infrequent, and the pulmonary valve is only rarely affected. Because of the increase in calcific aortic stenosis (see earlier) and the reduced frequency of RHD, rheumatic aortic stenosis now accounts for a small fraction of cases of acquired aortic stenosis.

In rheumatic mitral stenosis, calcification and fibrous bridging across the valvular commissures create "fish mouth" or "buttonhole" stenoses. 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 post-inflammatory 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, as a result of the long intervals between the initial insult and the development of the chronic deformity.

Clinical Features. RF is characterized by a constellation of findings: (1) migratory polyarthritis of the large joints, (2) pancarditis, (3) subcutaneous nodules, (4) erythema marginatum of the skin, and (5) Sydenham chorea, a neurologic disorder with involuntary rapid, purposeless 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 earlier or one major and two minor manifestations (nonspecific signs and symptoms that include fever, arthralgia, or elevated blood levels of acute-phase reactants).

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 ages 5 and 15, 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. Clinical manifestations appear years or even decades after the initial episode of RF and depend on which cardiac valves are involved. In addition to various 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 prosthetic replacement of diseased valves has greatly improved the outlook for persons with RHD.

Infective Endocarditis

Infective endocarditis (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. This subdivision reflects the range of the disease severity and tempo, which are determined in large part by the virulence of the infecting microorganism and whether underlying cardiac disease is present. *Acute infective endocarditis* is typically caused by infection of a previously normal heart valve by a highly virulent organism (e.g., *Staphylococcus aureus*) that rapidly produces necrotizing and destructive lesions. These infections may be difficult to cure with antibiotics alone, and usually require surgery. Despite appropriate treatment, death can ensue within days to weeks. 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 be achieved with antibiotics.

Pathogenesis. Although highly virulent organisms can infect previously normal valves, a variety of cardiac and vascular abnormalities increase the risk of developing IE. Rheumatic heart disease 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 unrepaired and repaired congenital defects.

The causal organisms differ among 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*, 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. Prosthetic valve endocarditis is caused most commonly by coagulase-negative staphylococci (e.g., *S. epidermidis*). Other agents causing endocarditis include gram-negative