2. Probable acute myocarditis is diagnosed when the above criteria are met and accompanied also by cardiac symptoms, such as shortness of breath or chest pain, which can result from pericarditis or myocarditis. When clinical findings of pericarditis (pleuritic chest pain, ECG abnormalities, pericardial rub or effusion) are accompanied by elevated troponin or CK-MB or abnormal cardiac wall motion, the terms perimyocarditis or myopericarditis are sometimes used.
3. Definite myocarditis is diagnosed when there is histologic or immunohistologic evidence of inflammation on endomyocardial biopsy (see below) and does *not* require any other laboratory or clinical criteria.

SPECIFIC VIRUSES IMPLICATED IN MYOCARDITIS

In humans, viruses are often suspected but rarely proven to be the direct cause of clinical myocarditis. First implicated was the picornavirus family of RNA viruses, principally the enteroviruses, coxsackie virus, echovirus, and poliovirus. Influenza, another RNA virus, is implicated with varying frequency every winter and spring as epitopes change. Of the DNA viruses, adenovirus, vaccinia (smallpox vaccine), and the herpesviruses (varicella zoster, cytomegalovirus, Epstein-Barr virus, and human herpesvirus 6 [HHV6]) are well-recognized to cause myocarditis but also occur commonly in the healthy population. Polymerase chain reaction (PCR) detects viral genomes in the majority of patients with dilated cardiomyopathy, but also in normal "control" hearts. Most often detected are parvovirus B19 and HHV6, which may affect the cardiovascular system, in part, through infection of vascular endothelial cells. However, their contribution to chronic cardiomyopathy is uncertain, as serologic evidence of exposure is present in many children and most adults.

Human immunodeficiency virus (HIV) was associated with an incidence of dilated cardiomyopathy of 1–2%; however, with the advent of highly active antiretroviral therapy (HAART), HIV has been associated with a significantly lower incidence of cardiac disease. Cardiomyopathy in HIV may result from cardiac involvement with other associated viruses, such as cytomegalovirus and hepatitis C, as well as by HIV directly. Antiviral drugs to treat chronic HIV can cause cardiomyopathy, both directly and through drug hypersensitivity. The clinical picture may be complicated by pericardial effusions and pulmonary hypertension. There is a high frequency of lymphocytic myocarditis found at autopsy, and viral particles have been demonstrated in the myocardium in some cases, consistent with direct causation.

Hepatitis C has been repeatedly implicated in cardiomyopathy, particularly in Germany and Asia. Cardiac dysfunction may improve after interferon therapy. As this cytokine itself often depresses cardiac function transiently, careful coordination of administration and ongoing clinical evaluation are critical. Involvement of the heart with hepatitis B is uncommon, but can be seen when associated with systemic vasculitis (polyarteritis nodosa).

Additional viruses implicated specifically in myocarditis include *mumps, respiratory syncytial virus,* the *arboviruses (dengue fever and yellow fever),* and *arenaviruses (Lassa fever)*. However, for any serious infection, the systemic inflammatory response can cause nonspecific depression of cardiac function, which is generally reversible if the patient survives.

THERAPY

There is currently no specific therapy recommended during any stage of viral myocarditis. During acute infection, therapy with anti-inflammatory or immunosuppressive medications is avoided, as their use has been shown to increase viral replication and myocardial injury in animal models. Therapy with specific antiviral agents (such as oseltamivir) has not been studied in relation to cardiac involvement. There is ongoing investigation into the impact of antiviral therapy to treat chronic viral persistence identified from endomyocardial biopsy. Large trials of immunosuppressive therapy for Dallas Criteria–positive myocarditis have been negative. There are some initial encouraging results and ongoing investigations with immunosuppressive therapy for immune-mediated myocarditis defined by immunohistologic criteria on biopsy or circulating anti-heart antibodies in the absence of myocardial viral genomes. However, neither antiviral nor anti-inflammatory therapies are currently recommended. Until we have a better understanding of the different phases of viral myocarditis and its sequelae and the effects of timed or targeted therapies, treatment will continue to be directed to the clinical cardiovascular stage of the disease, for dilated cardiomyopathy in general.

Parasitic Myocarditis *Chagas' disease* is the third most common parasitic infection in the world and the most common infective cause of cardiomyopathy. The protozoan *T. cruzi* is transmitted by the bite of the reduviid bug, endemic in the rural areas of South and Central America. Transmission can also occur through blood transfusion, organ donation, from mother to fetus, and occasionally orally. While programs to eradicate the insect vector have decreased the prevalence from about 16 million to less than 10 million in South America, cases are increasingly recognized in Western developed countries. Approximately 100,000 affected individuals are currently living in the United States, most of whom contracted the disease in endemic areas.

Multiple pathogenic mechanisms are implicated. The parasite itself can cause myocyte lysis and primary neuronal damage, and specific immune responses may recognize the parasites or related antigens and lead to chronic immune activation in the absence of detectable parasites. Molecular techniques have revealed persistent parasite DNA fragments in infected individuals. Further evidence for persistent infection is the eruption of parasitic skin lesions during immunosuppression after cardiac transplantation. As with viral myocarditis, the relative roles of persistent infection and of secondary autoimmune injury have not been resolved (Fig. 287-5). An additional factor in the progression of Chagas' disease is the autonomic dysfunction and microvascular damage that may contribute to cardiac and gastrointestinal disease.

The acute phase of Chagas' disease with parasitemia is usually unrecognized, but in fewer than 5% of cases, it presents clinically within a few weeks of infection, with nonspecific symptoms or occasionally with acute myocarditis and meningoencephalitis. In the absence of antiparasitic therapy, the silent stage progresses slowly over 10–30 years in almost half of patients to manifest in the cardiac and gastrointestinal systems in the chronic stages. Features typical of Chagas' disease are conduction system abnormalities, particularly sinus node and atrioventricular (AV) node dysfunction and right bundle branch block. Atrial fibrillation and ventricular tachyarrhythmias also occur. Small ventricular aneurysms are common, particularly at the ventricular apex. These dilated ventricles are particularly thrombogenic, giving rise to pulmonary and systemic emboli. Xenodiagnosis, detection of the parasite itself, is rarely performed. The serologic tests for specific IgG antibodies against the trypanosome lack sufficient specificity and sensitivity, thereby requiring two separate positive tests required to make a diagnosis.

Treatment of the advanced stages focuses on clinical manifestations of the disease and includes heart failure medications, pacemaker-defibrillators, and anticoagulation. Increasing attention is directed to antiparasitic therapy even in chronic disease without obvious active infection. The most common effective antiparasitic therapies are benznidazole and nifurtimox, both associated with multiple severe reactions, including dermatitis, gastrointestinal distress, and neuropathy. Survival is less than 30% at 5 years after the onset of overt clinical heart failure. Patients without major extracardiac disease have occasionally undergone transplantation, after which they may require lifelong therapy to suppress reactivation of infection.

African trypanosomiasis infection results from the tsetse fly bite and can occur in travelers exposed during trips to Africa. The West African form is caused by *Trypanosoma brucei gambiense* and progresses silently over years. The East African form caused by *T. brucei rhodesiense* can progress rapidly through perivascular infiltration to myocarditis and heart failure, with frequent arrhythmias. The diagnosis is made by identification of trypanosomes in blood, lymph nodes, or other affected sites. Antiparasitic therapy has limited efficacy and is determined by the specific type and the stage of infection (hemolymphatic or neurologic).