# Editorial Response: Microbial Persistence and Idiopathic Dilated Cardiomyopathy

Understanding of the microbial relationship to atherosclerotic coronary artery disease [1, 2] and idiopathic dilated cardiomyopathy (IDC) [3] is increasing. In the case of coronary artery disease, human cytomegalovirus (HCMV) and *Chlamydia pneumoniae* are involved. When IDC is apparent by the appearance of left ventricular dysfunction, it is a noninflammatory advanced degenerative disease of the myocardium with myofiber disarray and disordered myofiber branching, myofiber dissolution, myocyte dropout, myocardial fibrosis, and myofiber hypertrophy; IDC is sometimes associated with aberrant fat globules in the myocardium [4]. There is no inflammatory infiltrate in IDC. When a myocardial infiltrate is present, the diagnosis is myocarditis. Although 25% of the cases of heart failure in North America may be the result of IDC, its pathogenesis is largely unknown.

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See article by de Leeuw et al. on pages 522–5.

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In a murine model of coxsackievirus B3 myocarditis, Reyes et al. [5] showed that 1 year later some of the surviving mice developed IDC. This finding has been confirmed and expanded [6–8].

Direct coxsackievirus B3–induced pathogenic effects, virus-induced cell-mediated immunity, and cross-reactive autoimmunity to components of the myofiber membrane among other cellular components are confirmed [9, 10]. The pathogenic thesis is strengthened by the finding in many laboratories of enterovirus RNA in myocardial biopsy specimens from patients with IDC [3, 7, 10, 11]. The percentage of positive cases of IDC with demonstrable enterovirus RNA varies widely (zero to 67%). Generally, the more advanced the disease process of IDC, the fewer the cases with documented enterovirus RNA.

In a murine model, Sole and Liu [12] reported that viral myocarditis is associated with spasm of the coronary microvasculature, thus leading to myocyte necrosis, fibrosis, calcification, and cardiac dilatation. Antibody to $\alpha$-myosin heavy chain, antibody to $\beta$-myosin heavy chain, antibody to M7 mitochondrial antigen, antibody to nucleotide translocator, and anti-B adrenoreceptor autoantibodies have been found in IDC [7]. By binding of monoclonal antibody to cardiac myosin, disruption of the cardiac myocyte sarcolemma has been demonstrated in cases of dilated cardiomyopathy. Binding of an indium-labeled Fab fragment of antibody to myosin to myo-

cardium can be quantitated by scintigraphy and compared with uptake by the lung. Patients with myocarditis, acute myocardial infarction, rejection of the transplanted heart, and IDC have enhanced uptake of antibody to myosin. Patients with end-stage heart failure due to valvular disease, hypertensive heart disease, or coronary heart disease do not have increased uptake of antibody to myosin [11]. Persistence of enterovirus RNA in the myocardium may lead to damage of the myocardial cell membrane and uptake of antibody to myosin [13].

The coxsackievirus B genome is a single molecule of single-stranded positive-sense RNA about 7,400 nucleotides in length. The genome codes for four capsid proteins, found in 60 copies each in the virion as well as the nonstructural proteins necessary for viral replication. Nucleotide 234 affects the cardiovirulent phenotype. When this site is U, the strain is attenuated. When this site is C, the strain is cardiovirulent. With coxsackievirus B3, the host cell and its state of development (e.g., age of the mice) determine whether rapid myocyte lysis occurs [14].

de Leeuw et al. [15] reported no evidence for persistence of enterovirus RNA in end-stage IDC. In this issue of *Clinical Infectious Diseases*, these investigators [16] showed that PCR analysis found no evidence of HCMV, hepatitis B virus, hepatitis C virus, *Borrelia burgdorferi, Chlamydia* species, mycoplasmata, or *Toxoplasma gondii*. Multiple samples of myocardium were tested in each case. Although the relative sensitivity of PCR testing may explain these negative results, the preponderance of studies suggests that the more end stage the left ventricular dysfunction (e.g., ejection fraction of <20%), the more difficult it is to find enterovirus RNA in the heart. At best, persistence of the enterovirus coxsackievirus B3 is the unlikely cause of "most" cases of IDC. These cases remain unexplained.

The coxsackievirus B genome is not associated with viral latency (persistent infection). Recurrent permissive and persistent infection is characteristic of herpesviruses, including HCMV and Epstein-Barr virus (EBV). Is there another possible paradigm in IDC? Some cases of IDC certainly begin as an acute or subclinical episode of virulent permissive coxsackievirus B myocarditis, most often caused by cardiotropic coxsackievirus B3. Enterovirus RNA may persist in a variable percentage of surviving myocytes that function at varying levels of competence. "Progressive apoptosis" of these coxsackievirus B3–containing myocytes may be the ultimate fate; worsening end-stage IDC may result. When symptomatic therapy no longer is helpful and cardiac transplantation is the remaining recourse, enterovirus RNA, as reported by de Leeuw et al. [16] in this issue of *Clinical Infectious Diseases*, may no longer be present.

Another possible paradigm may be operative in the unknown cases. IDC may begin as persistent infection with herpesviruses, HCMV, EBV, or, in other cases, herpesvirus 6. Initial HCMV or EBV infection is occasionally inflammatory myo-

carditis, but often (with theoretically lower genome copy numbers in the affected heart) it is a waxing and waning recrudescent, permissive, persistent infection. Biochemical and microscopic disease may lead to a decrease in the left ventricular power function. Permissive infection at a higher genome copy number may be required for diffuse myocarditis, but a lower copy number may yield IDC. Infection of the heart occurs via the bloodstream (B-lymphocytes [EBV] or monocytes or macrophages [HCMV]). IDC may be a diffuse irregular herpesvirus infection of the myocardium with varying genome copy numbers and intensity in each affected patient. Even in progressive cases, inflammatory myocarditis may not be present, but cardiomyopathic changes are evident and vary in degree depending on the stage of disease [17–20].

Case reports suggest that specific antiviral therapy may be accompanied by inhibition of both permissive viral infection and recruitment of new myofibers. In one uncontrolled study [21], abnormal left ventricular dynamics of IDC improved with intravenous ganciclovir therapy. In two controlled studies [22, 23], abnormal Holter monitoring with oscillating abnormal flattening and inversions of T waves, some very deep (reminiscent of ischemic heart disease), accompanied abnormal left ventricular dynamics, findings suggesting that chronic fatigue syndrome (CFS) may be the missing clinical conundrum in the discovery of the inception of IDC. The absence of abnormal oscillating T wave flattening and inversions at 24-hour Holter monitoring excludes the diagnosis of CFS [23].

Fatigue and exercise intolerance are the cardinal symptoms of CFS; fatigue and exercise intolerance are the cardinal symptoms of left ventricular dysfunction. Tachycardia at rest occurs in IDC and CFS. Are these chance-only synchronous findings related? Is CFS early IDC? The data suggest that this working paradigm should be investigated in controlled studies [24].

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