Table 12-13 Major Causes of Myocarditis

Infections
Viruses (e.g., coxsackievirus, ECHO, influenza, HIV, cytomegalovirus)
Chlamydiae (e.g., *Chlamydophyla psittaci*)
Rickettsiae (e.g., *Rickettsia typhi*, typhus fever)
Bacteria (e.g., *Corynebacterium diphtheriae, Neisseria meningococcus, Borrelia* (Lyme disease)
Fungi (e.g., *Candida*)
Protozoa (e.g., *Trypanosoma cruzi* [Chagas disease], toxoplasmosis)
Helminths (e.g., trichinosis)
Immune-Mediated Reactions
Postviral
Poststreptococcal (rheumatic fever)
Systemic lupus erythematosus
Drug hypersensitivity (e.g., methyldopa, sulfonamides)
Transplant rejection
Unknown
Sarcoidosis
Giant cell myocarditis

HIV, Human immunodeficiency virus.

Nonviral agents are also important causes of infectious myocarditis, particularly the protozoan *Trypanosoma cruzi*, the agent of Chagas disease. Chagas disease is endemic in some regions of South America, with myocardial involvement in most infected individuals. About 10% of patients die during an acute attack; others develop a chronic immune-mediated myocarditis that may progress to cardiac insufficiency in 10 to 20 years. Trichinosis (*Trichinella spiralis*) is the most common helminthic disease associated with myocarditis. Parasitic diseases, including toxoplasmosis, and bacterial infections such as Lyme disease and diphtheria, can also cause myocarditis. In the case of diphtheritic myocarditis, the myocardial injury is a consequence of diphtheria toxin release by the causal organism, *Corynebacterium diphtheriae* (Chapter 8). Myocarditis occurs in approximately 5% of patients with Lyme disease, a systemic illness caused by the bacterial spirochete *Borrelia burgdorferi* (Chapter 8); it manifests primarily as a self-limited conduction system disorder that may require a temporary pacemaker. AIDS-associated myocarditis may reflect inflammation and myocyte damage without a clear etiologic agent, or a myocarditis attributable directly to HIV or to an opportunistic pathogen.

There are also noninfectious causes of myocarditis. Broadly speaking they are either immunologically mediated (*hypersensitivity myocarditis*) or idiopathic conditions with distinctive morphology (*giant cell myocarditis*) suspected to be of immunologic origin (Table 12-13).

MORPHOLOGY

Grossly, the heart in myocarditis may appear normal or dilated; some hypertrophy may be present depending on disease duration. In advanced stages the ventricular myocardium is flabby and often mottled by either pale foci or minute hemorrhagic lesions. Mural thrombi may be present.

Active myocarditis is characterized by an interstitial inflammatory infiltrate associated with focal myocyte necrosis (Fig. 12-35). A diffuse, mononuclear, predominantly lymphocytic infiltrate is most common (Fig. 12-35*A*). Although endomyocardial biopsies are diagnostic in some cases, they can be spuriously negative because inflammatory involvement of the myocardium may be focal or patchy. If the patient survives the acute phase of myocarditis, the inflammatory lesions either resolve, leaving no residual changes, or heal by progressive fibrosis.

Hypersensitivity myocarditis has interstitial infiltrates, principally perivascular, composed of lymphocytes, macrophages, and a high proportion of eosinophils (Fig. 12-35*B*). A morphologically distinctive form of myocarditis, called **giant-cell myocarditis**, is characterized by a widespread inflammatory cellular infiltrate containing multinucleate giant cells (fused macrophages) interspersed with lymphocytes, eosinophils, plasma cells, and macrophages. Focal to frequently extensive necrosis is present (Fig. 12-35*C*). This variant likely represents the fulminant end of the myocarditis spectrum and carries a poor prognosis.

The myocarditis of **Chagas disease** is distinctive by virtue of the parasitization of scattered myofibers by trypanosomes accompanied by a mixed inflammatory infiltrate of neutrophils, lymphocytes, macrophages, and occasional eosinophils (Fig. 12-35*D*).

Clinical Features. The clinical spectrum of myocarditis is broad. At one end, the disease is entirely asymptomatic, and patients can expect a complete recovery without sequelae; at the other extreme is the precipitous onset of heart failure or arrhythmias, occasionally with sudden death. Between these extremes are the many levels of involvement associated with symptoms such as fatigue, dyspnea, palpitations, precordial discomfort, and fever. The clinical features of myocarditis can mimic those of acute MI. As noted previously, patients can develop dilated cardiomyopathy as a late complication of myocarditis.

Other Causes of Myocardial Disease

Cardiotoxic Drugs. Cardiac complications of cancer therapy are an important clinical problem; cardiotoxicity has been associated with conventional chemotherapeutic agents, tyrosine kinase inhibitors, and certain forms of immunotherapy. The anthracyclines doxorubicin and daunorubicin are the chemotherapeutic agents most often associated with toxic myocardial injury; they cause dilated cardiomyopathy with heart failure attributed primarily to peroxidation of lipids in myocyte membranes. Anthra cycline toxicity is dose-dependent, with the cardiotoxicity risk increasing when cumulative life-time doses exceed 500 mg/m^2.

Many other therapeutic agents, including lithium, phenothiazines, and chloroquine can idiosyncratically induce myocardial injury and sometimes sudden death. Common findings in affected myocardium include myofiber swelling, cytoplasmic vacuolization, and fatty change. Discontinuing the offending agent often leads to prompt resolution, without apparent sequelae. Occasionally, however, more extensive damage produces myocyte necrosis that can evolve to a dilated cardiomyopathy.

Amyloidosis. Amyloidosis results from the extracellular accumulation of protein fibrils that are prone to forming insoluble β-pleated sheets (Chapter 6). Cardiac