Myocarditis—a case of mistaken identity?

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The first St Cyres lecture, delivered by Strickland Goodall in 1927 was devoted to the topic of myocarditis and was a brilliant, and at that time an up to date, account of the subject.¹ The list of previous topics is impressive but apart from 1939, when Dr W T Ritchie discussed rheumatic carditis and in 1942 when Dr T F Cotton gave his views on carditis in general, inflammatory changes of the myocardium have not appeared in the title of this lecture. In view of the interest in myocarditis that has been aroused recently, I considered it pertinent to consider this topic for the fiftieth St Cyres lecture.

Often, on occasions such as this, one is informed that a person of note, hitherto believed to have succumbed to a certain disease, has in fact died as a result of a totally different disease, which is of course the subject of this lecture. Alas, I could not find such a person who had retrospectively been credited of having died as a result of myocarditis. Why then should this be so? Surely myocarditis is not a new disease. I think the explanation will be found in the historical review.

Historical note

From the earliest documentation of medical events the association of symptoms with disease of the heart was slow to develop. Harvey's contribution in 1628 in establishing the role of the heart as a pump formed the basis of attributing its malfunction to diseases of the myocardium. Lower and Bonetus in the sixteenth century were among the first to relate symptoms to abnormality of the heart, at necropsy. In 1749 Senac's publication was the first to deal with effective drug treatment of arrhythmias attributed to diseases of the myocardium.²

The establishment of myocarditis—perhaps more than any other subject in medicine—has been intimately linked to the milestones of discoveries in medicine, especially the stethoscope, the microscope, and the development of the science of bacteriology. The stethoscope permitted a distinction to be made

between the two basic forms of heart disease, valvular and non-valvular. The microscope together with the subsequent improvement in optics established a firm basis for myocarditis, a term introduced by Sobernheim in 1837.³

Other highlights of the development of the concept of myocarditis included the description of interstitial myocarditis by Fiedler,⁴ primary myocarditis by Jossier and Gallavardin,⁵ and of the Aschoff nodule of rheumatic myocarditis,⁶ so that by the beginning of the twentieth century myocarditis was clearly established, based on morphological changes. Clinically, however, no clear concept of myocarditis existed, despite the recognition of an inflammatory cellular response of the myocardium to injury. Earlier clinical reports included under the term "carditis" conditions such as pericarditis, pleuritis, and pneumonia.² Separation of changes due to acute vascular lesions from those due to acute infections did also not exist. Clinical association with morphological changes was often lacking or not sought, yet despite this chronic myocarditis became a favourite diagnosis in the early nineteenth century. This state of affairs persisted into the first three decades of the twentieth century, despite the momentous work of Herrick,⁷ who clearly showed that myocardial damage, secondary to vascular causes, occurred and could be separated from myocarditis due to inflammation. The introduction of the sphygmomanometer allowed confirmation of hypertensive heart disease. Yet, despite this, patients in this group were described as having myocarditis.⁸ A paper entitled "Hypertension heart: the most common form of so-called chronic myocarditis" published in 1923 bears witness to that statement. Thus myocarditis was excessively overdiagnosed, not only because of the lack of diagnostic aids but also as a matter of convenience, and many different pathogenetic mechanisms were mistakenly endowed with this label.

The indiscriminate use of myocarditis as part of the clinical diagnosis did not, however, go unnoticed and authorities including Sir Thomas Lewis and Paul White⁹ urged that the term "myocarditis," having so often been applied wrongly in the past (to cases of hypertensive heart disease and coronary arterial disease) should be abandoned. It was, however, emphas-

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Fig. 1 Electrocardiogram showing T wave changes in leads I aVL and V5 and V6 from a patient with myocarditis. The changes could also represent anterolateral ischaemia.

ised that myocarditis did occasionally exist. After such admonition a diagnosis of myocarditis was, if not totally avoided, only rarely made. Thus Wood stated that over the years, of 10 000 new patients, myocarditis (excluding diphtheria, thyroid disease, myxoedema, digitalis or quinidine reaction) was diagnosed in only 30.¹⁰

More recently, electrocardiography, radiology, bacteriology, serology, and necropsy have firmly established the existence of myocarditis, both in an idiopathic form and in association with various other diseases. The spectrum of aetiological agents or associated conditions continues to widen.

Definition, classification, and incidence

Myocarditis may be defined as "an involvement of the myocardium by an inflammatory process: it may be focal or diffuse." In many texts of cardiology the classification of myocarditis is based on that of Gore and Saphir,¹¹ who divided myocarditis into that occurring after infection (with or without associated endocarditis) and that due to specific agents with characteristic anatomical structures or identifiable organisms. A third category was myocarditis due to chemical poisoning, cases of which constituted an isolated group.

Myocarditis may be conveniently divided into specific and non-specific types. The specific types are viral, bacterial, rickettsial, fungal, protozoal, and metazoal. The non-specific types are due to chemical and physical agents and immunological and hypersensitivity reactions and include the diffuse idiopathic types, in which giant cells and granulomatous forms are also recognised.

As with other types of diseases the incidence of myocarditis is difficult to assess since reports and surveys often come from specialised centres. Before the antibiotic era an incidence of 4.3% of 5626 cases was found at necropsy.¹² Another series gave an overall incidence of myocarditis of 5.5%, the highest occurring in children under the age of 15 years (10.9%) and in adults from 16 to 59 years (14%). Newborn infants and patients over 60 years old showed the lowest inci-

dence.¹³ Patients of any age may be affected and in the larger series both sexes are equally represented.

Clinically, the signs and symptoms are well documented and include chest pain, fever, cardiomegaly, flu-like symptoms, pulmonary oedema, palpitations, and lymphadenopathy.¹⁴ Electrocardiographic changes are almost always present.¹⁴ The clinical symptoms and the electrocardiographic changes are non-specific and perhaps it is understandable that myocarditis has been mistaken for other conditions, particularly ischaemic heart disease (Fig. 1).

Morphological distinction between myocarditis and inflammatory cells due to infarction may be difficult. In both conditions an interstitial chronic inflammatory infiltrate is found together with fraying of adjacent myocardial fibres. There is, however, one fundamental difference between the two conditions in that the damage due to coronary arterial disease results in sequential changes of myocardial degeneration.¹⁵ In myocarditis most cells are preserved and do not show the sequential changes (Figs. 2 and 3). In view of this fundamental difference a new definition stressing these features is indicated.

Myocarditis is now defined as "the presence of inflammatory cells in the myocardium with evidence of fraying of adjacent myocardial fibres but without concomitant sequential fibre necrosis."¹⁶ When in the nineteenth century an association between changes in the myocardium and infectious diseases was actively searched for but could not be established because of absence of morphological proof new concepts of heart disease emerged. These were referred to as idiopathic diseases of the myocardium,¹⁷ nowadays known as cardiomyopathies.

Myocarditis in the pathogenesis of cardiomyopathies

With the increasing use of the bioprobe as an adjunct to cardiological investigation fresh endomyocardial tissue can now be obtained with relative ease and safety.¹⁸ Essentially the instrument consists of a

Fig. 2 Photomicrograph of myocardial infarction showing, apart from myocytolysis, a chronic inflammatory infiltrate in the interstitium of the myocardium. No myocardial cell nuclei can be identified. (Haematoxylin and eosin, original magnification $\times 200$.)

Fig. 3 Frozen section of endomyocardial tissue showing myocarditis from a patient clinically suspected of dilated cardiomyopathy but with high neutralisation titres to Coxsackie B virus. Chronic inflammatory cells are seen in the interstitium but the nuclei of the myocardial fibres are present. (Haematoxylin and eosin, original magnification $\times 300$.)

Table 1 *Neutralising antibody titres to Coxsackie B virus in 74 patients with suspected dilated cardiomyopathy investigated between January 1980 and May 1982*

Histological diagnosis	Total No. of patients	No. of patients with antibody titres at following dilutions				
		<1/80 (peak)	1/160	1/320	1/640	>1/1280
Acute myocarditis	22	9	3	4	3	3
Healing or healed myocarditis	16	9	4	2		1
Congestive cardiomyopathy	36	23	6	6	1	

Table 2 *Results of myocardial biopsy in patients with clinical evidence of congestive cardiomyopathy and viral carditis*

Biopsy	Congestive cardiomyopathy	Viral carditis
No. (%) showing morphological evidence	1/53 (2)	13/29 (45)

catheter with a cutting device at one end and an operating handle at the other.^{19 20} One of the major indications for this form of investigation is the clinical suspicion of one or other form of cardiomyopathy. To date I have examined 500 patients suspected of having dilated (congestive) cardiomyopathy. In 101 patients the non-specific changes of a hypertrophied dilated heart could not be found but morphological changes—particularly those of myocarditis—were evident in 45 of these. The histological (and ultra-structural) findings fulfilled the criteria of myocarditis.

In a subsequent collaborative study of 74 patients with suspected clinical diagnosis of dilated cardiomyopathy biopsy tissue showed active, healing, or healed myocarditis or dilated cardiomyopathy (Table 1).²¹ In the active phase neutralising antibody titres to Coxsackie B virus at a dilution of 1/320 or more were found in 45% of patients. Similar results have been obtained from another group of patients clinically suspected of having myocarditis (Table 2). Myocarditis is, however, not always present. In another study of 50 patients with dilated cardiomyopathy in whom microneutralisation antibody tests for Coxsackie B virus were carried out, titres at a dilution of $\geq 1/1024$ were found in 15 of the 50 patients compared with only one of 50 controls matched for age and sex.²² Biopsy specimens were examined by me in 11 of the 15 cases and apart from hypertrophy and dilatation signs of active myocarditis or past myocarditis could not be found.

Thus in an appreciable number of patients with suspected dilated cardiomyopathy evidence of myocarditis has been found which was usually not severe. An immunological disturbance can result in myocarditis. What evidence is there that immunological mechanisms may be operative? Clinical evidence

of a possible immunological pathogenetic process occurring in at least some patients with dilated cardiomyopathy may be summarised as follows: (a) cardiac symptoms often follow upper respiratory infection after a lag period in previously healthy patients; (b) the clinical course is punctuated by episodes of heart failure without obvious cause; (c) a good clinical response to corticosteroids in some patients, particularly early in the disease, is achieved and; (d) the demonstration of heart reactive antibodies and immunoglobulins and antinuclear factors and the presence of bound gammaglobulin in the heart tissue of these patients suggest an immunological process. The histological features of active myocarditis or myocarditis in the past complete the observations made in some of these patients.²³ Thus myocarditis plays a fundamental role in the pathogenesis in a substantial number of patients with dilated cardiomyopathy.

IMMUNOLOGICAL REACTIONS

Heart reactive antibodies, which probably do not play a pathogenetic role,²⁴ have been found in various cardiovascular diseases including cardiomyopathy. One group of workers has, however, shown that the presence of these antibodies correlates with the severity and the duration of the cardiomyopathy.²⁵ In severely disabled patients who had undergone transplantation these antibodies were not found, but examination of heart tissue showed deposits of bound gammaglobulin as well as complement. It is likely that cardiomyopathic tissue may fix heart reactive immunoglobulins to specific sarcolemmal and subsarcolemmal antigens which may explain the presence of these antibodies in the serum.²⁶ Another study of biopsy tissue obtained by biptome has shown preferential binding of IgG and IgA in patients with dilated cardiomyopathy.²⁵

The possibility of a cell mediated immunity in this type of cardiomyopathy has also been extensively explored. One such study using the *in vitro* lymphocytic transformation to phytohaemagglutinin from patients with dilated cardiomyopathy and other heart conditions—including ischaemic, rheumatic, and congenital heart disease—has shown that patients with dilated cardiomyopathy represent a heterogene-

ous group. Abnormal cell mediated immunity was found in about 40% of patients with dilated cardiomyopathy.²⁷ Similarly, stimulation of lymphocytes to human heart extract showed evidence of cardiac sensitisation to heart muscle in some patients with this type of cardiomyopathy.²⁷ Another study reported reduced lymphocytic stimulation to phytohaemagglutinin as well as an absolute reduction in the percentage of circulating T lymphocytes.²⁸

Another approach, that of leucocyte migration inhibition using concanavalin A (mitogen) and human heart muscle extract acting as the antigen, has also been undertaken in patients with dilated cardiomyopathy and ischaemic heart disease. Though no significant differences in the mean leucocyte migration inhibition responses to concanavalin A were found, a distinct bimodal response above and below the 90% confidence limit of the control migration index occurred in patients with dilated cardiomyopathy.²³

Other studies have investigated cell mediated cytotoxicity in various types of heart disease, including dilated cardiomyopathy.²⁹ The conclusion reached was that lymphocytic cytotoxicity to heart muscle was not specific to dilated cardiomyopathy but might also occur as a result of myocardial damage from other causes. Experimental evidence that T lymphocytes from infected mice with Cocksackie B3 virus were cytotoxic to infected syngeneic myocardial cells in vitro but abolished by antithymocyte serum also exists.³⁰ It may be that sensitised lymphocytes could be responsible for chronic myocardial damage.

Defective T suppressor cell function in dilated cardiomyopathy in man has also been found in dilated cardiomyopathy but not in coronary heart disease.³¹ Virus infection may trigger antibody production directed at suppressor cells, which may inactivate or possibly coat T cell receptors interfering with the normal regulatory role in modulating B cell function. This results in increased B cell activity with production of autoimmune antibodies. T suppressor cell dysfunction may also affect cell mediated immunity.²³

These investigations have shown that at least in a substantial number of cases of dilated cardiomyopathy evidence of an immune disturbance exists initiated by a viral infection, such as that due to Cocksackie B virus. The immunological disturbances result in myocarditis and may also explain recurrent episodes of heart failure. This has also been shown experimentally. After the acute phases in which the virus replicates and is recovered from the myocardium, chronic inflammatory changes may result.³² It is tempting to speculate that this is similar to the pathogenetic mechanism which may occur in dilated cardiomyopathy in man and could be the result of an immune response initiated by persistent non-

infectious virus antigen or by new antigen formed from necrotic myocardial fibres.

These pathogenetic mechanisms may find another morphological expression. Counting of neuronal cells in strips of right atrial muscle situated between the venae cavae has shown an appreciable reduction in their number in patients with dilated cardiomyopathy. In control hearts the mean ($\pm$ SE) neuronal count was 6412 ± 377 , whereas the mean count in patients with dilated cardiomyopathy was 4565 ± 471 ($p < 0.002$).³³ A causal relation of neuronal cell depopulation may possibly exist in some patients with dilated cardiomyopathy which may be the final common pathway of the various immunological disturbances.

Restrictive cardiomyopathy

The other type of cardiomyopathy in which myocarditis is involved in the pathogenesis is restrictive cardiomyopathy. This includes two separately named cardiac conditions. The first, endomyocardial fibrosis, was first described pathologically by Davies in 1948³⁴ and was believed to be confined to Africa. It soon became evident that this condition also occurred in other tropical and subtropical areas. The other condition, endocarditis parietalis fibroplastica, described by Löffler in 1936³⁵ was considered to be a disease associated with an eosinophilia which affected patients in the temperate zones.

The association of eosinophilia with endomyocardial disease has been known for almost a century but the reasons for these observations have not been studied in detail. Wider recognition of this condition followed reports from the tropics and elsewhere in the late 1960s and early 1970s.³⁶ Infections, such as filariasis or eosinophilic leukaemia, were found to coexist with endomyocardial disease. Furthermore, it was suggested that the two conditions, hitherto believed to be two separate entities, were in fact one disease, irrespective of the geographical origin. In a retrospective study of some 90 previously reported cases in patients who had died as a result of endomyocardial disease in association with an eosinophilia and in whom a full necropsy had been performed, morphological tissue was available for study. The cause of eosinophilia was either idiopathic, reactive, or leukaemic.³⁷ The reactive causes of hypereosinophilia included polyarteritis nodosa, parasitic infections, sensitivity to antituberculous drugs, asthma, and carcinoma.

Morphologically, three major stages based on the length of history could be established. In the earliest stage (after a history of an average of five weeks) the *necrotic stage* was reached, which manifested itself as a myocarditis (Fig. 4). The inflammatory infiltrate in

Fig. 4 Photomicrograph of myocarditis (necrotic stage) in endomyocardial disease. All cells with lighter cytoplasm are degenerated eosinophils. (Carbol chromotrope, original magnification $\times 400$.)

the myocardium consisted almost entirely of eosinophils.³⁷ The subsequent stage, the *thrombotic stage* (average history of 10 months) was characterised by extensive thrombus superimposition on an already thickened endocardium. At that stage the myocarditic

changes had largely disappeared. The final stage, the *fibrotic stage*, represented the healing phase of this cardiac involvement which originated in myocarditis and was found when the length of history had lasted for 24.5 months. When these features were compared

Table 3 Histological findings in cases of restrictive cardiomyopathy

Variables	Total	EPF	EMF (non-tropical cases without eosinophilia)	EMF (Europeans)	EMF (Nigerians)	EMF (Ugandans)	EMF (Brazilians)
No. of patients	48	16	6	7	9	5	5
Superimposed thrombus	32	14	4	4	7	1	2
Hyaline layer							
Mean thickness (μm)	2.8	3.4	2.1	3.0	1.8	2.7	3.6
Range (μm)	0.7–10.1	1.1–10.1	1.2–2.6	1.9–5.3	0.7–2.7	1.1–5.1	1.4–6.4
Elastic condensation							
Superficial	1	0	0	0	1	0	0
Deep	20	8	3	5	1	2	1
Both	16	5	1	0	2	4	4
Granulation layer	44	15	5	7	8	4	5
Tissue eosinophilia	13	8 (50%)	0	2 (30%)	3 (33%)	0	0
Fibrous septa	45	16	6	7	6	5	5
Myocardial fibrosis	46	16	6	7	8	5	4
Pericardial infiltration	12	6	4	0	0	0	2

EPF, endocarditis parietalis fibroplastica; EMF, endomyocardial fibrosis.
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Fig. 5 Electron micrograph of degranulated eosinophils. Some granules show reversal of electron density (electron dense centre surrounded by a less dense zone). (Uranyl acetate and lead citrate $\times 15\,000$.)

with those of endomyocardial fibrosis in patients from the tropics no differences were observed (Table 3). This study strongly supported the unitarian theory that whatever the geographical origin may be Löfller's endocarditis parietalis fibroplastica and endomyocardial fibrosis belonged to the same disease process, originating in a myocarditis and rich in eosinophils.^{37 38} Although some differences in clinical observations, such as age and embolic phenomena, exist they do not detract from the unitarian concept. So far unexplained regional differences also exist. Another difference was the occurrence of an arteritis in the "European" type but not in the "tropical" type. Arteritis is seen in the necrotic stage in patients from all regions, but once the thrombotic stage is reached it is no longer evident but affected small vessels are occluded by thrombi. In the fibrotic stage the arterial changes are totally non-specific showing only occasionally some intimal thickening. Arteritis is probably not detected in the tropics as often as in the temperate zones since patients in the tropical regions do not seek medical care until the late stages of the disease.³⁸

EOSINOPHIL ABNORMALITIES

More recent studies have shown that the eosinophils are abnormal. This takes the form of vacuolation and, more importantly, degranulation (Fig. 5). If over 15% (that is, $>1 \times 10^9/l$) of circulating eosinophils are degranulated endomyocardial disease occurs, irrespective of the degree of eosinophilia.³⁸ Clinical studies supported by non-invasive and invasive techniques including examination of endomyocardial biopsy specimens have amply confirmed these observations.^{39 40} Degranulated eosinophils have been found in the blood as well as in the inflammatory infiltrates in tissue obtained by endomyocardial biopsies. Raised serum concentrations of eosinophilic granule basic proteins have been found. In healthy subjects the concentration of normal cationic proteins in the serum is less than $55\ \mu g/l$ whereas in patients a mean concentration of $146\ \mu g/l$ has been found with a range of 64 to $300\ \mu g/l$. The aim is to make a diagnosis as early as possible when myocarditis is still present and to treat these patients vigorously with corticosteroids or vincristine. Once the fibrotic stage is

reached surgical intervention by decortication of the thick endocardium has proved beneficial.

The modern concept of endomyocardial disease is that stimulation of the eosinophil leads to an unmasking of additional Fc receptors which in turn leads to more effective binding of IgG (or C3b) coated particles or parasites. This induces degranulation which may accompany various inflammatory processes.³⁸ Furthermore, the granules, which consist of cationic proteins, have been shown to be thrombogenic. The abnormal eosinophils get into the microcirculation of the myocardium and through additional noxious substances, such as peroxidases, induce fibre necrosis and myocarditis. At the same time the cationic proteins also involve the endocardium causing thrombus superimposition. The fibrotic stage represents the healing phase of myocarditis and the organisation of the thrombus. Low concentration of eosinophil secretion products, including the eosinophilic granule basic proteins, have been shown to injure isolated heart cells in vitro. Furthermore, a specific toxic effect of eosinophil cationic protein is exerted on the plasma membrane and on two enzyme complexes: pyruvate dehydrogenase and oxoglutarate dehydrogenase. There is, therefore, now ample evidence that abnormal eosinophils and myocarditis form the underlying pathogenetic mechanism in restrictive cardiomyopathy.⁴¹

Myocarditis, a clinical and morphological enigma in the past which often masqueraded under various guises, is no longer such a problem. This has been achieved by improved clinical and virological recognition and, in no small measure, by examining endomyocardial tissue obtained at biopsy. Though many questions remain unanswered the findings so far have clearly shown that in two of the three types of cardiomyopathy,⁴² an inflammatory process in the myocardium is intimately linked to the pathogenesis of the disease. In 1927 Strickland Goodall stated that some causes of myocarditis were universally accepted—for example, the virus of rheumatism, syphilis, or diphtheria.¹ This brings a smile to one's lips in 1983. Much has been learnt since 1927. New concepts will undoubtedly continue to be formulated so that 50 years from now, when the centenary St Cyres lecture will be delivered, a smile of incredulity may play on the reader's lips in 2033, if the topic is myocarditis.

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