Immunological reactions in heart disease

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Immunological mechanisms play a part in disease of the heart, as they do in every other organ of the body. Our understanding of the pathological role of these reactions has changed, however, since the first suggestion that a number of chronic inflammatory disorders are in fact autonomous and self-destructive autoimmune diseases.

Autoantibodies, which react with the body's own tissues, are found in some, but by no means all of these chronic diseases. They may be specific for such tissues as thyroid or heart, or can react, less specifically, with a wide variety of nuclei, mitochondria, or cell products. Even when an autoimmune response is evident, it sometimes represents the indirect results of an infection and a mopping-up reaction to tissue breakdown. Such a reaction, at its most vigorous, includes a local lymphocytic infiltration with a wide variety of cells, some of which also have a regulatory effect on antibody production. If this response is inadequate, as it seems to be in systemic lupus, a deficiency of 'suppressor' T lymphocytes may result (Bresnihan and Jasin, 1977). This appears to lead to a further rise in the production of antibodies, including those antibodies which are capable of reacting with the body's own tissues.

Of the four classical types of immune reaction, there is little evidence of immediate allergy and anaphylaxis in the heart (Type 1), but the other types of response may be present in any combination. Cytotoxic antibodies can either destroy cells (Type 2) or stimulate an attack by killer lymphocytes. Immune complexes of antigen and antibody, trapped within small blood vessels, can trigger the complement system of enzymes and cause both an inflammatory reaction and an activation of the clotting sequence (Type 3). There may be extensive tissue damage associated with lymphocyte infiltration (Type 4).

In proposing the concept of rheumatic fever as an autoimmune disease, Kaplan and Meyers (1962) suggested that an infection with β -haemo-

lytic streptococci can stimulate the production of antibodies which crossreact with heart muscle cells. Antibodies to streptococcal cells have not been shown to damage the heart muscle but nevertheless have an affinity for the sarcolemma and subsarcolemmal sarcoplasm of heart muscle fibres. This affinity is lost when the serum is adsorbed with streptococcal cell membranes (Kaplan and Rakita, 1971). M protein, which is the factor associated with virulence in group A β -haemolytic streptococci, appears to be involved in this cross-reaction (Kaplan and Frengley, 1969), and there is also evidence of a lymphocyte-mediated delayed hypersensitivity to streptococcal products (Read *et al.*, 1974; Sapru *et al.*, 1977).

The concept of an autoimmune reaction provoked by an infection is echoed by the findings in Chagas' disease (Cossio *et al.*, 1974), in which the diagnostically useful EVI antibody is detectable in most patients with chronic cardiomyopathy. This antibody reacts with interstitial tissue, endocardium, and vascular endothelium, but is adsorbed by antigens from the causative agent, *Trypanosoma cruzi*.

The mere presence of anti-heart antibodies cannot explain the presence of cardiac damage, since they have been reported in the serum in a wide range of diseases, from coronary artery disease (Bauer *et al.*, 1972) and cardiomyopathy (Das *et al.*, 1972), to glomerulonephritis and rheumatoid arthritis (Hess *et al.*, 1964). This suggests either that these antibodies lack specificity or that their production represents a secondary reaction to damaged heart muscle cells. In support of the first of these explanations, the well-known affinity of syphilitic serum for cardiolipin provides a reminder that non-specific reactions may sometimes appear to be directed predominantly against heart muscle. In support of the second explanation, it has been noted that there is an increase in detectable anti-heart antibodies for 2 or 3 weeks after a myocardial infarct (Heine *et al.*, 1966; Kuch, 1973). In

addition, it has been shown in dogs by Pinckard and his colleagues (1971) that cardiac infarcts produced by coronary ligation, or by the intra-arterial injection of microspheres, are nearly always followed by the release of anti-heart antibodies, appearing about 10 days after the infarction and disappearing within 4 to 6 weeks.

It is unfortunate that the antigens concerned in these various autoantibody studies have in the past been poorly defined, and the methods used in their detection have varied greatly (Roberts and Lessof, 1973). Different patterns of staining may be recognised in immunofluorescent tests, but though the diffuse and striational staining patterns appear to be the most specific (Nicholson *et al.*, 1977), these tests do not distinguish between those diseases in which antibodies are suspected of having a pathogenic role and those in which they may be seen as a reaction to cardiac damage. While a better separation of cardiac antigens may help this type of study, it is possible, at least in the damage caused by immune complexes, that the magnitude of the antibody reaction is more important than the precise type of antigen involved.

Other heart diseases with immunological features

One of the theoretical attractions of the autoimmune concept is that it explains why different organs of the body should be involved in a similar, destructive type of lymphocyte infiltration, in each case accompanied by the release of high levels of organ-specific antibodies. Alongside this there is a link with a variety of genetic factors, as reflected in the high familial incidence of immunological disorders and a significant association with particular HLA types. As far as the heart is concerned, patients with chronic heart block have an increased prevalence of vitiligo, hypothyroidism, and pernicious anaemia (Fairfax and Leatham, 1975), diseases which are all associated with striking evidence of autoimmunity. Many of these patients have an idiopathic fibrotic process in the conducting tissue, with scanty inflammatory infiltration (Davies, 1971), but the underlying myocardium, which has the same blood supply, is spared. Fairfax (1977) has reported that a small group of patients with long-standing heart block possess a serum antibody which reacts with Purkinje tissue but not cardiac muscle. This emphasises the antigenic differences between conducting tissue and myocardium, though the relevance of these findings to idiopathic heart block remains uncertain. Despite the continuing interest in organ-specific immunological markers of disease, this remains an incomplete story.

More pertinent to the practising clinician has been

the work on the post-cardiotomy syndrome and the somewhat similar post-infarction syndrome of Dressler. A week or more after a cardiotomy or myocardial infarction, any patient with prolonged fever and recurrent pain, with pericardial, pleural, and pulmonary involvement presents a diagnostic difficulty. In patients who develop a lymphocytosis, the diagnostic possibilities include a fresh infarction or the reactivation of a virus. Antibody tests to cytomegalovirus or to EB virus may be helpful (Foster and Jack, 1969; Gerber *et al.*, 1969); but even in the absence of a lymphocytosis, it is not easy to exclude a viral infection—for example with Coxsackie B virus. The growth or reactivation of a virus may lead to tissue damage and this itself can, as in other infectious diseases, lead to autoantibody formation and immune complex deposition. In this respect the detection of circulatory immune complexes in the post-cardiotomy syndrome may help to establish one of the mechanisms of tissue damage without identifying the underlying cause (Versey and Gabriel, 1974; Lessof, 1976).

A second precipitating factor which needs to be considered is blood in the pericardium, since a similar reaction was described by Segal and Tabatznik (1960) after closed puncture wounds of the heart. The high incidence of post-cardiotomy reactions in the sixties fell sharply when surgeons directed their attention to pericardial toilet and drainage, and this, too, suggested a reaction to blood in the pericardium. Finally, a similar reaction has been reported after the implantation of a pacemaker (Dressler, 1962). Blood in the pericardium, muscle damage, and viral infection have all, therefore, been suspected as the provoking cause of a hypersensitivity reaction in the post-cardiotomy syndrome. Whatever the underlying cause, the immunological reaction may be sufficiently severe to justify corticosteroid treatment on an empirical basis (Bernstein, 1977). This is especially true after coronary artery bypass operations, in which there is a danger of graft occlusion (Urschel *et al.*, 1976).

It is not merely in the post-cardiotomy and post-infarction syndromes that immune complexes appear to be involved. There have been controversial reports on a high incidence of milk antibodies in coronary artery disease (Davies *et al.*, 1974), and Mathews and his colleagues (1974) have suggested that immunological factors and immune complex deposition could play a part in atherosclerosis. Immune complexes are also demonstrable in the renal lesions seen in poorly controlled bacterial endocarditis and have been identified in the blood in such connective tissue disorders as systemic lupus (Harbeck *et al.*, 1973; Cano *et al.*, 1977) and polyarteritis nodosa (Trepo *et al.*, 1974). In both of

these conditions, the presence of immune complexes appears to be correlated with vascular lesions. Nevertheless it is now evident that corticosteroids and immunosuppressive drugs have only a limited ability to mitigate the clinical pattern of these diseases. The key to this disappointing fact may lie in the suggestion that systemic lupus, like its famous animal counterpart in NZB mice, is in fact a slow virus infection (Phillips, 1975; Utermohlen *et al.*, 1976). Similarly, at least some cases of polyarteritis appear to be caused by hepatitis B or other infective agents (Gocke *et al.*, 1970). If so, immunosuppression may be able merely to modify the immunopathological consequences while the more direct virus effects continue. The logical corollary is that immune complex formation ought to diminish if the lymphocytes could be stimulated to a more effective role, either in combating virus infections or in suppressing antibody and auto-antibody formation. This explains current attempts to stimulate lymphocyte function by drugs such as levamisole (Rosenthal, 1977) or by leucocyte extracts containing the much debated transfer factor (Levin *et al.*, 1974).

Immunosuppression and transplantation

The limitations of immunosuppressive treatment are less obvious after cardiac transplantation, since here the patient's clinical problems depend exclusively on the immunological response to a foreign graft. If this could be suppressed without an increased susceptibility to infection or to cancer, the problem would be solved. While cardiac transplantation has been taken up less widely than at one time seemed likely, the immunological aspects have continued to advance and are of relevance to other clinical diseases. As in all conditions in which immune complexes are formed, there is a close relation between the immunologically stimulated cascade of complement enzymes and the clotting system. It now appears (Losman *et al.*, 1977) that the measurement of fibrinolytic activity and other aspects of the clotting mechanism may be as good as the histological examination of myocardial biopsy material in detecting early transplant rejection. In this type of immune response, the inflammatory process and the release of chemical mediators are followed by platelet aggregation and clotting, the effects of which are made worse by a depression of the normal ability to lyse clots and to resolve the lesion. It is, therefore, possible to justify current attempts to use anticoagulant therapy and antiplatelet agents as an adjunct to various types of immunosuppressive treatment, not only in transplant cases but also in such conditions as systemic lupus and

polyarteritis. It remains to be seen whether clinical trials can provide supporting evidence for the practical value of this approach.

One other recent report on cardiac transplant patients concerns the postoperative viral infections that are also the hallmark of the immunosuppressed subject. Severe infections with herpes simplex may occur despite the presence of high serum antibody levels to this virus (Rand *et al.*, 1977). This appears to be associated with a depression of lymphocytic reactions and of interferon release, a depression which nevertheless is usually corrected over a period of months or years. Immunity to herpes zoster does not appear to be stimulated so readily—perhaps because this is a less ubiquitous virus—and it is notable that sporadic cases of zoster continued to occur over a period of up to 6 years. Such recurring virus effects merely add to the long list of immunosuppressive drug side effects.

It remains evident that immunosuppressive treatment and its consequences can themselves constitute a disease. When immunosuppressive therapy is given, as in the post-infarction syndrome and in cardiac transplantation, high doses and prolonged courses lead, inevitably, to complications of their own. New, selective methods of suppression are, therefore, needed or, alternatively, there is a need for more effective antiviral or lymphocyte-modulating agents which can prevent or suppress the more troublesome forms of immune complex damage. Despite the considerable advances which have been made in basic immunology, it is salutary that none of these new forms of treatment has yet been established in clinical practice.

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