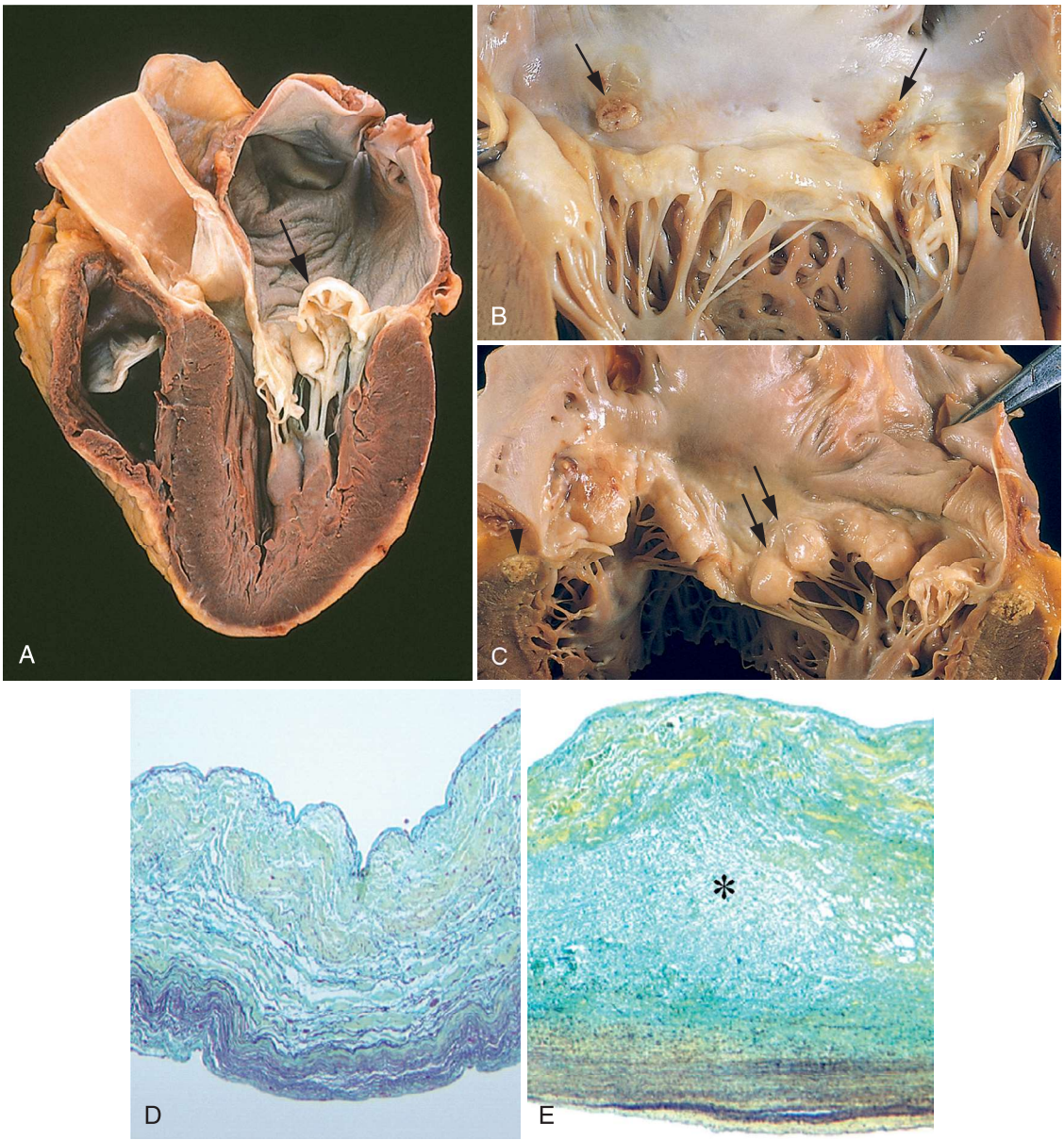

Figure 12.21 Myxomatous degeneration of the mitral valve. (A) Long axis view (left ventricle is on the *right*) demonstrating hooding with prolapse of the posterior mitral leaflet into the left atrium *(arrow)*. (B) Opened valve, showing pronounced hooding of the posterior mitral leaflet with thrombotic plaques at sites of leaflet-left atrium contact *(arrows)*. (C) Opened valve with pronounced hooding *(double arrows)* in a patient who died suddenly. Note also mitral annular calcification on the left side *(arrowhead)*. Normal heart valve (D) and myxomatous mitral valve (E). In myxomatous valves, collagen in the fibrosa layer is loose and disorganized, proteoglycan deposition *(asterisk)* in the central spongiosa layer is markedly expanded, and elastin in the atrialis layer is disorganized. (A, Courtesy William D. Edwards, MD, Mayo Clinic, Rochester, Minn; D and E, Movat pentachrome stain, in which collagen is yellow, elastin is black, and proteoglycans are blue). From Rabkin E, et al: Activated interstitial myofibroblasts express catabolic enzymes and mediate matrix remodeling in myxomatous heart valves, *Circulation* 104:2525–2532, 2001.)

death. Valve repair or replacement surgery can be done for symptomatic patients or those with increased risk for significant complications.

Rheumatic Fever and Rheumatic Heart Disease

Rheumatic fever (RF) is an acute, immunologically mediated, multisystem inflammatory disease classically occurring a few weeks after group A streptococcal pharyngitis; occasionally, RF can follow streptococcal infections at other sites, such as the skin. Acute rheumatic carditis is a common manifestation of active RF and may progress over time to chronic rheumatic heart disease (RHD).

RHD is characterized principally by deforming fibrotic valvular disease, particularly involving the mitral valve; indeed, RHD is virtually the only cause of mitral stenosis. The incidence and mortality rate of RF and RHD have declined remarkably in many parts of the world over the past century, as a result of improved sanitation, and rapid diagnosis and treatment of streptococcal pharyngitis.

Nevertheless, in low income countries, and in many crowded, economically depressed urban areas, RHD remains an important public health problem.

Pathogenesis

Acute rheumatic fever results from host immune responses to group A streptococcal antigens that cross-react with host proteins. The characteristic 2- to 3-week delay in symptom onset after infection is explained by the time needed to generate an immune response; In particular, antibodies and CD4+ T cells directed against streptococcal M proteins can also in some cases recognize cardiac self antigens. Antibody binding can activate complement, as well as recruit Fc-receptor–bearing cells (neutrophils and macrophages); cytokine production by the stimulated T cells leads to macrophage activation (e.g., within Aschoff bodies). Damage to heart tissue may thus be caused by a combination of antibody- and T cell–mediated reactions (Chapter 6). In keeping with an immunologic basis of RHD, streptococci are completely absent from the lesions. Because only a small minority of infected patients develop rheumatic fever (estimated at 3%), a genetic susceptibility is likely to influence the development of the cross-reactive immune responses. The chronic fibrotic lesions are the predictable consequence of healing and scarring associated with the resolution of the acute inflammation.

MORPHOLOGY

Key pathologic features of acute RF and chronic RHD are shown in Fig. 12.22. During acute RF, focal inflammatory lesions are found in various tissues. Distinctive lesions in the heart—called **Aschoff bodies**—are composed of foci of T lymphocytes, occasional plasma cells, and plump activated macrophages called **Anitschkow cells.** These macrophages have abundant cytoplasm and central round-to-ovoid nuclei (occasionally binucleate) in which the chromatin condenses into a central, slender, wavy ribbon (hence the designation "caterpillar cells").

During acute RF, diffuse inflammation and Aschoff bodies may be found in any of the three layers of the heart, resulting in pericarditis, myocarditis, or endocarditis **(pancarditis).**

Inflammation of the endocardium and the left-sided valves typically results in fibrinoid necrosis within the cusps or tendinous

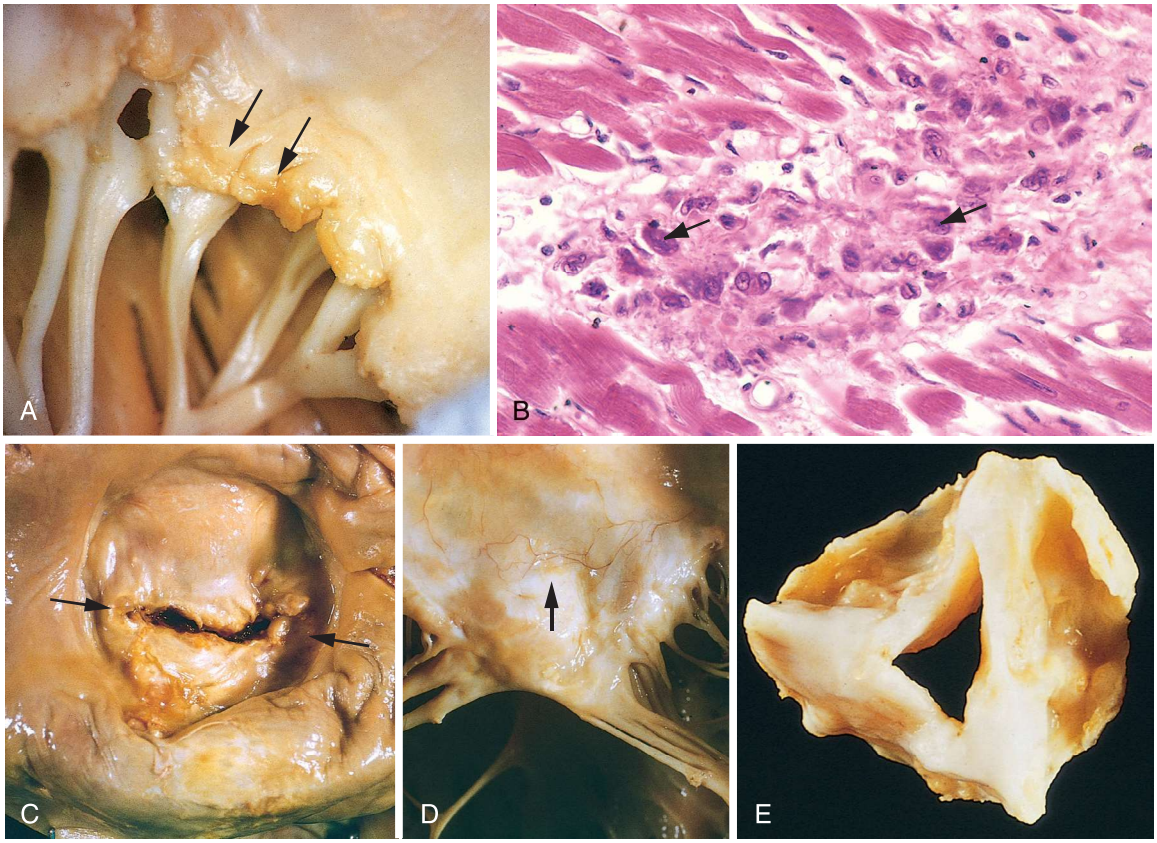

Figure 12.22 Acute and chronic rheumatic heart disease. (A) Acute rheumatic mitral valvulitis superimposed on chronic rheumatic heart disease. Small vegetations (verrucae) are visible along the line of closure of the mitral valve leaflet *(arrows)*. Previous episodes of rheumatic valvulitis have caused fibrous thickening and fusion of the chordae tendineae. (B) Microscopic appearance of an Aschoff body in a patient with acute rheumatic carditis. The myocardium exhibits a circumscribed nodule of mixed mononuclear inflammatory cells with associated necrosis; within the inflammation, large activated macrophages show prominent nucleoli, as well as chromatin condensed into long, wavy ribbons (caterpillar cells; *arrows*). (C and D) Mitral stenosis with diffuse fibrous thickening and distortion of the valve leaflets and commissural fusion (*arrows*, C), and thickening of the chordae tendineae (D). Note the neovascularization of the anterior mitral leaflet (*arrow*, D). (E) Surgically resected 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 issues in the pathology of valvular heart disease, *Hum Pathol* 18:568, 1967.)

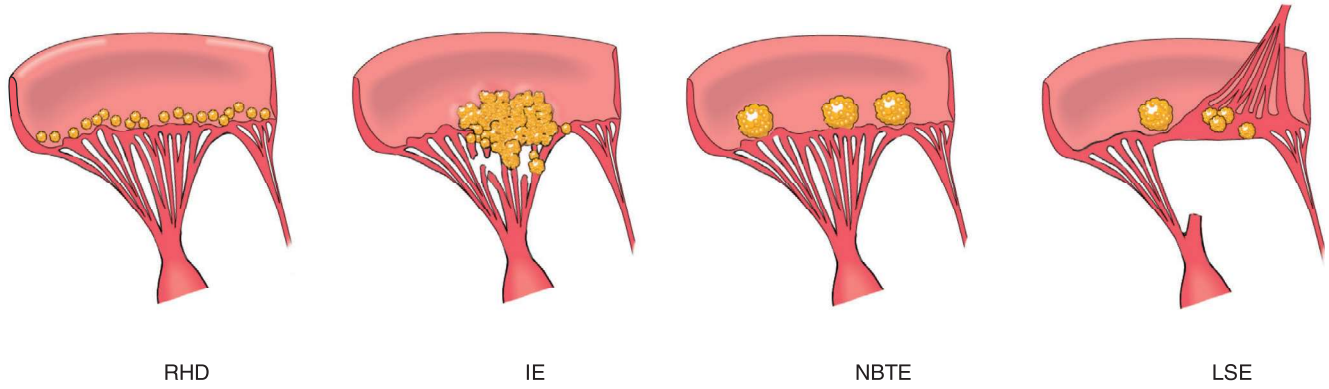

Figure 12.23 Comparison of the four major forms of vegetative endocarditis. The rheumatic fever phase of rheumatic heart disease *(RHD)* is marked by small, warty vegetations along the lines of closure of the valve leaflets. Infective endocarditis *(IE)* is characterized by large, irregular masses on the valve cusps that can extend onto the chordae (see Fig. 12.24A). Nonbacterial thrombotic endocarditis *(NBTE)* typically exhibits small, bland vegetations, usually attached at the line of closure. One or many may be present (see Fig. 12.25). Libman-Sacks endocarditis *(LSE)* has small- or medium-sized vegetations on either or both sides of the valve leaflets.

cords. Overlying these necrotic foci and along the lines of closure are small (1 to 2 mm) vegetations, called **verrucae.** Thus, RHD is one of the forms of vegetative valve disease, each of which exhibit their own characteristic morphologic features (Fig. 12.23). Subendocardial lesions, perhaps exacerbated by regurgitant jets, can induce irregular thickenings called **MacCallum plaques,** usually in the left atrium.

The cardinal anatomic changes of the mitral valve in chronic RHD are **leaflet thickening, commissural fusion and shortening, and thickening and fusion of the tendinous cords** (see Fig. 12.22D). The mitral valve is virtually always involved in chronic RHD; it is affected in isolation in roughly two-thirds of cases, and along with the aortic valve in another 25%. Tricuspid valve involvement is infrequent, and the pulmonary valve is only rarely affected.

In rheumatic mitral stenosis, calcification and fibrous bridging across the valvular commissures create "fish mouth" stenoses (see Fig. 12.22C). With tight mitral stenosis, the left atrium progressively dilates and may harbor mural thrombi that can embolize. Long-standing congestive changes in the lungs may induce pulmonary vascular and parenchymal changes; over time, these can lead to right ventricular hypertrophy. The left ventricle is largely unaffected by isolated pure mitral stenosis. Microscopically, valves show organization of the acute inflammation, with postinflammatory neovascularization and transmural fibrosis that obliterate the leaflet architecture. Aschoff bodies are rarely seen in surgical specimens or autopsy tissue from patients with chronic RHD, because of the long intervals between the initial insult and the development of the chronic deformity.

Clinical Features

RF is characterized by a constellation of major manifestations:

- *Migratory polyarthritis* of the large joints
- *Pancarditis* (myocarditis, pericarditis, or endocarditis)
- *Subcutaneous nodules* (typically on extensor surfaces of extremities)
- *Erythema marginatum*, an irregular circinate skin rash
- *Sydenham chorea*, a neurologic disorder with involuntary rapid movements

The diagnosis is established in accordance with the revised Jones criteria: evidence of a preceding group A streptococcal infection, and the presence of two major manifestations, or one major and two minor manifestations (nonspecific signs and symptoms that include fever, arthralgia, or elevated blood levels of acute-phase reactants); notably, these criteria are evolving and are applied differently in low- and high-risk settings.

Acute RF typically appears 10 days to 6 weeks after a group A streptococcal infection in about 3% of patients. It occurs most often in children between 5 and 15 years of age, but first attacks can 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, can be detected in the sera of most patients with RF. The predominant clinical manifestations are carditis and arthritis, the latter more common in adults than in children. Arthritis 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, tachycardia, and arrhythmias. Myocarditis can cause cardiac dilation that may culminate in functional mitral valve insufficiency or even heart failure. Approximately 1% of affected individuals die of fulminant RF involvement of the heart.

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. Damage to the valves is cumulative. Turbulence induced by ongoing valvular deformities leads to additional fibrosis. This is a prime example of a common theme in valvular heart disease in which the consequences of valve pathology may contribute to progression of that valve pathology in a positive feedback loop.

Clinical manifestations of RHD appear years or even decades after the initial episode of RF and depend on which valves are involved. In addition to cardiac murmurs, cardiac hypertrophy and dilation, and heart failure, individuals with chronic RHD may suffer from arrhythmias (particularly atrial fibrillation in the setting of mitral stenosis),

thromboembolic complications, and infective endocarditis (see later). The long-term prognosis is highly variable. Surgical repair or replacement of diseased valves has greatly improved the outlook for persons with RHD.

Infective Endocarditis (IE)

IE is a microbial infection of the heart valves or the mural endocardium that leads to the formation of vegetations composed of thrombotic debris and organisms, often associated with destruction of the underlying cardiac tissues. The aorta, aneurysms, other blood vessels, and prosthetic devices can also become infected. Although fungi and other classes of microorganisms can be responsible, most infections are bacterial (bacterial endocarditis). Prompt diagnosis, identification of the offending agent, and effective treatment of IE is important in limiting morbidity and mortality.

Traditionally, IE has been classified on clinical grounds into acute and subacute forms based on severity and tempo (reflecting microbial virulence), and whether there is underlying valvular pathology. Thus, acute IE is typically caused by infection of a previously normal heart valve by a highly virulent organism (e.g., *Staphylococcus aureus*) that rapidly produces destructive lesions. These infections may be difficult to cure with antibiotics alone and often require surgery; despite appropriate treatment, there can be substantial morbidity and even mortality. In contrast, subacute IE is characterized by organisms with lower virulence (e.g., viridans streptococci) that cause insidious infections of deformed valves with overall less destruction. In such cases the disease may pursue a protracted course of weeks to months, and cures can often be achieved with antibiotics alone. Of note, a clear delineation between acute and subacute endocarditis does not always exist, and many cases fall somewhere along the spectrum between the two forms.

Pathogenesis

Although highly virulent organisms can infect previously normal valves, a variety of cardiac abnormalities increase the risk of developing IE. RHD with valvular scarring has historically been the major antecedent disorder; as RHD becomes less common, it has been supplanted by mitral valve prolapse, degenerative calcific valvular stenosis, bicuspid aortic valve (whether calcified or not), artificial (prosthetic) valves, and congenital defects.

Endocarditis of native but previously damaged or otherwise abnormal valves is caused most commonly (50% to 60% of cases) by *Streptococcus viridans*, a normal component of the oral cavity flora. In contrast, more virulent *S. aureus* organisms commonly found on the skin can infect either healthy or deformed valves and are responsible for 20% to 30% of cases overall; notably, *S. aureus* is the major offender in IE among intravenous drug abusers. Other bacterial causes include enterococci and the so-called HACEK group (*Haemophilus, Actinobacillus, Cardiobacterium, Eikenella,* and *Kingella*), all commensals in the oral cavity. More rarely, Gram-negative bacilli and fungi can be involved. Prosthetic valve endocarditis occurring in the 1 to 2 months after surgical implantation is typically caused by skin flora (*S. aureus* and *S. epidermidis*); prosthetic valve infections 1 year or more after surgery tend to be streptococci and *S. aureus* (see later discussion of prosthetic valves). In about 10% of all cases of endocarditis, no organism can be isolated from the blood ("culture-negative" endocarditis); reasons include 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 endocarditis are those that cause microorganism seeding into the bloodstream (bacteremia or fungemia). The source may be an obvious infection elsewhere, a dental or surgical procedure, a contaminated needle shared by intravenous drug users, or seemingly trivial breaks in the epithelial barriers of the gut, oral cavity, or skin. In patients with valve abnormalities, or with known bacteremia, IE risk can be lowered by antibiotic prophylaxis.

MORPHOLOGY

Vegetations on heart valves are the classic hallmark of IE; these are friable, bulky, potentially destructive lesions containing fibrin, inflammatory cells, and bacteria or other organisms (Figs. 12.23 and 12.24). The aortic and mitral valves are the most common

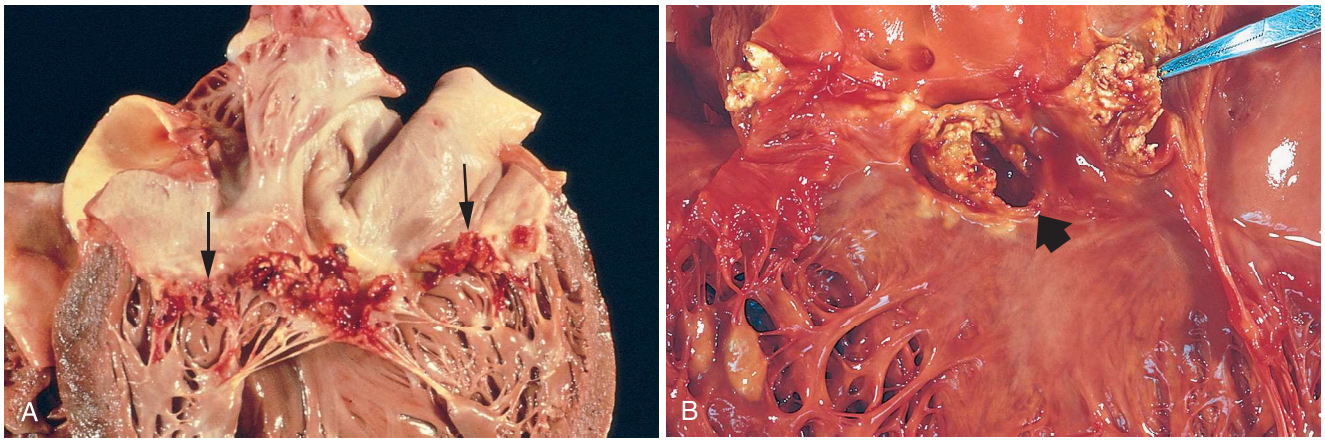

Figure 12.24 Infective (bacterial) endocarditis. (A) Endocarditis of mitral valve (subacute, caused by *Streptococcus viridans*). The large, friable vegetations are denoted by *arrows*. (B) Acute endocarditis of congenitally bicuspid aortic valve (caused by *Staphylococcus aureus*) with extensive cuspal destruction and ring abscess *(arrow)*.

sites of infection, although the valves of the right heart may also be involved, particularly in intravenous drug abusers. Vegetations can be single or multiple and may involve more than one valve; they can occasionally erode into the underlying myocardium and produce an abscess (ring abscess; see Fig. 12.24B). Vegetations are prone to embolization; because the embolic fragments often contain virulent organisms, abscesses frequently develop where they lodge, leading to sequelae such as septic infarcts or mycotic aneurysms.

The vegetations of subacute endocarditis are associated with less valvular destruction than those of acute endocarditis, although the distinction can be subtle. Microscopically, the vegetations of subacute IE typically exhibit granulation tissue at their bases indicative of healing. With time, fibrosis, calcification, and a chronic inflammatory infiltrate can develop.

Clinical Features

Acute endocarditis has a stormy onset with rapid onset of fever, chills, weakness, and lassitude. Although fever is the most consistent sign of IE, it can be slight or absent, particularly in older adults, and the only manifestations may be nonspecific fatigue, weight loss, and a flulike syndrome. Murmurs are present in the majority of patients with left-sided IE, either from a new valvular defect or from a preexisting abnormality. The modified Duke criteria (Table 12.9) facilitate diagnosis of individuals with suspected IE by taking into account predisposing factors, physical findings, blood culture results, echocardiographic findings, and laboratory information.

Complications of IE generally begin within the first few weeks of onset and can include glomerular antigen-antibody complex deposition causing glomerulonephritis (Chapter 20). Sepsis, arrhythmias (suggesting invasion into underlying myocardium and conduction system), and systemic embolization bode particularly ill for the patient. Left untreated, IE generally is fatal. However, with appropriate long-term (6 weeks or more) antibiotic therapy and/or valve replacement, mortality is reduced. For infections involving low-virulence organisms (e.g., *S. viridans*), the cure rate is 98%, and for enterococci and *S. aureus* infections, cure rates range from 60% to 90%; however, with infections due to gram-negative bacilli or fungi, one-half of the patients ultimately succumb. The cure rate for endocarditis arising on prosthetic valves is uniformly worse, and valve replacement is commonly required.

Earlier diagnosis and effective treatment has nearly eliminated some previously common clinical manifestations of long-standing IE—for example, microthromboemboli (manifest as 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), and retinal hemorrhages in the eyes (Roth spots).

Noninfected Vegetations

Noninfected (sterile) vegetations occur in nonbacterial thrombotic endocarditis (NBTE) and the endocarditis of systemic lupus erythematosus (SLE).

Table 12.9 Diagnostic Criteria for Infective Endocarditis[a]

Pathologic Criteria
Microorganisms, demonstrated by culture or histologic examination, in a vegetation, embolus from a vegetation, or intracardiac abscess
Histologic confirmation of active endocarditis in a vegetation or intracardiac abscess
Clinical Criteria
Major
Blood culture(s) positive for a characteristic organism or persistently positive for an unusual organism
Echocardiographic identification of a valve-related or implant-related oscillating mass or abscess, or partial separation of artificial valve
New valvular regurgitation
Minor
Predisposing heart lesion or intravenous drug use
Fever
Vascular lesions, including major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway lesions[b]
Immunological phenomena, including glomerulonephritis, Osler nodes,[c] Roth spots,[d] and rheumatoid factor
Microbiologic evidence, including a single culture positive for an unusual organism

[a]Diagnosis by these guidelines, often called the Modified Duke Criteria, requires either pathologic or clinical criteria; if clinical criteria are used, 2 major, 1 major + 3 minor, or 5 minor criteria are required for definitive diagnosis. "Possible" infective endocarditis diagnosis requires either 1 major +1 minor, or 3 minor.

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

[c]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.

[d]Roth spots are oval retinal hemorrhages with pale centers.

Modified from Li JS, Sexton DJ, Mick N, et al: Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis, *Clin Infect Dis* 30(4):633–638, 2000; Baddour LM: Cardiovascular infections. In Mann D, et al., editors: *Braunwald's Heart Disease. a Textbook of Cardiovascular Medicine*, ed 10, Philadelphia, 2015, WB Saunders, p 1524.

Nonbacterial Thrombotic Endocarditis (NBTE)

NBTE is characterized by the deposition of small (1 to 5 mm) sterile thrombi on the leaflets of the cardiac valves (Figs. 12.23 and 12.25). Histologically, these are bland thrombi, loosely attached to the underlying valve; the vegetations are nondestructive and do not elicit any inflammatory reaction. Although the local effect of the vegetations is usually trivial, they can be the source of systemic emboli that produce significant infarcts in the brain, heart, or elsewhere.

NBTE is often encountered in debilitated patients, such as those with cancer or sepsis—hence the previous term marantic endocarditis (root word *marasmus*, relating to malnutrition). Valvular damage is not a prerequisite for NBTE; indeed, the condition usually occurs on previously normal valves. Rather, hypercoagulable states are the usual precursor to NBTE; such conditions include chronic disseminated intravascular coagulation, hyperestrogenic states, and those associated with underlying malignancy, particularly mucinous adenocarcinomas. The latter association is likely related to the procoagulant effects of tumor-derived mucin or tissue factor that can also cause migratory thrombophlebitis (*Trousseau syndrome*, Chapter 4). Endocardial trauma, as from an indwelling catheter, is another well-recognized predisposing condition.

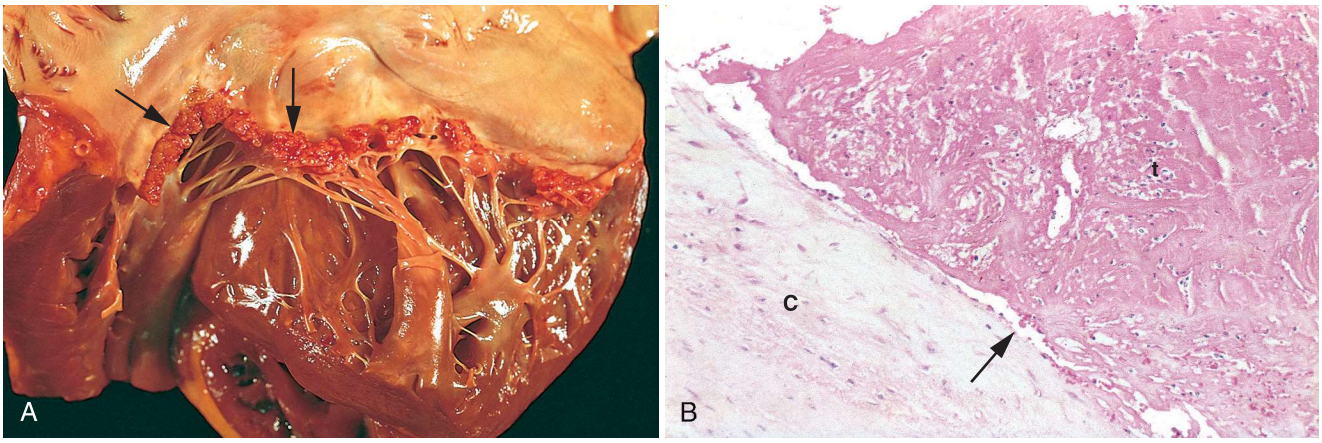

Figure 12.25 Nonbacterial thrombotic endocarditis (NBTE). (A) Nearly complete row of thrombotic vegetations along the line of closure of the mitral valve leaflets *(arrows)*. (B) Photomicrograph of NBTE, showing bland thrombus, with virtually no inflammation in the valve cusp *(c)* or the thrombotic deposit *(t)*. The thrombus is only loosely attached to the cusp *(arrow)*.

Endocarditis of Systemic Lupus Erythematosus (Libman-Sacks Disease)

Small (1 to 4 mm), sterile vegetations in the setting of systemic lupus erythematosus are termed Libman-Sacks endocarditis. The lesions develop as a consequence of immune complex deposition, with activation of complement and recruitment of Fc-receptor–bearing cells; histologically, there is an intense valvulitis and fibrinoid necrosis of the valve substance. The vegetations can occur anywhere on the valve surface, on the chordae, or even on the atrial or ventricular endocardium (see Fig. 12.23). Persistent injury can eventually result in valvular scarring and leaflet fusion, analogous to that seen in RHD. Similar lesions can occur in the antiphospholipid antibody syndrome (Chapter 4).

Carcinoid Heart Disease

The carcinoid syndrome refers to a systemic disorder marked by flushing, diarrhea, dermatitis, and bronchoconstriction that is caused by bioactive compounds such as serotonin released by carcinoid tumors (Chapter 17). Carcinoid heart disease refers to the cardiac manifestations caused by the bioactive compounds and occurs in roughly one-half of the patients in whom the systemic syndrome develops. Cardiac lesions do not typically occur until there is a massive hepatic metastatic burden, because the liver normally catabolizes circulating mediators before they can affect the heart. Classically, endocardium and valves of the right heart are primarily affected because they are the first cardiac tissues bathed by the mediators released by gastrointestinal carcinoid tumors. The left side of the heart is afforded some measure of protection because the pulmonary vascular bed degrades the mediators. However, left heart carcinoid lesions can occur in the setting of atrial or septal defects and right-to-left flow, or they can be induced by primary pulmonary carcinoid tumors.

Pathogenesis

The mediators elaborated by carcinoid tumors include serotonin (5-hydroxytryptamine), kallikrein, bradykinin, histamine, prostaglandins, and tachykinins. Although it is not clear which of these is causal, plasma levels of serotonin and urinary excretion of the serotonin metabolite 5-hydroxyindoleacetic acid correlate with the severity of the cardiac lesions. The valvular plaques in carcinoid syndrome are also similar to lesions that occured in patients taking fenfluramine (an appetite suppressant, no longer marketed) or ergot alkaloids (used previously for migraine headaches); interestingly, these agents affect systemic serotonin metabolism. Similarly, left-sided plaques have been reported after methysergide or ergotamine therapy for migraines; notably, these drugs are metabolized to serotonin as they pass through the pulmonary vasculature.

MORPHOLOGY

The cardiovascular lesions associated with the carcinoid syndrome are distinctive, glistening white intimal plaquelike thickenings of the endocardial surfaces of the cardiac chambers and valve leaflets (Fig. 12.26). The lesions are composed of smooth muscle cells and sparse collagen fibers embedded in an acid mucopolysaccharide-rich matrix material. Underlying structures are intact. With right-sided involvement, typical findings are tricuspid insufficiency and pulmonary stenosis.

Complications of Prosthetic Valves

Although prosthetic heart valves are less-than-perfect substitutes for the native tissues, their introduction has radically altered the prognosis for patients with valve disease. Two types of prosthetic valves are currently used, each with its own advantages and disadvantages:

- *Mechanical valves*. These consist of different configurations of rigid nonphysiologic material, such as caged balls, tilting disks, or hinged semicircular flaps (bileaflet tilting disk valves).
- *Tissue valves (bioprostheses)*. Porcine aortic valves or bovine pericardium are preserved in a dilute glutaraldehyde solution and then mounted on a prosthetic frame. Alternatively, frozen human valves from deceased donors