Editorial Comment

New Serologic Marker of Cardiac Autoimmunity in Dilated Cardiomyopathy*

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The present study. The report by Caforio and colleagues (1) in this issue of the Journal adds new data to the subject of an autoimmune complex disorder in dilated cardiomyopathy and the possible implication of previous viral infection. Sixty-five patients with dilated cardiomyopathy, 205 patients with other forms of heart disease (coronary, hypertrophic cardiomyopathy, rheumatic, right ventricular dysplasia and congenital) and 41 patients with heart failure following myocardial infarction were studied and compared with 200 normal subjects. The criteria for diagnosis of dilated cardiomyopathy were satisfactorily strict, depending on the demonstration of a poorly contracting left or right ventricle, or both, in the absence of evidence by appropriate investigation of coronary heart disease, hypertension, specific heart muscle disease and excessive alcohol consumption. The diagnosis was made after 2 years of symptoms in the majority and earlier in the minority of patients.

Cardiac antibody screening was performed with standard indirect immunofluorescence techniques confirmed by quantitative absorption studies. Sera giving diffuse cytoplasmic staining of both atrial and ventricular myocytes, but which were negative on skeletal muscle, were classified as organ specific. These organ-specific cardiac autoantibodies were present more frequently in patients with dilated cardiomyopathy (26%) than in normal subjects (3.5%) or patients with other cardiac disease (1%) or heart failure (0%). Sera that gave immunofluorescence on skeletal muscle as well as myocytes were classified as being cross-reactive autoantibodies and were found in 11% of patients with dilated cardiomyopathy, 7% of patients with other heart disease, 2% of patients with heart failure and 5.5% of normal subjects. Other organ-specific antibodies such as islet cell and gastric parietal cell antibodies were found in a similar proportion of sera from patients with cardiomyopathy and normal subjects. Thyroid microsomal antibodies were slightly increased in dilated cardiomyopathy. Other organ-specific antibodies such as antinuclear antibodies were increased in dilated cardiomyopathy and rheumatic heart disease as compared with normal. The clear-cut incidence of organ-specific cardiac antibodies in patients with dilated cardiomyopathy in excess of those in patients with other forms of heart disease and in control subjects was not related to age or gender but was more common in those patients with fewer and more recent onset (<2 years) of symptoms.

Implications of the study. These results raise many interesting questions. The definite increase in cardiac organ-specific antibodies in patients with dilated cardiomyopathy compared with levels in other groups supports the theories of cell-mediated autoimmune causation of dilated cardiomyopathy (2,3). Heterogeneity of immunologic findings in similar patients is characteristic of organ-specific autoimmunity. Islet cells, gastric parietal and thyroid antibodies were more frequently increased in dilated cardiomyopathy than in other cardiac disorders. The absence of organic-specific cardiac antibodies in 74 patients with dilated cardiomyopathy also raises interesting questions that are discussed by Caforio et al. (1), notably, different causes in different patients and reduction of antibodies with progression of the disease. The latter suggestion is in accord with the finding of more antibodies in patients with a shorter history. There is little doubt that there are many different causes of dilated cardiomyopathy.

The importance of the study of Caforio et al. (1) is the demonstration that organ-specific cardiac antibodies were present in a significant number of patients with dilated cardiomyopathy and to a degree far in excess of such antibodies found in patients with other forms of heart disease and in control subjects. These findings strongly suggest that some autoimmune process is involved in causation, although the antibodies may, of course, be markers of risk rather than the actual cause.

Role of viral infection. Experimental and clinical work (4,5) has suggested that viral myocarditis can set up an autoimmune reaction that leads to dilated cardiomyopathy (6–8). It could well be that the organic-specific antibodies in dilated cardiomyopathy are due to the stimulus of a previous viral infection, although proof is lacking. However, there is little doubt that viral myocardial infection does occur in dilated cardiomyopathy and that an immunologic disorder may be involved. Archard et al. (9–11), using molecular hybridization probes specific for enteroviral ribonucleic acid (RNA), detected viral RNA sequences in 55% of hearts with dilated cardiomyopathy as well as in those with myocarditis.
The RNA fragments persisted until end-stage disease but without necessarily eliciting a full immunologic response. The proportion of probe-positive biopsy specimens was higher in patients with dilated cardiomyopathy (41%) than in explanted hearts (29%). This finding might suggest, in accord with the results of Caforio et al. (1), that virus may be eliminated late in the disease.

The evidence provided by progression from myocarditis to dilated cardiomyopathy clinically and hemodynamically, together with the molecular biologic data and immunologic studies, strongly suggests a causal role of viral infection. However, caution is still necessary because association does not inevitably imply causation and the virus-immune theory would explain no more than about 50% of cases of dilated cardiomyopathy. Because autoimmune disturbance can be inherited, Caforio et al. (1) should study relatives of their patients with dilated cardiomyopathy. It might be that there is a genetic basis in some patients with dilated cardiomyopathy and that viral infection acts as the trigger to precipitate a latent autoimmune destructive cardiac response.

Conclusions. The enigma of dilated cardiomyopathy is not solved, although the work of Caforio and colleagues (1) provides an important landmark of progress both in the experimental field and in the clinical realm. The place of immunologic therapy and viral chemotherapy is being explored and myocarditis is treated (sometimes incorrectly) with steroids. Furthermore, because patients after cardiac transplantation are immunologically depressed, it will be vitally important to determine whether the presence of viral particles in the myocardium of the explanted heart has any implications for the transplant patient’s management and prognosis.

References