. Because calcific nodules may provide a site for thrombi that can embolize, some patients with mitral annular calcification have an increased risk of stroke. The calcific nodules can also be the nidus for infective endocarditis. Heavy calcific deposits are sometimes visualized on echocardiography or seen as a distinctive, ring-like opacity on chest radiographs. Mitral annular calcification is most common in women over age 60 and individuals with myxomatous mitral valve (see below) or elevated left ventricular pressure (as in systemic hypertension, aortic stenosis, or hypertrophic cardiomyopathy).

**MYXOMATOUS DEGENERATION OF THE MITRAL VALVE (MITRAL VALVE PROLAPSE)**

In this valvular abnormality, one or both mitral leaflets are "floppy" and prolapse, or balloon back into the left atrium during systole. Mitral valve prolapse, as it is known clinically, is estimated to affect 3% or more of adults in the United States, most often young women. Myxomatous degeneration of the mitral valve, as it is known pathologically, is one of the most common forms of valvular heart disease in the industrialized world. Usually an incidental finding on physical examination, mitral valve prolapse may lead to serious complications in a small minority of those who are affected.

**Morphology.**

The characteristic anatomic change in myxomatous degeneration is intercossal ballooning (hooding) of the mitral leaflets or portions thereof (Fig. 12-23). The affected leaflets are often enlarged, redundant, thick, and rubbery. Frequently involved, the tendinous cords are elongated, thinned, and occasionally ruptured. Annular dilation is characteristic, a finding that is rare in other causes of mitral insufficiency. Concomitant involvement of the tricuspid valve is present in 20% to 40% of cases, and the aortic or pulmonic valve (or both) may also be affected. Commissural fusion that typifies rheumatic heart disease is absent. Histologically, the essential change is attenuation of
the fibrosa layer of the valve, on which the structural integrity of the leaflet depends, accompanied by focally marked thickening of the spongiosa layer with deposition of mucoid (myxomatous) material. The collagenous structure of the cords is attenuated.

Figure 12-23  Myxomatous degeneration of the mitral valve. A, Long axis of left ventricle demonstrating hooding with prolapse of the posterior mitral leaflet into the left atrium (arrow). The left ventricle is on right in this apical four-chamber view. B, Opened valve, showing pronounced hooding of the posterior mitral leaflet with thrombotic plaques at sites of leaflet-left atrium contact (arrows). C, Opened valve with pronounced hooding from patient who died suddenly (double arrows). Note also mitral annular calcification (arrowhead). (Courtesy of William D. Edwards, M.D., Mayo Clinic, Rochester, MN.)

Secondary changes reflect the stresses and 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 abnormally long cords snap 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 leaflets; (4) thrombi on the atrial surfaces of the
leaflets, particularly in the recesses behind the ballooned cusps, and on the atrial walls these thrombi contact; and (5) focal calcifications at the base of the posterior mitral leaflet.

Secondary changes of myxomatous degeneration can also occur in mitral valves having regurgitation of another etiology (e.g., ischemic dysfunction).

Pathogenesis.

The basis for the changes within the valve leaflets and associated structures is unknown. Favored is the proposition that there is an underlying developmental defect of connective tissue, possibly systemic. In keeping with this, myxomatous is degeneration of the mitral valve is a common feature of Marfan syndrome (caused by mutations in the gene encoding fibrillin-1; Chapter 5), and occasionally occurs in other hereditary disorders of connective tissues. Even in the absence of these well-defined conditions, in some individuals with the floppy mitral valve syndrome, there are hints of systemic structural abnormalities in connective tissue, such as scoliosis, straight back, and high-arched palate. Subtle defects in structural proteins may predispose connective tissues rich in microfibrils and elastin (such as cardiac valves) to damage by long-standing hemodynamic stress. Alternatively, the prominent destruction and remodeling of the valvular connective tissue evident in this disorder may be induced by a primary hemodynamic, cellular, or metabolic abnormality.

Clinical Features.

Mitral valve prolapse is defined and revealed by echocardiography. Most patients with mitral valve prolapse are asymptomatic, and the condition is discovered only on routine examination by the presence of a midsystolic click as an incidental finding on physical examination. In those cases where mitral regurgitation occurs, there is a late systolic or sometimes holosystolic murmur. A minority of patients have chest pain mimicking angina, dyspnea, and fatigue or, curiously, psychiatric manifestations, such as depression, anxiety reactions, and personality disorders. Although the great majority of patients with mitral valve prolapse have no untoward effects, approximately 3% develop one of four serious complications:

- **Infective endocarditis**, much more frequent in these patients than in the general population
- **Mitr al insufficiency requiring surgery**, either slow onset attributed to leaflet deformity, dilation of the mitral annulus, or cordal lengthening, or sudden onset owing to cordal rupture
- **Stroke or other systemic infarct**, resulting from embolism of leaflet thrombi
- **Arrhythmias**, both ventricular and atrial. Sudden death occurs occasionally (see Fig. 12-23). The mechanism of ventricular arrhythmia is unknown in most cases.

The risk of these complications is higher in men, older patients, and those with either arrhythmias or some mitral regurgitation, as evidenced by holosystolic murmurs and left-sided chamber enlargement. For patients with symptoms or at high risk for serious complications, surgical valve repair is often done.

**RHEUMATIC FEVER AND RHEUMATIC HEART DISEASE**
Rheumatic fever (RF) is an acute, immunologically mediated, multisystem inflammatory disease that occurs a few weeks following an episode of group A streptococcal pharyngitis. Acute rheumatic carditis during the active phase of RF may progress to chronic rheumatic heart disease (RHD).

The most important consequence of RF are chronic valvular deformities, characterized principally by deforming fibrotic valvular disease (particularly mitral stenosis), which produces permanent dysfunction and severe, sometimes fatal, cardiac problems decades later. Rheumatic fever does not follow infections by streptococci at other sites, such as the skin. The incidence and mortality rate of RF have declined remarkably in many parts of the world over the past 30 years, owing to improved socioeconomic conditions, rapid diagnosis and treatment of streptococcal pharyngitis, and an unexplained decrease in the virulence of group A streptococci. Nevertheless, in developing countries, and in many crowded, economically depressed urban areas in the Western world, RHD remains an important public health problem.

Morphology.

Key pathologic features of acute RF and chronic RHD are shown in Figure 12-24. During acute RF, focal inflammatory lesions are found in various tissues. They are most distinctive within the heart, where they are called Aschoff bodies. They consist of foci of swollen eosinophilic collagen surrounded by lymphocytes (primarily T cells), occasional plasma cells, and plump macrophages called Anitschkow cells (pathognomonic for RF). These distinctive cells have abundant cytoplasm and central round-to-ovoid nuclei in which the chromatin is disposed in a central, slender, wavy ribbon (hence the designation "caterpillar cells"). Some of the larger macrophages become multinucleated to form Aschoff giant cells.
Figure 12-24  Acute and chronic rheumatic heart disease. A, Acute rheumatic mitral valvulitis superimposed on chronic rheumatic heart disease. Small vegetations (verrucae) are visible along the line of closure of the mitral valve leaflet (arrows). Previous episodes of rheumatic valvulitis have caused fibrous thickening and fusion of the chordae tendineae. B, Microscopic appearance of Aschoff body in a patient with acute rheumatic carditis. The myocardial interstitium has a circumscribed collection of mononuclear inflammatory cells, including some large histiocytes with prominent nucleoli and a prominent binuclear histiocyte, and central necrosis. C and D, Mitral stenosis with diffuse fibrous thickening and distortion of the valve leaflets, commissural fusion (arrows), and thickening and shortening of the chordae tendineae. Marked dilation of the left atrium is noted in the left atrial view (C). D, Opened valve. Note neovascularization of anterior mitral leaflet (arrow). E, Surgically removed specimen of rheumatic aortic stenosis, demonstrating thickening and distortion of the cusps with commissural fusion. (E, reproduced from Schoen FJ, St. John-Sutton M: Contemporary
During acute RF, diffuse inflammation and Aschoff bodies may be found in any of the three layers of the heart—pericardium, myocardium, or endocardium—hence the lesion is called a **pancarditis**. In the pericardium, the inflammation is accompanied by a fibrinous or serofibrinous pericardial exudate, described as a "bread-and-butter" pericarditis, which generally resolves without sequelae. The myocardial involvement—myocarditis—takes the form of scattered Aschoff bodies within the interstitial connective tissue, often perivascular.

Concomitant involvement of the endocardium and the left-sided valves by inflammatory foci typically results in fibrinoid necrosis within the cusps or along the tendinous cords on which sit small (1- to 2-mm) vegetations—verrucae—along the lines of closure. These irregular, warty projections probably arise from the precipitation of fibrin at sites of erosion, related to underlying inflammation and collagen degeneration, and cause little disturbance in cardiac function. Subendocardial lesions, perhaps exacerbated by regurgitant jets, may induce irregular thickenings called **MacCallum plaques**, usually in the left atrium.

Chronic RHD is characterized by organization of the acute inflammation and subsequent fibrosis. In particular, the valvular leaflets become thickened and retracted, causing permanent deformity. The cardinal anatomic changes of the mitral (or tricuspid) valve are **leaflet thickening, commissural fusion and shortening, and thickening and fusion of the tendinous cords** (see Fig. 12-24). In chronic disease, the mitral valve is virtually always abnormal, but involvement of another valve, such as the aortic, may be the most clinically important in some cases. Microscopically there is diffuse fibrosis and often neovascularization that obliterate the originally layered and avascular leaflet architecture. Aschoff bodies are replaced by fibrous scar so that diagnostic forms of these lesions are rarely seen in surgical specimens or autopsy tissue from patients with chronic RHD. Fibrosis resulting from healed inflammation outside the valves is usually of no consequence.

RHD is overwhelmingly the most frequent cause of mitral stenosis (99% of cases). In patients with RHD, the mitral valve alone is involved in 65% to 70% of cases, and mitral and aortic in about 25%; similar but generally less severe fibrous thickenings and stenoses can occur in the tricuspid valve and rarely in the pulmonic. Fibrous bridging across the valvular commissures and calcification create "fish mouth" or "buttonhole" stenoses. With tight mitral stenosis, the left atrium progressively dilates and may harbor mural thrombus either in the appendage or along the wall. Long-standing congestive changes in the lungs may induce pulmonary vascular and parenchymal changes and in time lead to right ventricular hypertrophy. The left ventricle is generally normal with isolated pure mitral stenosis.

**Pathogenesis.**
It is strongly suspected that acute rheumatic fever is a hypersensitivity reaction induced by group A streptococci, but the exact pathogenesis remains uncertain despite many years of investigation. It is thought that antibodies directed against the M proteins of certain strains of streptococci cross-react with glycoprotein antigens in the heart, joints, and other tissues. The onset of symptoms 2 to 3 weeks after infection and the absence of streptococci from the lesions support the concept that RF results from an immune response against the offending bacteria. Because the nature of cross-reacting antigens has been difficult to define, it has also been suggested that the streptococcal infection evokes an autoimmune response against self-antigens. Only a minority of infected patients develop RF, suggesting that genetic susceptibility influences the hypersensitivity reaction. The proposed pathogenetic sequence and time course of the disease are summarized in Figure 12-25. The chronic sequelae result from progressive fibrosis due to both healing of the acute inflammatory lesions and the turbulence induced by ongoing valvular deformities.

Figure 12-25  The pathogenetic sequence and key morphologic features of acute rheumatic heart disease.
Clinical Features.

RF is characterized by a constellation of findings that includes as major manifestations (1) migratory polyarthritis of the large joints, (2) carditis, (3) subcutaneous nodules, (4) erythema marginatum of the skin, and (5) Sydenham chorea, a neurologic disorder with involuntary purposeless, rapid movements. The diagnosis is established by the so-called Jones criteria: evidence of a preceding group A streptococcal infection, with the presence of two of the major manifestations listed above or one major and two minor manifestations (nonspecific signs and symptoms that include fever, arthralgia, or elevated blood levels of acute phase reactants).

Acute rheumatic fever typically occurs 10 days to 6 weeks after an episode of pharyngitis caused by group A streptococci in about 3% of patients. Acute RF appears most often in children between ages 5 and 15, but about 20% of first attacks occur in middle to later life. Although pharyngeal cultures for streptococci are negative by the time the illness begins, antibodies to one or more streptococcal enzymes, such as streptolysin O and DNAse B, are present and can be detected in the sera of most patients. The predominant clinical manifestations are those of arthritis and carditis. Arthritis is far more common in adults than in children. It typically begins with migratory polyarthritis accompanied by fever in which one large joint after another becomes painful and swollen for a period of days and then subsides spontaneously, leaving no residual disability. Clinical features related to acute carditis include pericardial friction rubs, weak heart sounds, tachycardia, and arrhythmias. The myocarditis may cause cardiac dilation that may evolve to functional mitral valve insufficiency or even heart failure. Overall the prognosis for the primary attack is generally good, and only 1% of patients die from fulminant RF.

After an initial attack, there is increased vulnerability to reactivation of the disease with subsequent pharyngeal infections, and the same manifestations are likely to appear with each recurrent attack. Carditis is likely to worsen with each recurrence, and damage is cumulative. Other hazards include embolization from mural thrombi, primarily within the atria or their appendages, and infective endocarditis superimposed on deformed valves. Chronic rheumatic carditis usually does not cause clinical manifestations for years or even decades after the initial episode of RF. The signs and symptoms of valvular disease depend on which cardiac valve(s) are involved. In addition to various cardiac murmurs, cardiac hypertrophy and dilation, and heart failure, patients with chronic rheumatic heart disease may suffer from arrhythmias (particularly atrial fibrillation in the setting of mitral stenosis), thromboembolic complications, and infective endocarditis. The long-term prognosis is highly variable. In some cases, there is a relentless cycle of valvular deformity yielding hemodynamic abnormality, which begets further deforming fibrosis. Surgical repair of diseased valves by incising the fused mitral valve commissures and replacement with prosthetic devices has greatly improved the outlook for patients with RHD.

INFECTIVE ENDOCARDITIS (IE)

Infective endocarditis, one of the most serious of all infections, is characterized by colonization or invasion of the heart valves or the mural endocardium by a microbe, leading to the formation of bulky, friable vegetations composed of thrombotic debris and organisms, often associated with destruction of the underlying cardiac tissues. The aorta, aneurysmal sacs, other blood vessels, and prosthetic devices can also become infected. Although fungi, rickettsiae (Q fever), and
Chlamydiae have at one time or another been responsible for these infections, most cases are bacterial (bacterial endocarditis). Prompt diagnosis and effective treatment of IE can significantly alter the outlook for the patient.

Traditionally, IE has been classified on clinical grounds into acute and subacute forms. This subdivision expresses the range of severity of the disease and its tempo, determined in large part by the virulence of the infecting microorganism and whether underlying cardiac disease is present. Acute endocarditis describes a destructive, tumultuous infection, frequently of a previously normal heart valve, with a highly virulent organism, that leads to death within days to weeks of more than 50% of patients despite antibiotics and surgery. In contrast, organisms of low virulence can cause infection in a previously abnormal heart, particularly on deformed valves. In such cases, the disease may appear insidiously and, even untreated, pursue a protracted course of weeks to months (subacute endocarditis). Most patients with subacute IE recover after appropriate antibiotic therapy.

The highly virulent organisms of acute endocarditis tend to produce necrotizing, ulcerative, invasive valvular infections that are difficult to cure by antibiotics and usually require surgery. In contrast, the lower-virulence organisms of subacute disease are less destructive than those of acute endocarditis, and the vegetations often show evidence of healing. Both the clinical and the morphologic patterns, however, are points along a spectrum, and a clear delineation between acute and subacute disease does not always exist.

Etiology and Pathogenesis.

As stated previously, IE may develop on previously normal valves, but a variety of cardiac and vascular abnormalities predispose to this form of infection. In years past, RHD was the major antecedent disorder, but more common now are myxomatous mitral valve, degenerative calcific valvular stenosis, bicuspid aortic valve (whether calcified or not), and artificial (prosthetic) valves. Host factors such as neutropenia, immunodeficiency, malignancy, therapeutic immunosuppression, diabetes mellitus, and alcohol or intravenous drug abuse are predisposing influences. Sterile platelet-fibrin deposits that accumulate at sites of impingement of jet streams caused by pre-existing cardiac disease or indwelling vascular catheters may also be important in the development of endocarditis.

The causative organisms differ somewhat in the major high-risk groups. Endocarditis of native but previously damaged or otherwise abnormal valves is caused most commonly (50% to 60% of cases) by Streptococcus viridans; this is not the organism responsible for rheumatic disease discussed earlier. In contrast, the more virulent S. aureus organisms commonly found on the skin can attack either healthy or deformed valves and are responsible for 10% to 20% of cases overall; S. aureus is the major offender in intravenous drug abusers. The roster of the remaining bacteria includes enterococci and the so-called HACEK group (Haemophilus, Actinobacillus, Cardiobacterium, Eikenella, and Kingella), all commensals in the oral cavity. Prosthetic valve endocarditis is caused most commonly by coagulase-negative staphylococci (e.g., S. epidermidis). Other agents causing endocarditis include gram-negative bacilli and fungi. In about 10% of all cases of endocarditis, no organism can be isolated from the blood ("culture-negative" endocarditis).
because of prior antibiotic therapy, difficulties in isolating the offending agent, or because deeply embedded organisms within the enlarging vegetation are not released into the blood.

Foremost among the factors predisposing to the development of endocarditis is seeding of the blood with microbes. The portal of entry of the agent into the bloodstream may be an obvious infection elsewhere, a dental or surgical procedure that causes a transient bacteremia, injection of contaminated material directly into the bloodstream by intravenous drug users, or an occult source from the gut, oral cavity, or trivial injuries. Recognition of predisposing anatomic substrates and clinical conditions causing bacteremia facilitates prevention by appropriate antibiotic prophylaxis. 

Morphology.

In both the subacute and acute forms of the disease, friable, bulky, and potentially destructive vegetations containing fibrin, inflammatory cells, and bacteria or other organisms are present on the heart valves (Fig. 12-26). The aortic and mitral valves are the most common sites of infection, although the valves of the right heart may also be involved, particularly in intravenous drug abusers. The vegetations may be single or multiple and may involve more than one valve. Vegetations sometimes erode into the underlying myocardium to produce an abscess cavity (ring abscess), one of several important complications. The appearance of the vegetations is influenced by the type of organism responsible, the degree of host reaction to the infection, and previous antibiotic therapy. Fungal endocarditis, for example, tends to cause large vegetations than does bacterial infection. Systemic emboli may occur at any time because of the friable nature of the vegetations, and they may cause infarcts in the brain, kidneys, myocardium, and other tissues. Because the embolic fragments contain large numbers of virulent organisms, abscesses often develop at the sites of such infarcts (septic infarcts).
Figure 12-26  Infective (bacterial) endocarditis.  

A, Endocarditis of mitral valve (subacute, caused by Strep. viridans). The large, friable vegetations are denoted by arrows.  

B, Acute endocarditis of congenitally bicuspid aortic valve (caused by Staph. aureus) with extensive cuspal destruction and ring abscess (arrow).  

C, Histologic appearance of vegetation of endocarditis with extensive acute inflammatory cells and fibrin. Bacterial organisms were demonstrated by tissue Gram stain.  

D, Healed endocarditis, demonstrating mitral valvular destruction but no active vegetations.  

(C, reproduced from Schoen FJ: Surgical pathology of removed natural and prosthetic heart valves. Human Pathol 18:558, 1987.)

The vegetations of subacute endocarditis are associated with less valvular destruction than those of acute endocarditis, although the distinction between the two forms may be difficult.  

Microscopically, the vegetations of typical subacute IE often have granulation tissue at their bases (suggesting chronicity). With the passage of time, fibrosis, calcification, and a chronic inflammatory infiltrate may develop.

Figure 12-27 compares the gross appearance of the vegetations of infective endocarditis with those of the valve lesions characterized by non-infective thrombotic vegetations (NBTE), and with the endocarditis of systemic lupus erythematosus (SLE), called Libman-Sacks endocarditis (see later).

Figure 12-27  Diagrammatic comparison of the lesions in the four major forms of vegetative endocarditis. The rheumatic fever phase of RHD (rheumatic heart disease) is marked by a row of small, warty vegetations along the lines of closure of the valve leaflets. IE (infective endocarditis) is characterized by large, irregular masses on the valve cusps that can extend onto the chordae (see Fig. 12-26). NBTE (nonbacterial thrombotic endocarditis) typically exhibits small, bland vegetations, usually attached at the line of closure. One or many may be present (see Fig. 12-28). LSE (Libman-Sacks endocarditis) has small or medium-sized vegetations on either or both sides of the valve leaflets.
Clinical Features.

Fever is the most consistent sign of IE. However, with subacute disease, particularly in the elderly, fever may be slight or absent, and the only manifestations are sometimes nonspecific fatigue, loss of weight, and a flulike syndrome. In contrast, acute endocarditis has a stormy onset with rapidly developing fever, chills, weakness, and lassitude. Complications generally begin within the first weeks of the onset of the disease. They may be immunologically mediated as exemplified by glomerulonephritis, owing to trapping of antigen-antibody complexes, which can cause hematuria, albuminuria, or renal failure (Chapter 20). Sometimes complications involving the heart or extracardiac sites call attention to endocarditis. Murmurs are present in 90% of patients with left-sided lesions but may merely relate to the pre-existing cardiac abnormality predisposing to IE. The so-called Duke criteria (Table 12-8) provide a standardized assessment of patients with suspected IE that integrates factors predisposing patients to the development of IE, blood-culture evidence of infection, echocardiographic findings, and clinical and laboratory information in assessing patients with potential IE. Previously important clinical findings secondary to microemboli are now uncommon. They include petechiae, red, linear, or flame-shaped streaks in the nail bed of the digits (splinter or subungual hemorrhages), erythematous or hemorrhagic nontender lesions on the palms or soles (Janeway lesions), subcutaneous nodules in the pulp of the digits (Osler nodes). Also included are retinal hemorrhages (Roth spots) in the eyes owing to the shortened clinical course of the disease as a result of antibiotic therapy.

<table>
<thead>
<tr>
<th>Table 12-8 -- Diagnostic Criteria for Infective Endocarditis *</th>
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<tbody>
<tr>
<td><strong>Pathologic Criteria</strong></td>
</tr>
<tr>
<td>Microorganisms, demonstrated by culture or histologic examination, in a vegetation, embolus from a vegetation, or intracardiac abscess</td>
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<tr>
<td>Histologic confirmation of active endocarditis in vegetation or intracardiac abscess</td>
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<tr>
<td><strong>Clinical Criteria</strong></td>
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<tr>
<td><strong>Major</strong></td>
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<tr>
<td>Positive blood culture(s) indicating characteristic organism or persistence of unusual organism</td>
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<tr>
<td>Echocardiographic findings, including valve-related or implant-related mass or abscess, or partial separation of artificial valve</td>
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<tr>
<td>New valvular regurgitation</td>
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<tr>
<td><strong>Minor</strong></td>
</tr>
<tr>
<td>Predisposing heart lesion or intravenous drug use</td>
</tr>
<tr>
<td>Fever</td>
</tr>
<tr>
<td>Vascular lesions, including arterial petechiae, subungual/splinter hemorrhages, emboli, septic infarcts, mycotic aneurysm, intracranial hemorrhage, Janeway lesions</td>
</tr>
<tr>
<td>Immunologic phenomena, including glomerulonephritis, Osler nodes, Roth spots, rheumatoid factor</td>
</tr>
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</table>

Janeway lesions are small erythematous or hemorrhagic, macular, nontender lesions on the palms and soles and are the consequence of septic embolic events.

Osler nodes are small, tender subcutaneous nodules that develop in the pulp of the digits or occasionally more proximally in the fingers and persist for hours to several days.

Roth spots are oval retinal hemorrhages with pale centers.

Prevention of IE is important and is done by the prophylactic use of antibiotics in the patient with some form of cardiac anomaly or artificial valve who is about to have a dental, surgical, or other invasive procedure.

NONINFECTED VEGETATIONS
Nonbacterial Thrombotic Endocarditis (NBTE)

NBTE is characterized by the deposition of small masses of fibrin, platelets, and other blood components on the leaflets of the cardiac valves. In contrast to the vegetations of IE, discussed previously, the valvular lesions of NBTE are sterile and do not contain microorganisms. NBTE is often encountered in debilitated patients, such as those with cancer or sepsis—hence the previously used term marantic endocarditis. Although the local effect on the valves is usually unimportant, NBTE may achieve clinical significance by producing emboli and resultant infarcts in the brain, heart, or elsewhere.

Morphology.

In contrast to IE, the vegetations of NBTE are sterile, nondestructive, and small (1 to 5 mm), and occur singly or multiply along the line of closure of the leaflets or cusps (Fig. 12-28). Histologically, they are composed of bland thrombus without accompanying inflammatory reaction or induced valve damage. Should the patient survive the underlying disease, organization may occur, leaving delicate strands of fibrous tissue.
Figure 12-28  Nonbacterial thrombotic endocarditis (NBTE). A, Nearly complete row of thrombotic vegetations along the line of closure of the mitral valve leaflets (arrows). B, Photomicrograph of NBTE, showing bland thrombus, with virtually no inflammation in the valve cusp (c) or the thrombotic deposit (t). The thrombus is only loosely attached to the cusp (arrow).

Pathogenesis.

NBTE frequently occurs concomitantly with venous thromboses or pulmonary embolism, suggesting a common origin in a hypercoagulable state with systemic activation of blood coagulation such as disseminated intravascular coagulation (Chapter 4). This may be related to some underlying disease, such as a cancer, and, in particular, mucinous adenocarcinomas of the pancreas. The striking association with mucinous adenocarcinomas in general may relate to the procoagulant effect of circulating mucin, and thus NBTE can be a part of the Trousseau syndrome (Chapter 7). Lesions of NBTE, however, are also seen occasionally in association with nonmucin-producing malignancy, such as acute promyelocytic leukemia, and in other debilitating diseases or conditions (e.g., hyperestrogenic states, extensive burns, or sepsis) promoting hypercoagulability. Endocardial trauma, as from an indwelling catheter, is also a well-recognized predisposing condition, and one frequently notes right-sided valvular and endocardial thrombotic lesions along the track of a Swan-Ganz pulmonary artery catheter.

Endocarditis of Systemic Lupus Erythematosus (Libman-Sacks Disease)

In SLE, mitral and tricuspid valvulitis with small, sterile vegetations, called Libman-Sacks endocarditis is occasionally encountered.

Thrombotic heart valve lesions with sterile vegetations or rarely fibrous thickening commonly occur with the antiphospholipid syndrome (discussed in Chapter 4). Circulating antiphospholipid antibodies are also commonly associated with venous or arterial thrombosis, recurrent pregnancy loss, or thrombocytopenia. The mitral valve is more frequently involved than the aortic; regurgitation is the usual functional abnormality.

Morphology.
The lesions are small single or multiple, sterile, granular pink vegetations ranging from 1 to 4 mm in diameter. The lesions may be located on the undersurfaces of the atrioventricular valves, on the valvular endocardium, on the cords, or on the mural endocardium of atria or ventricles. Histologically the verrucae consist of a finely granular, fibrinous eosinophilic material that may contain hematoxylin bodies (the tissue equivalent of the lupus erythematosus cell of the blood and bone marrow, see Chapter 6). An intense valvulitis may be present, characterized by fibrinoid necrosis of the valve substance that is often contiguous with the vegetation. Leaflet vegetations can be difficult in some cases to distinguish from those of IE or NBTE (see Fig. 12-27). Subsequent fibrosis and serious deformity can result that resemble chronic RHD and require surgery.

CARCINOID HEART DISEASE

Carcinoid heart disease is the cardiac manifestation of the systemic syndrome caused by carcinoid tumors. It involves the endocardium and valves of the right heart. Cardiac lesions are present in one half of patients with the carcinoid syndrome which is characterized by episodic flushing of the skin, cramps, nausea, vomiting, and diarrhea (see Chapter 17).

Morphology.

The cardiovascular lesions associated with the carcinoid syndrome are distinctive, consisting of fibrous intimal thickenings on the inside surfaces of the cardiac chambers and valvular leaflets. They are located mainly in the right ventricle, tricuspid and pulmonic valves, and occasionally in the major blood vessels (Fig. 12-29). The endocardial plaquelike thickenings are composed predominantly of smooth muscle cells and sparse collagen fibers embedded in an acid mucopolysaccharide-rich matrix material. Elastic fibers are not present. Underlying structures are intact, including the valve layers and the subendocardial elastic tissue layer. Occasionally, left-sided lesions are also encountered.

Figure 12-29 Carcinoid heart disease. A, Characteristic endocardial fibrotic lesion involving the right ventricle and tricuspid valve. B, Microscopic appearance of carcinoid heart disease with intimal thickening. Movat stain shows underlying myocardial elastic tissue black and acid mucopolysaccharides blue-green.
The clinical and pathologic findings relate to the elaboration by carcinoid tumors of a variety of bioactive products, such as serotonin (5-hydroxytryptamine), kallikrein, bradykinin, histamine, prostaglandins, and tachykinins. Which of the secretory products induces the syndrome or the cardiac pathology is still not clear. Nevertheless, plasma levels of serotonin and urinary excretion of the serotonin metabolite 5-hydroxyindoleacetic acid correlate with the severity of the right heart lesions.\textsuperscript{90}

The fact that the cardiac changes are largely right-sided is explained by inactivation of both serotonin and bradykinin in the blood during passage through the lungs by the monoamine oxidase present in the pulmonary vascular endothelium. In the absence of hepatic metastases, gastrointestinal carcinoids (with venous drainage via the portal system) do not usually induce the carcinoid syndrome because there is rapid metabolism of serotonin during passage of blood through the liver. In contrast, primary carcinoid tumors in organs outside of the portal system of venous drainage (e.g., ovary and lung), may induce the syndrome without producing hepatic metastases. Left-sided lesions can occur when blood containing the responsible mediator enters the left heart owing to incomplete inactivation because of very high blood levels. Left side lesions may also be a consequence of a pulmonary carcinoid or patent foramen ovale with right to left flow.

Left-sided valve lesions with pathologic features similar to those seen in the carcinoid syndrome have been reported to complicate the use of fenfluramine and phentermine (fenphen), appetite suppressants used for the treatment of obesity; these agents may affect systemic serotonin metabolism.\textsuperscript{91} Occasionally, similar left-sided plaques are found in patients who receive methysergide or ergotamine therapy for migraine headaches; these serotonin analogs are metabolized to serotonin as they pass through the pulmonary vasculature.

**COMPLICATIONS OF ARTIFICIAL VALVES**

Replacement of damaged cardiac valves with prostheses has now become a common and often life-saving mode of therapy.\textsuperscript{92,93} Artificial valves fall primarily into two categories: (1) **mechanical prostheses** using different types of rigid, mobile occluders composed of nonphysiologic biomaterials, such as caged balls, tilting disks, or hinged semicircular flaps, and (2) **tissue valves**, usually **bioprostheses** consisting of chemically treated animal tissue, especially porcine aortic valve tissue, which has been preserved in a dilute glutaraldehyde solution and subsequently mounted on a prosthetic frame. Tissue valves are flexible and function somewhat like natural semilunar valves.

Approximately 60% of substitute valve recipients develop a serious prosthesis-related problem within 10 years postoperatively.\textsuperscript{94} Although the frequency of total prosthetic valve-related events is similar among valve types, the nature of these complications differs among types (Table 12-9 and Fig. 12-30).

- Thromboembolic complications constituting local obstruction of the prosthesis by thrombus or distant thromboemboli are the major problem with mechanical valves (Fig. 12-30A). This...
necessitates long-term anticoagulation in patients with these devices. However, hemorrhagic complications such as stroke or gastrointestinal bleeding may arise secondarily in patients who receive long-term anticoagulation.

? **Infective endocarditis** is an infrequent but potentially serious complication. Endocarditis is located at the prosthesis-tissue interface, causing a ring abscess, which can eventually lead to a paravalvular regurgitant blood leak. In addition, vegetations may directly involve bioprosthetic valvular cusps. The major organisms causing such infections are staphylococcal skin contaminants (e.g., *S. aureus, S. epidermidis*), streptococci, and fungi.

? **Structural deterioration** uncommonly causes failure of contemporary mechanical valves. However, it is a major failure mode of bioprostheses, with calcification and/or tearing causing secondary regurgitation (see [Fig. 12-30B](#)).

? Other complications include hemolysis induced by high blood shear, mechanical obstruction to flow inherent in all artificial valves, and inadequate or exuberant healing, causing a paravalvular leak or overgrowth of fibrous tissue, respectively.

![Figure 12-30](image) **Complications of artificial heart valves.** A, Thrombosis of a mechanical prosthetic valve. B, Calcification with secondary tearing of a porcine bioprosthetic heart valve, viewed from the inflow aspect.

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<thead>
<tr>
<th>Table 12-9 -- Causes of Failure of Cardiac Valve Prostheses</th>
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<tbody>
<tr>
<td>Thrombosis/thromboembolism</td>
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<tr>
<td>Anticoagulant-related hemorrhage</td>
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<tr>
<td>Prosthetic valve endocarditis</td>
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<tr>
<td>Structural deterioration (intrinsic)</td>
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<tr>
<td>Wear, fracture, poppet failure in ball valves, cuspal tear, calcification</td>
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<tr>
<td>Nonstructural dysfunction</td>
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<tr>
<td>---------------------------</td>
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<tr>
<td>Granulation tissue, suture, tissue entrapment, paravalvular leak, disproportion, hemolytic anemia, noise</td>
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