

Autoimmune Heart Disease
NOBLE O. FOWLER

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EDITORIAL

Autoimmune Heart Disease

AUTOIMMUNE heart disease may be defined as a variety of myocardial, pericardial, or endocardial disease in which antibodies are produced against the host's cardiac tissues which serve as antigens.

Whether or not there is convincing evidence of autoimmune mechanisms in heart disease in man is the question to be dealt with in this discussion.

A host may produce antibodies to its own tissues through one of several mechanisms. First, certain tissues of the host previously unavailable to the circulation may act as antigens if their components enter the blood stream, e.g. the cornea of the eye. Secondly, a host tissue component may become antigenic when altered by a drug or an infectious agent. Thirdly, a host tissue and an invading infectious agent may have a common antigen. For example, in acute rheumatic fever, heart muscle and the cell wall of the beta-hemolytic streptococcus are believed to have a common antigen.^{1,2} Finally, a host antigen may be normal and previously available to the circulation but the host response may be abnormal through failure of tolerance, mutation, or virus infection. For example, an abnormal host antibody response occurs in systemic lupus erythematosus. An experimental model of

autoimmune heart disease in rabbits, rats, or hamsters can be produced by repeated injections of homologous or heterologous heart tissue which may result in focal necrotic lesions in the myocardium.³

There are a number of problems in the investigation of possible autoimmune heart disease. One of these is the large number and variety of potential heart antigens.⁴ There are intermyofibrillar antigens, soluble antigens common to the heart and skeletal muscle present in sarcolemmal-subsarcolemmal sites, organ-specific soluble antigens, soluble antigens common to heart and skeletal muscle including myoglobin and heart-stable haptens, and a soluble antigen common to heart, kidney and possibly liver. There are also antigens in reticulin, basement membrane, blood vessels, and connective tissue common to all organs. Heart valves also contain antigens.

Not only are there a number of potential cardiac antigens, but also many methods of antibody testing. These include immunofluorescent techniques,⁵ hemagglutination using tanned red cells, precipitin tests, and complement fixation procedures to look for heart antibodies.⁶ By immunofluorescent methods one may study pathological specimens of heart to look for bound IgA, IgM, and IgG globulins⁷ or to look for bound complement, which is found at times in

Address for reprints: Noble D. Fowler, M.D., University of Cincinnati College of Medicine, Cincinnati, Ohio 45229.

rheumatic fever and perhaps in certain myocardopathies.

A number of cardiac diseases have been investigated for the possibility of autoimmune mechanisms.⁸ These include acute rheumatic fever, chronic rheumatic heart disease, endomyocardial fibrosis, idiopathic cardiomyopathy, and certain of the connective tissue diseases, specifically, rheumatoid arthritis and systemic lupus erythematosus. Of especial interest are four similar syndromes which may possibly represent autoimmune diseases. These include the four febrile pleuropericarditis syndromes: the postthoracic injury syndrome which may follow either blunt or penetrating trauma, the postthoracotomy or postpericardiotomy syndrome, the post-myocardial infarction or Dressler's syndrome, and the syndrome of idiopathic non-specific pericarditis. It is possible that this last syndrome, which often is manifest after a latent period following an infection, may be analogous to rheumatic fever in that there may be an antigen in common with a virus, or the host antigen may have been altered by a virus.

One must also consider the possibility of immune responses in the pleuropericarditis syndromes which may follow the administration of certain drugs, especially hydralazine, dilantin and other anticonvulsants, isoniazid, and procainamide.⁹

Studies of patients with acute rheumatic fever have shown a high incidence of circulating antiheart antibodies with a range from 25 to 63%.⁸ However, in chronic rheumatic heart disease the incidence is much smaller, namely 12 to 21%.⁸ van der Geld found antiheart antibodies to be common in endomyocardial fibrosis.¹⁰ Studies of antiheart antibodies have shown a high incidence in patients with postcardiotomy or post-myocardial infarction syndrome, but they are not universally present.⁸ Investigation of antiheart antibodies in patients with idiopathic cardiomyopathy has yielded varying results. Sanders found bound gamma globulin in the myocardium of five of nine patients with idiopathic cardiomyopathy.⁷ We have carried

out studies of circulating heart antibodies in two groups of approximately 30 patients each. In the first group of 33 patients with idiopathic cardiomyopathy,¹¹ we found a prevalence of antiheart antibodies of only 12%. This incidence was greater than in controls but lower than in patients with miscellaneous varieties of heart disease. The second group of patients was studied serially over a period of 2 years.¹² In these 32 patients, a higher prevalence of antiheart antibodies was found; nine of them had antiheart antibodies at one time. Of 14 patients whose cardiac compensation was unstable during the study, the appearance and disappearance of antiheart antibodies bore no relation to the clinical course. Thus, there would seem to be no strong evidence that circulating antiheart antibodies were related to the disease in these patients. Das and Cassidy found antiheart antibodies in more patients with systemic lupus erythematosus than in those with idiopathic cardiomyopathy.¹³ In our investigations,¹¹ we did not find antiheart antibodies in a small number of patients with systemic lupus erythematosus, some of whom had heart disease.

The question should be asked as to what might constitute acceptable evidence for the existence of autoimmune heart disease. One would like to have a fairly consistent finding of antiheart antibodies in the disease. Prospective studies should demonstrate that these antibodies precede the appearance of the clinical symptoms and that the serologic titer of antiheart antibodies falls as the patients improve. Such antibodies should be absent or of lower titer in patients who were exposed to similar injury but did not develop clinical symptoms. For example, in patients with acute cardiac infarction or those subjected to thoracotomy, one has a good opportunity for serial study of antiheart antibodies.⁸ In one study of patients subjected to mitral valvotomy, circulating antiheart antibodies were found commonly to precede the onset of the postthoracotomy syndrome, and the antibody titers were found to fall as the patients improved.¹⁴ However, following myocardial

infarction, circulating antiheart antibodies may appear without the development of the post-myocardial infarction syndrome.⁶ One would anticipate that some patients might show the antibodies in lower titer without developing clinical symptoms.

A second piece of supportive evidence would be that patients with the disease in question might improve in response to the use of immunosuppressive agents. Response of patients with the several varieties of febrile pleuropericarditis syndromes to corticosteroid therapy is often quite gratifying. However, this improvement may represent a nonspecific anti-inflammatory response. The response to agents such as azathioprine¹⁵ or indomethacin might give useful information. A third area of supportive evidence could be implication of the cellular immune system. To date there is little available data on which to make any judgment.

Finally, one would like to show that autoimmune heart disease can be reproduced in animal experiments. Although heart disease with circulating antiheart antibodies was produced in rabbits injected with beef or rat heart homogenates and there was bound gamma globulin in myofibers, the myocardial disease was focal and did not resemble the clinical syndrome of idiopathic cardiomyopathy.¹⁶

At present it seems that the evidence for the existence of autoimmune mechanisms in heart disease is inconclusive, and much further work needs to be done. A basic problem is the interpretation of cause-and-effect relationships. When myocardial sarcomeres are damaged, their components are released into the circulation. These circulating antigens may well incite the production of antibodies which follow rather than precede the original injury to the myocardium. Such initial injury might consist of myocardial damage produced by drugs or viruses, or the result of an acute myocardial infarction or of cardiac trauma. Hence, the existence of antiheart antibodies, whether circulating or bound to the myocardium, does not necessarily provide a mechanism for autoimmune heart disease. We still

need an answer to a critical question: when antiheart antibodies are demonstrated in a patient with myocardial, endocardial, or pericardial disease, are they the result or the cause of injury to the heart? Further careful studies are needed to help answer this question.

NOBLE O. FOWLER, M.D.

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