

## SESSION I

*Chairman:* PROFESSOR J. F. GOODWIN

### **Pathological aspects of endomyocardial fibrosis**

E. G. J. OLSEN  
M.D., F.R.C.Path., F.A.C.C.

*National Heart Hospital, Westmoreland Street, London W1M 8BA*

#### **Summary**

The studies leading up to the unitarian concept suggesting that endomyocardial fibrosis, described in the tropics, and Löffler's endocarditis parietalis fibroplastica (Löffler's endomyocardial disease), described in the temperate zone, belong to the same disease spectrum are detailed. Evidence that the eosinophil is involved in the pathogenesis of endomyocardial diseases, irrespective of the geographical origin, is presented. The findings of a similar abnormality in these cells obtained from patients in the tropical and temperate zones are briefly mentioned. In view of the evidence it is proposed that endomyocardial disease, associated with abnormal eosinophils, hitherto classified under the restrictive type of cardiomyopathy, be removed from this classification and reclassified under 'specific heart muscle disease'.

KEY WORDS: endomyocardial fibrosis, eosinophil.

#### **Introduction and pathology**

The term 'endomyocardial disease' includes endomyocardial fibrosis and Löffler's endocarditis parietalis fibroplastica (Löffler's endomyocardial disease) which have long been considered separate entities. The former condition was described clinically as unexplained heart failure by Bedford and Konstam (1946). The pathology was detailed by Davies (1948). Endomyocardial fibrosis was believed to be confined to the tropical regions, and Löffler's endomyocardial disease to temperate zones and associated with eosinophilia. Endomyocardial fibrosis and Löffler's endomyocardial disease are included under the term 'cardiomyopathies', defined by the WHO/ISFC\*

Task Force (1980) as heart muscle disease of unknown causes and classified under the restrictive type (the other two types being 'dilated' and 'hypertrophic' cardiomyopathy).

Since the original detailed descriptions, the geographical limitations of the tropical type of endomyocardial fibrosis, suggesting confinement to the African continent, has proved unwarranted and cases from India, Ceylon, Brazil, Venezuela and Colombia have been reported. These findings have been summarized by Olsen and Spry (1979) and Hutt (1983).

An association with eosinophils in the pathogenesis of endomyocardial fibrosis was already suggested by Davies and Ball (1955). Subsequently, Parry and Abrahams (1965) noted patients in Nigeria, either diagnosed as Löffler's disease or heart muscle disease due to filariasis. French, Belgian and Nigerian workers also described patients with endomyocardial disease from West Africa and from what was then the Belgian Congo (Oakley and Olsen, 1977). Ive and Brockington (1966) and Ive *et al.* (1967) drew attention to the association between filariasis and eosinophilia. Europeans, working in the tropical zones who developed endomyocardial fibrosis in association with eosinophils, were described by Brockington, Olsen and Goodwin (1967). Thus, the important role of the eosinophil in the pathogenesis of endomyocardial disease was already noted in these early years. Roberts, Liegler and Carbone (1969) described 2 patients diagnosed as eosinophilic leukaemia resembling endomyocardial fibrosis. A spectrum of the disease of tropical eosinophilia developing into eosinophilic leukaemia without the abnormal myelopoiesis and culminating in Löffler's disease with the Ugandan type of endomyocardial fibrosis was suggested.

\*International Society and Federation of Cardiology.

At that time, Brockington and Olsen (1973) were already considering such a spectrum and this work tracing pathologically the stages involved suggested a unitarian theory of the disease.

### Pathology of endomyocardial fibrosis

Macroscopically, the hearts are hypertrophied and the ventricular cavity may be dilated or reduced in size. The striking feature is the immense thickening of the endocardium, often several millimeters in dimension. Strands of fibrous tissue frequently extend into the underlying myocardium, usually, but not always, limited to the inner third of the myocardial wall (Davies and Ball, 1955; Olsen, 1972). The right ventricle (11%), the left ventricle (38%) or both ventricles (51%) may be involved (Shaper, Hutt and Coles, 1968).

Typically, in right-sided involvement, the apex is affected, gradually being drawn towards the tricuspid valve, which may also be affected by this process (Fig. 1). Thus, the cavity is progressively obliterated. The chordae tendineae and papillary muscles may also be involved. In left ventricular involvement, the inflow tract, apex and part of the outflow tract is usually affected. The thick endocardium ends, usually abruptly, in a rolled edge in the region beneath the anterior mitral valve leaflet (Davies, 1968). Mitral valve leaflets, chordae tendineae and papillary muscles may also be involved. In addition, the atria may also be affected but usually in association with ventricular involvement. Thrombus is not infrequently superimposed (Olsen, 1979).

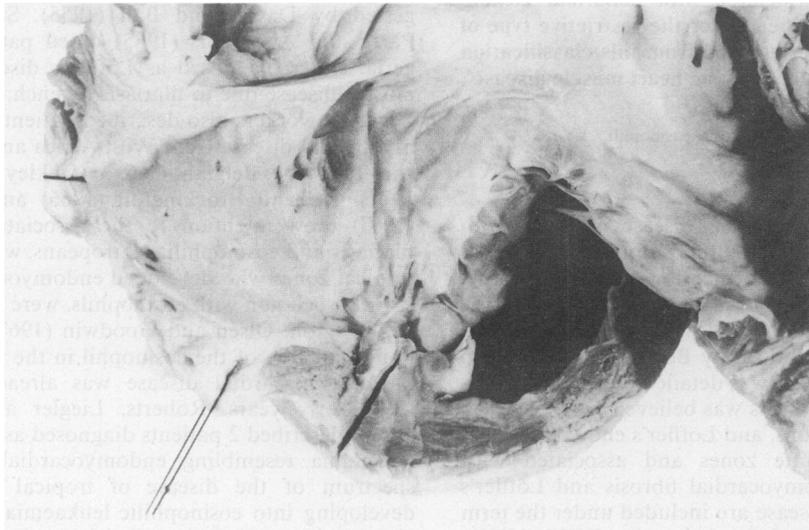


FIG. 1. The right side of the reduced right ventricular cavity is shown. The apex is obliterated. Note severe endocardial thickening. The tricuspid valve has not been involved.

Histologically, the abnormal endocardium is arranged in layers. Beneath the thrombus, a zone of collagen tissue is found, occasionally separated into two layers. The deepest layer, the so-called granulation tissue layer, consists of loosely arranged connective tissue in which dilated blood vessels abound (Fig. 2), as well as varying degrees of inflammatory cells including occasionally some eosinophils (Olsen, 1979). It is from this layer that strands, noted macroscopically, extend into the underlying myocardium. Small intracardiac vessels show either non-specific intimal thickening or no abnormalities.

### Löffler's endomyocardial disease

From the original description (Löffler, 1936) and subsequent reports by Weiss-Carmine (1957) and Olsen (1977), it has been shown that no significant differences exist pathologically between endomyocardial fibrosis and Löffler's endomyocardial disease.

The stages that take place, culminating in the fibrotic phase of endomyocardial disease, were studied.

### Materials and methods

Authorities who had previously published studies on patients with endomyocardial disease associated with eosinophilia, were approached, provided a post mortem had been carried out. Some 90 cases were collected. Pathological material was also made available in 30 cases, either by the submission of stained or unstained sections or formalin-preserved tissue. This was processed along routine procedures.

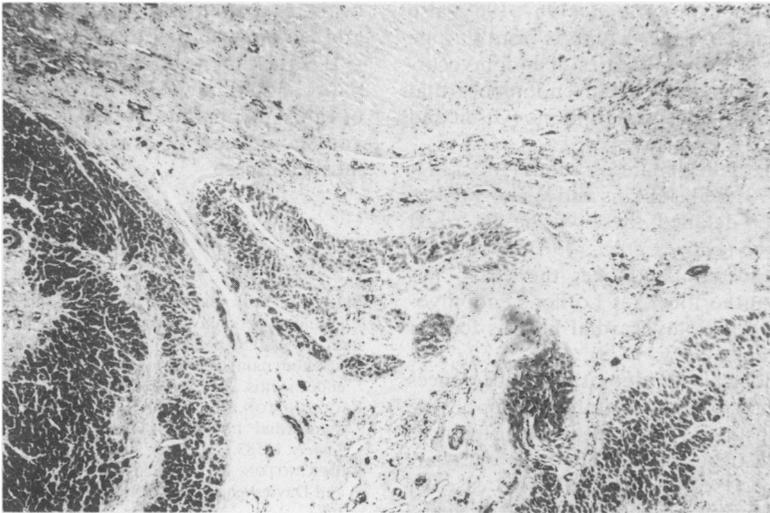


FIG. 2. Photomicrograph of severe endocardial thickening. The superficial two-thirds of the endocardium consist of dense collagen tissue beneath which the granulation tissue layer can be identified. Dilated blood vessels and a sparse chronic inflammatory infiltrate are present in this layer. The strands extending into the underlying myocardium originate from the granulation tissue layers. H.E.,  $\times 50$ .

paraffin embedded and stained with haematoxylin and eosin or Weigert's elastic van Gieson.

## Results

The cause of eosinophilia was predominantly idiopathic (43 patients). In another group of 25 patients eosinophilia was associated with polyarteritis nodosa, Hodgkin's disease and other reticulo-endothelial tumours, carcinomas, sensitivity to antituberculous drugs, parasitic infections and, possibly, asthma (25 patients). Another 22 patients were described as eosinophilic leukaemia, but abnormal myelopoiesis was identified in only 4 patients. The remaining 28 cases belonged therefore to the idiopathic group. From the histopathological material supplied, three major stages could be identified, dependent on the length of history.

### *The necrotic phase*

This consisted of an intense myocarditis, rich in eosinophils, together with an arteritis. This stage was reached when the average length of history had lasted for 5.5 weeks.

### *The thrombotic stage*

This was reached when the average length of symptomatology had lasted for 10 months. The myocarditic process had receded and some non-specific thickening of the endocardium was already present. Varying degrees of thrombus, often extensive, were superimposed. At this stage, the arteritis

had also receded but thrombi were frequently found occluding the small intramyocardial blood vessels.

### *The fibrotic stage*

This was reached after a mean interval of 24.5 months and resembled endomyocardial fibrosis in every detail. At this late stage, the arteries showed either some non-specific intimal thickening consisting predominantly of fibro-elastic tissue or no abnormalities.

Additionally, tissue from patients firmly diagnosed as endomyocardial fibrosis from Uganda, Brazil and Nigeria was compared with the 16 cases in the fibrotic stage of Löffler's disease without knowledge of origin or other details. Extensive morphometric analysis was undertaken but no differences between these, the fibrotic stage of Löffler's disease and endomyocardial fibrosis obtained from the tropics, could be identified. We therefore concluded that Löffler's endomyocardial disease and endomyocardial fibrosis belong to the same disease spectrum, the origin of which could be traced back to the presence of eosinophils in the myocardium.

## Discussion

It has already been pointed out that, many years ago, the possible association of eosinophilia in the pathogenesis of endomyocardial fibrosis in the tropics had been considered. Twelve out of the 24 patients in Davies' (1948) original description

showed a significant eosinophilia and 6 out of 16 patients described by Connor *et al.* (1967, 1968) also showed this association. Several reports from Europe have also testified to the similarities of endomyocardial disease with eosinophilia and endomyocardial fibrosis in their pathological descriptions (Olsen and Spry, 1979).

The similarity of clinical manifestations (Brockington and Olsen, 1973; Bell, Jenkins and Webb-Peploe, 1976) has also been detailed; these will be described and discussed later (Davies *et al.*, 1983; Goodwin, 1983). Evidence, accumulated over the years, has convinced many authorities that Löffler's endomyocardial disease and endomyocardial fibrosis form a continuum (Olsen and Spry, 1979).

From a pathological standpoint, the differences that have been upheld by those authorities opposing the unitarian concept have included the differences of macroscopic distribution of the thick endocardium. Shaper *et al.* (1968) in a study of 173 cases of endomyocardial fibrosis has shown 5 types of distribution which include those thought to have been noted only in Löffler's endomyocardial disease. The other points of differences have been the absence of an arteritic process in endomyocardial fibrosis. In the study by Brockington and Olsen (1973), arteritis was consistently found in the more acute stage but never in the chronic stages. Non-specific intimal thickening or no abnormalities was all that was found. It may be that in the tropical zones when patients come to the attention of the physician, the later stages have been reached and therefore arteritis has not been observed.

Spry and Tai (1976) drew attention to abnormalities of eosinophils in patients with associated endomyocardial disease. If a significant number of eosinophils showed degranulation, even in the absence of eosinophilia, endomyocardial disease was inevitably associated. With the wider use of the biptome (Konno and Sakakibara, 1963; Richardson, 1974), fresh endomyocardial tissue can now be examined without special risks to the patients. The association between degranulated eosinophils and endomyocardial disease has been repeatedly substantiated (Olsen, personal observations).

The final link demonstrating degranulation of eosinophils in the early phases of the disease in patients in the tropics has recently been achieved (Davies *et al.*, 1983).

The aetiology of endomyocardial disease is unknown and suggestions including geographical and immunological factors have been reviewed (Olsen, 1980). Many aspects remain unsolved including why the heart appears to be the target organ when eosinophils show degranulation, the exact stimuli leading to degranulation and the geographical manifestations disproportionately affecting immigrant tribes from the upland regions of Rwanda and

Burundi in Uganda. There is, however, now ample evidence that an association of abnormal eosinophils and endomyocardial disease exists.

It is therefore suggested that restrictive cardiomyopathy should now be removed from the classification of cardiomyopathies (WHO/ISFC Task Force, 1980) and should now be re-classified under specific heart muscle disease.

## References

- BEDFORD, D.E. & KONSTAM, G.L.S. (1946) Heart failure of unknown aetiology in Africans. *British Heart Journal*, **8**, 236.
- BELL, J.A., JENKINS, B.S. & WEBB-PEPLOE, M.M. (1976) Clinical haemodynamic and angiography findings in Löffler's eosinophilic endocarditis. *British Heart Journal*, **38**, 541.
- BROCKINGTON, I.F., OLSEN, E.G.J. & GOODWIN, J.F. (1967) Endomyocardial fibrosis in Europeans resident in tropical Africa. *Lancet*, **i**, 583.
- BROCKINGTON, I.F. & OLSEN, E.G.J. (1973) Löffler's endocarditis and Davies' endomyocardial fibrosis. *American Heart Journal*, **85**, 308.
- CONNOR, D.H., SOMERS, K., HUTT, M.S.R., MANION, W.C. & D'ARBELA, P.G. (1967) Endomyocardial fibrosis in Uganda (Davies' disease). An epidemiologic, clinical and pathologic study. Part I. *American Heart Journal*, **74**, 687.
- CONNOR, D.H., SOMERS, K., HUTT, M.S.R., MANION, W.C. & D'ARBELA, P.G. (1968) Endomyocardial fibrosis in Uganda (Davies' disease) An epidemiologic, clinical and pathologic study. Part II. *American Heart Journal*, **75**, 107.
- DAVIES, J.N.P. (1948) Endomyocardial necrosis. A heart disease of obscure aetiology in Africans. *M.D. Thesis*, University of Bristol.
- DAVIES, J.N.P. (1968) The ridge in endomyocardial fibrosis. *Lancet*, **i**, 631.
- DAVIES, J.N.P. & BALL, J.D. (1955) The pathology of endomyocardial fibrosis in Uganda. *British Heart Journal*, **17**, 337.
- DAVIES, J., SPRY, C.J.F., VIJAYARAGHAVAN, G. & DESOUZA, J.A. (1983) A comparison of the clinical and cardiologic features of endomyocardial disease in temperate and tropical regions. *Postgraduate Medical Journal*, **59**, 179.
- GOODWIN, J. (1983) Endomyocardial disease: Clinical features. *Postgraduate Medical Journal*, **59**, 154.
- HUTT, M.S.R. (1983) Epidemiology aspects of endomyocardial disease. *Postgraduate Medical Journal*, **59**, 142.
- IVE, F.A. & BROCKINGTON, I.F. (1966) Endomyocardial fibrosis and filariasis. (letter) *Lancet*, **i**, 212.
- IVE, F.A., WILLIS, A.J.P., IKEME, A.C. & BROCKINGTON, I.F. (1967) Endomyocardial fibrosis and filariasis. *Quarterly Journal of Medicine*, **36**, 495.
- KONNO, S. & SAKAKIBARA, S. (1963) Endomyocardial biopsy. *Diseases of the Chest*, **44**, 345.
- LÖFFLER, W. (1936) Endocarditis parietalis fibroplastica mit Bluteosinophilie. Ein eigenartiges Krankheitsbild. *Schweizerische medizinische Wochenschrift*, **17**, 817.
- OAKLEY, C.M. & OLSEN, E.G.J. (1977) Eosinophilia and heart disease. (Editorial) *British Heart Journal*, **39**, 233.
- OLSEN, E.G.J. (1972) Cardiomyopathies. *Cardiovascular Clinics*, **4**, 240.
- OLSEN, E.G.J. (1977) Endomyocardial fibrosis and Löffler's endocarditis parietalis fibroplastica. *Postgraduate Medical Journal*, **53**, 538.
- OLSEN, E.G.J. (1979) The pathology of cardiomyopathies. A critical analysis. *American Heart Journal*, **98**, 385.
- OLSEN, E.G.J. (1980) *The Pathology of the Heart*. 2nd edition, p. 329. Macmillan Press, Basingstoke and London.
- OLSEN, E.G.J. & SPRY, C.J.F. (1979) The pathogenesis of Löffler's endomyocardial disease and its relationship to endomyocardial

- fibrosis. In: *Progress in Cardiology, Vol. 8* (eds. P. Yu and J.F. Goodwin), p. 281. Lea & Febiger, Philadelphia.
- PARRY, E.H. & ABRAHAMS, D.G. (1965) The natural history of endomyocardial fibrosis. *Quarterly Journal of Medicine*, **34**, 383.
- PATEL, A.K., D'ARBELA, P.G. & SOMERS, K. (1977) Endomyocardial fibrosis and eosinophilia. *British Heart Journal*, **39**, 238.
- RICHARDSON, P.J. (1974) King's endomyocardial bioptome. *Lancet*, **i**, 660.
- ROBERTS, W.C., LIEGLER, D.G. & CARBONE, P.P. (1969) Endomyocardial disease and eosinophilia. *American Journal of Medicine*, **46**, 28.
- SHAPER, A.G., HUTT, M.S.R. & COLES, R.M. (1968) Necropsy studies of endomyocardial fibrosis and rheumatic heart disease in Uganda. *British Heart Journal*, **30**, 391.
- SPRY, C.J.F. & TAI, P.C. (1976) Studies on blood eosinophils. II. Patients with Löfller's cardiomyopathy. *Clinical and Experimental Immunology*, **24**, 423.
- WEISS-CARMINE, S. (1957) Die Endocarditis parietalis fibroplastica mit Bluteosinophilie (Löfller) und ihre Stellung im Rahmen der Parietalendokardfibrosen. *Schweizerische medizinische Wochenschrift*, **87**, 890.
- WHO/ISFC (1980) Report of the WHO/ISFC Task Force on the definition and classification of cardiomyopathies. *British Heart Journal*, **44**, 672.