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IMMUNOLOGY IN CARDIOMYOPATHIES

The cardiomyopathies include a number of conditions which need to be more fully characterised. In following international practice and distinguishing cardiomyopathies from specific heart muscle disease, it should be recognised that there are disorders in both groups which begin with inflammation and continue with a reactive myopathy in which immunological factors play a part. A clear sequence of events has been established in the specific heart muscle diseases of rheumatic carditis and Chagas' cardiomyopathy, starting with infection and inflammation, with some evidence of immunologically mediated damage, and then continuing to an end stage disease in which the evidence of active inflammatory change has subsided. Despite differences in the infective agents concerned and the tissue damage which arises, a similar sequence can be demonstrated in many cases of endocardial fibroelastosis, in restrictive cardiomyopathy of all types, and probably in a small subgroup of cases of dilated cardiomyopathy. In any future classification, those cardiomyopathies which occur as a sequel to reactive carditis may therefore need to be distinguished from the rest.

The international classification, which lists hypertrophic, dilated and restrictive cardiomyopathies, leaves a number of conditions uncategorised[1]. For some of the cardiomyopathies - hypertrophic cardiomyopathy for example - there is little evidence that immunological mechanisms play any part. In others, the early stages of the disease are characterised by an inflammatory reaction (and accompanying immunological change), which subsides as the condition progresses and is replaced by restrictive changes or dilatation of the chambers of the heart There is a similarity between the active and inactive phases of this process - of inflammation followed by myopathy and that which is seen in the heart muscle disorders of rheumatic heart disease or chagasic myopathy. Indeed, while accepting the concept of cardiomyopathy as 'a heart muscle disease of unknown cause' there is something to be said for, grouping reactive heart diseases in a category of their own, to include all those cardiomyopathic disorders in which an active inflammatory phase in the early stages of the disease leads to further myopathic developments later on. (table I).

As some of the causes of the cardiomyopathies have come to be identified, there have been many suggestions that virus induced carditis, in particular, may lead to a cardiomyopathy which should be distinguished from the rest. This is implicit in the infectious, immune theory of Kawai[2], which postulated that, when viral

TABLE I - Mechanisms which are involved in some of the more common cardiomyopathies.

Types of Cardiomyopathy	Evidence of		
	Infection	inflammatory infiltrate in myocardium	Antibody reaction
Hypertrophic	0	0	0
Dilated	In up to 20%*	Some cases	Some cases
Restrictive	Some cases (filariasis malaria	Early stages (eosinophils)	+
EndocardiaM fibroemastosis	Mumps or other viruses	Early stages	0

Ref. 34; ≠Ref. 29; º Ref. 30.

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antigen is fixed in the heart. a secondary immune or auto-allergic process can continue to damage the heart muscle and valves, the pericardium and the pleura. By no means all of the more insidious cardiomyopathies are explicable in this way; but by demonstrating a sequence of events leading from infection to endocardial fibroelastosis, the work of St. Geme and others [3] has shown how inflammation and the immunological events which follow can result in irreversible disease of the myocardium. The mechanisms which are involved still require further study.

Viruses are mot alone in their ability to provoke heart muscle damage which persists while the infective agent is being eliminated or has disappeared. In essence, the idea of a reactive myocarditis has long been taken as proved in rheumatic fever and regarded as probable in Chagas' disease and toxoplasmosis. The self-damaging aspect of the immune response is also widely accepted, especially in the case of rheumatic carditis, where corticosteroids can appear to be lifesaving. Nor is a self-replicating infective agent alone in its ability to imitate this type of response. It is of interest that the development of reactive changes in the heart has been reported in a patient with farmer's lung - associated with an immunological reaction to mouldy hay[4].

Possible mechanisms of "end stage" myocardial damage

In such diseases as rheumatic heart disease or endomyocardial fibrosis, the evidence for a tissue-damaging immune reaction has usually been based on both serological and cellular findings, together with evidence of an inflammatory reaction in the tissues. In addition, it has sometimes been possible to demonstrate the damaging effect of immunological reactions in animals with similar cardiac diseases The mechanism by which tissue damage is caused in individual cases is imperfectly understood, but many advances have been made. In the production of infection-triggered local lesions, the concepts of immune complex-mediated damage and complement activation are now widely accepted and appear to involve a cascading series of enzyme reactions which lead to inflammation, cell damage, coagulation, and the attraction of many leucocytes to the site. Cellular reactions are also capable of initiating or magnifying local tissue damage whether the cells are eosinophils, other polymorphonuclear leucocytes, or lymphocytes with the help of specific antisera, it is possible to analyse lymphocyte reaction in the tissues in terms of macrophages, antibody producing B cells, helper or suppressor T cells or Killer (K) cells It has been shown that sensitized T and K cells can come into direct contact and kill virally infected or other target cells. In addition, T cells release mediators of inflammation and this can activate macrophages or recruit other cells to the area.

If such mechanisms operate in any of the cardiomyopathies, it should be possible to demonstrate inflammatory myocardial infiltrates, at least in the early stages of the disease. By the time patients develop symptoms and present themselves for investigation, however, there is usually little evidence of inflammation. Sequential studies over a period of time may therefore be necessary in any individual disease if the appearances of 'end stage' myocardial disease are to be attributed to inflammatory or immunological processes.

Regardless of whether immunological factors do or do not contribute, viral infection can certainly cause persisting myocardial damage, as in the neonatal myocarditis which is sometimes seen in the congenital rubella syndrome and which may progress to cause congestive cardiac failure[5]. If death occurs, it is from extensive myocardial necrosis but if, instead, some healing occurs, the infant is left with a damaged myocardium and eletrocardiographic evidence of resolving myocardial injury. The immunological reaction includes the production of IgM antibodies which are mot of maternal origin[6], but, perhaps because of a relative deficiency in the cell mediated response[7,8], virus may persist in the throat, urine, lymphocytes and other tissues. In this case, the infectious and immune aspects may be difficult to disentangle from one another.

Children who are congenitally infected with cytomegalovirus[9] or who acquire this infection in early childhood[10] may also show a deficient cellular immune response to the virus despite considerable antibody production. This pattern is, again, accompanied by persistent viral infection - a fact which may be of relevance, because the magnitude and the type of response cannot only determine whether a virus is eliminated but could well influence the clinical pattern which follows (fig. 1). Since immunological differences are known to influence the wide range of clinical features which are seen in chronic baterial infections such as leprosy[11] and syphilis[12] this explanation seems likely, although it remains unproven. Indeed, little attention has so far been given to the consequences which follow abnormal humoral or cellular immune responses to viral infections.

For the discussion on cardiomyopathy in the following pages, the international classification has in general been followed. Recent observations on the 'unclassified' cardiomyopathy of endocardial fibroelastosis seem, however, to be so central to any understanding of the potential relationship between infection, immunological events and heart muscle damage that this condition is considered first.

ENDOCARDIAL FIBROELASTOSIS

In the case of neonatal endocardial fibroelastosis (EFE) there appears to be a sequence of changes which begins with either an infective myocarditis or the inflammatory process associated with an infection and progresses to a cardiomyopathy in which there is no longer any evidence of inflammation. When Noren and his colleagues[13] first investigated the pathogenesis of EFE, they found that many mothers of the affected children had been exposed to mumps or had actually had the disease in the first trimester of their pregnancy. Furthermore, they could demonstrate a delayed cutaneous hypersensitivity to mumps in almost all clinically documented and necropsy confirmed cases of EFE. There was nevertheless no evidence of

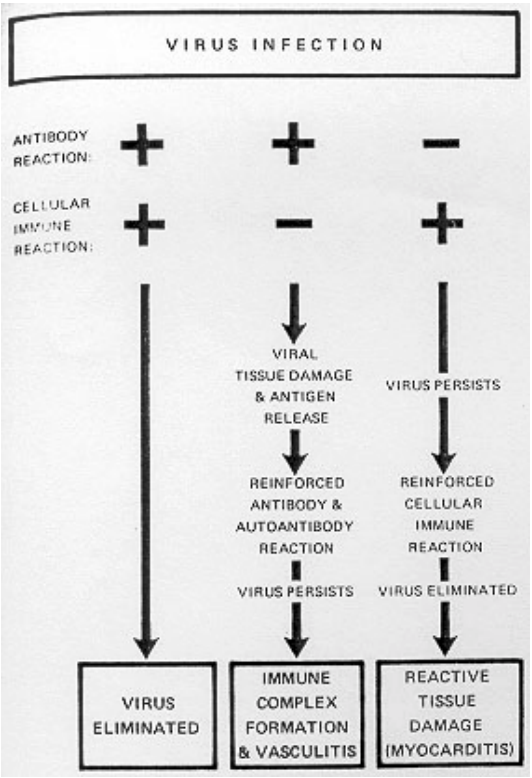

Fig 1 - Reaction patterns to virus infection.

circulating antibody to mumps which Noren's group interpreted as being a failure due to a fetal, 'phylogenetically primitive' response to foreign antigen. This explanation was at first greeted with scepticism. However, out of 64 children with EFE studied by Hutchins and Vie[14] had interstitital inflammatory changes in the myocardium which were consistent with a possible viral origin. In the longer surviving cases these inflammatory changes showed evidence of subsiding, and at the same time the reaction of fibroelastosis appeared to increase in severity.

There have also been instances where endocardial fibroelastosis has developed following postnatal infection with mumps[15], Coxsackie B virus and poliovirus type2[16]. In a detailed study of a single case of EFE, Factor [17] showed that viruslike particles were present in many myocardial and endothelial cells, in addition to a chronic inflammatory reaction that was present throughout the interstitium.

It at first seemed an anomalous idea that there should be a 'split immunological recognition' in which a delayed hyper sensitivity reaction to mumps developed in the absence of circulating antibody. This was quite different from the finding in the congenital rubella syndrome in which - as noted above - there may be a poor cell mediated immune response and a failure to eliminate the virus despite a brisk. Production of antibody. There is, however further evidence that the same kind of 'split' reaction can occur after intra-uterine virus infection in other primates. Noren. St. Geme and their colleagues infected rhesus monkeys with mumps early in pregnancy, and the four infant monkeys which were born showed the same defect of immunological behaviour, with evidence of a cellular immune response but no antibodies[18]. Differing patterns of immune response must therefore be taken into account in analysing the early and late results of viral infection - just as in infection caused by bacteria.

The fibroelastotic reaction also occurs in other species, and the spontaneous myocarditis of turkeys - known as round heart disease - has many similar features to EFE. In this disease, Noren and his colleagues[19] have shown a clear progression from neonatal myocarditis to endocardial fibroelastosis. Histologically, the most severe changes in the myocardium have been found between the ages of 5 and 12 days, including severe myocardial damage and mononuclear cell infiltrates as well as the beginnings of collagen accumulation beneath the endocardium. Virus like particles 60 to 90 nm in diameter were present in the myocardial cells, resembling avian leucosis virus. The clinical and histological developments were followed by studying birds in the later stages of the disease. Marked emdocardial fibroelastotic changes were found to develop within a month, with collagen accumulation, mitral valve and papillary muscle damage, and dilatation or hypertrophy of the left ventricle. As the birds matured further they acquired all the clinical and microscopic findings that might be expected in human fibroelastosis, with congestive heart failure, congested lungs and liver, pleural effusions and ascites. While this in itself provided no proof that immunological mechanisms add to the damage caused by the virus, it is of interest that cyclophosphamide has been found to reduce early mortality, improve cardiac function end diminish cardiac dilatation[2°].

The evidence for an important inflammatory and immunological component in some types of cardiomyopathy is thus persuasive, but the mechanism is difficult to understand. Factor[17]. suggested that the association between endocardial. and other congenital malformations might be related to the microvascular obliteration which was evident in both conditions, and that this was the mechanism which caused damage to the myocardium and other parts of the heart in fetal life. Fibroelastotic change may, however, have a different explanation, since it is also found as a normal development in the valve of the foramen o vale of the heart after it closes neonatally. It has therefore been suggested[2l] that this type of fibroelastotic change may be provoked by the increased mural tension which is found at this time. The two theories are not necessarily incompatible.

RESTRICTIVE CARDIOMYOPATHY

Endomyocardial Fibrosis - The tropical disease of endomyocardial fibrosis is most common in childhood and adolescence and often begins with a febrile illness accompanied by anorexia tachycardia, and pericardial and pleural effusion[22]. This process could be fatal within a few months, but those who survive develop the features of a constrictive cardiac disease. Congestive cardiac failure develops, with ascites,

cardiomegaly and evidence of tricuspid incompetence in many cases. In others, there is a predominantly left sided heart failure, with progressive dyspnea, orthopnea, and the signs of mitral regurgitation and pulmonary hypertension. Pathologically, the process is mainly endocardial and involves focal necrosis of muscle fibres and infiltration by lymphocytes and plasma cells. As the process continues, a very thick fibrous plaque spreads out from the intimal surface and there is a loose, vascularised fibrous tissue reaction. Eventually, fibrosis extends to involve the inner third of the myocardium as well as the papillary muscles, chordi tendinae and sometimes the valves themselves. Endocardial thrombosis is added and the heart is small but often with aneurysmal dilatation of the right atrium.

Such immunological studies as have been carried out suggest an immune or autoimmune reaction to prolonged antigenic stimulation - possibly associated with the more chronic infections or infestations that are found in the various geographical areas. In Uganda, 88% of patients have been found to have serum cryoglobulins containing both IgG and IgM. Immunofluorescence and antiglobulin consumption tests can be used to demonstrate the presence of autoantibodies to the heart, and autoantibodies to other organs may be present as well[23,24]. High levels of antimalarial antibody have also been found - at least in Uganda - suggesting that an abnormal response to malaria may well be a factor in this region[25].

The part played by the immunological reaction is still unclear. Although deposits of gam maglobulin and fibrin have been demonstrated in the endocardium and also in cardiac muscle fibres[23] it remains uncertain whether antiheart antibody actually contributes to the myocardial damage. Nor is it clear whether the localisation of the lesions depends primarily on the distribution of parasitic antigens and the sequence of events which attracts eosinophils and other cells which help to stimulate the fibrotic process. This is still an incomplete story.

Endomyocardial fibrosis and eosinophilic endomyocardial disease - The association of endomyocardial fibrosis with eosinophilia has been noted in a number of cases and it seems possible that endomyocardial fibrosis and eosinophilic endomyocardial disease (Löffler's endocarditis) represent the same disease process, with eosinophilia occurring mainly in the early stages of the disease[26,27]. In the thrombotic endocarditis that is found in patients who die a cardiac death after prolonged eosinophilia, there is often a florid myocardial necrosis, eosinophilia infiltration and vasculitis. However, those who survive develop extensive fibrous scarring of the endocardium and valves, with mural thrombi and histological appearances which are indistinguishable from those of endomyocardial fibrosis (fig. 2).

As in endomyocardial fibrosis without eosinophilia, there is a striking association with infections and infestations which may differ from region to region. Ive and his colleagues[28] found a high incidence of filariasis and eosinophilia among Nigerians who presented with endomyocardial fibrosis. Even after

Fig 2 - Photomicrograph of the thick endocardium from a patient in the fibrotic stage of Löffler's endocarditis, showing that the endocardium is arranged in layers. Superficially organizing thrombus is present. The middle layer consists of fibrous tissue, and the deepest layer - the granulation tissue layer - contains several dilated vascular channels and a sparse chronic inflammatory infiltrate. From this layer the beginning of a septum can be seen extending into the myocardium. (Weigert's elastic Van Gieson stain, x 50). The appearances are identical to endomyocardial fibrosis. Reproduced, with permission from Lessof MH and Olsen EGJ (43).

filariasis had been successfully treated with diethylcarbamazine and the eosinophilia returned to normal, eight out of 11 patients who were followed for an average of two years[29] developed clinical features of cardiac constriction and tricuspid regurgitation. These findings were confirmed by cardiac catheterisation in six cases and at necropsy in one: a patient who was shown to have the classical changes of endomyocardial fibrosis. In view of this evidence, a close association between filariasis and this type of heart disease has been proposed. A different pattern is, however, seen in Uganda, where patients with endomyocardial fibrosis have been found to have malaria parasites, high malaria antibody titres, and other causes of eosinophilia such as hookworms or **strongyloides** more frequently than filariasis[30].

The role of eosinophilic infiltration in contributing to damage in the heart remains uncertain. It appears that lung tumours which produce eosinophilic chemotactic factors are Capable of stimulating a massive acumulation of eosinophils in the tissues including the heart, and that wherever the eosinophils accumulate there is a considerable

degree of associated tissue damage[31,32]. The mechanism is uncertain, but since these eosinophils show a considerable degree of degranulation and vacuolisation, it has been suggested[33] that the tissue damage in such cases results from the release of enzymes of other substances from the eosinophil granules.

DILATED (CONGESTIVE) CARDIOMYOPATHY

Dilated cardiomyopathy may well represent the end result of a number of different disease processes. The concept of myocardial damage after a 'forgotten' viral infection is therefore difficult to prove or disprove in relationship to the group as a whole. Indeed, many cases of insidious heart disease have no evidence of an inflammatory process or of any immunological abnormality at any time. Out of 104 patients with dilated cardiomyopathy studied at the Mayo Clinic[34], 20% had a history of a severe influenza-like illness within 60 days before the appearance of cardiac manifestations. A further 21% had a history of an excessive alcohol intake and 8% were diagnosed as having had rheumatic fever without involvement of the cardiac valves. Within the wide range of aetiological factors that were suspected, there was thus a possibility that a group of v cases might have been triggered by infection. Cambridge and his colleagues35 have claimed that when the patient with cardiomyopathy presents with a fever, high neutralisation titres of antibody - especially against coxsackie B viruses - are commonly found. This possibility of a relationship to coxsackie virus infection has also been raised in other studies.

Coxsackie-specific IgM antibody was reported in 2 out of 28 patients with congestive cardiomyopathy by El-Hagrassy and his colleagues[36]. Both of these patients had had am influenza-like illness followed within three to four weeks by symptoms of congestive heart failure. In 10 out of 18 patients studied by Fowles et al[37] there was similar history of a 'flu-like syndrome' which preceded the onset of cardiac symptoms by an interval of 1 week to 4 months. In 8 out of 113 patients in another study, the development of cardiomyopathy was associated with a rising titre of antibody to coxsackie B or Echo viruses[38]. Where paired serum samples showed no actual rise in antibody levels, there was still a significantly raised titre of complement fixing and neutralising antibody as compared to controls in those patients with congestive cardiomyopathy. However, endomyocardial biopsy specimens showed no signs of myocarditis in 61 such cases and virological studies of the biopsy specimens gave negative results. The study of subgroups of patients with dilated cardiomyopathy therefore needs to be pursued further.

One unexpected observation has arisen from a study of patients with idiopathic cardiomyopathy who have survived a cardiac transplant operation[39] An increased incidence of lymphoma has been reported in such patients[40] Suppressor cell activity was then studied in the Peripheral blood monocytes of 10 patients with congestive cardiomyopathy and found to be defective[37]. It remains to be seen whether this immunological defect may prove to be the consequence of viral infection, or whether it has a direct relevance to the disease process.

HYPERTROPHIC CARDIOMYOPATHY

Okada[38] has claimed that, in Japan, patients with carditis who subsequetnly develop a cardiomyopathy have hypertrophic changes in a substantial number of cases. This observation may, however, depend on the criteria used for the diagnosis of hypertrophic cardiomyopathy and extensive ventricular septal cellular disarray (fig. 3), the vast majority have an inherited disease in which there is no evidence of an inflammatory component but much to suggest am enhanced catecholamine effect during developmental life[4l]. There is, in fact, very little published evidence to support an immunological role in this disease. The involvement of autoimmune mechanisms in cardiomyopathy has been proposed by Das, Cassidy and Petty[42] because of a high incidence of antinuclear and anti-heart antibodies - especially in those patients with hypertrophic subaortic stenosis. It now seems more likely that such serological findings represent a secondary reaction to myocardial destruction.

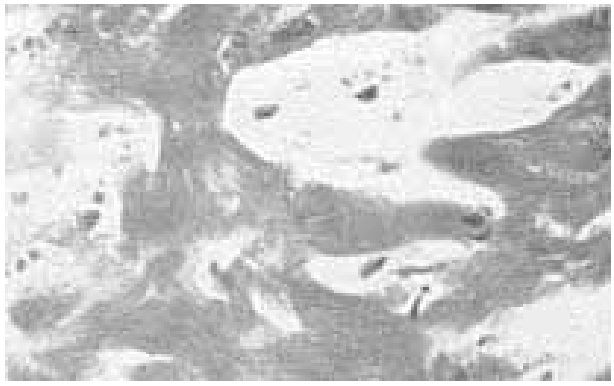

Fig. 3 - Photomicrograph from de septal area of patient with hypertrophic obstructive cardiomyopathy. Total disarray of severely hypertrophied myocardial fibres is prsent together with several abnormally shaped nuclei (Hematoxy-Lessof MH and Olsen EGJ (43).

RESUMO

No grupo das cardiomiopatias (etiologia mão determinada) e no grupo das doenças específicas do músculo cardíaco (etiologia conhecida), há enfermidades que começam com um processo inflamatório e continuam com uma miopatia reativa, em que fatores imunológicos certamente têm participação. Em certas doenças específicas do músculo cardíaco (e.g. cardite reumática e cardiopatia chagásica) existe razoável conhecimento da seqüência de eventos, começando com infecção e inflamação, com dano de mediação imunológica, progredindo para uma etapa final em que não é conspícua a evidência de atividade inflamatória ativa. A despeito das diferenças de agentes infecciosos e da lesão por eles produzida, uma seqüência semelhante pode ser demonstrada em inúmeros casos de endocardiofibrolastose, em todos os tipos de cardiomiopatia restritiva e, provavelmente, também em um pequeno subgrupo de casos de cardiomiopatia congestiva.

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