Eosinophilia and heart disease

C. M. OAKLEY AND E. G. J. OLSEN

From the Department of Clinical Cardiology, Division of Cardiovascular Diseases, Hammersmith Hospital, Royal Postgraduate Medical School, London; and the Department of Histopathology, National Heart Hospital, Cardiothoracic Institute, London

A wealth of literature testifies to the existence of an association between blood eosinophilia and cardiac disorder. Ever since Löffler described his two cases of 'endocarditis parietalis fibroplastica' with blood eosinophilia in 1936, this rare and dramatic clinical syndrome has excited attention (Brink and Weber, 1963; Jennings and Pengelly, 1968; Nagy *et al.*, 1969; Cline, 1969; Gardner-Thorpe *et al.*, 1971; Raizner *et al.*, 1972; Rasche *et al.*, 1973; Blair *et al.*, 1974; Bell *et al.*, 1976). Löffler's eponym is much used, especially when the eosinophilia is prominent and its cause obscure but other names abound to describe both overtly similar and seemingly adjacent disorders (Smith and Furth, 1943; Ware and Chapman, 1947; Becker *et al.*, 1953; Engfeldt and Zetterström, 1956; Odeberg, 1965)—*are they really different or are they merely variants of the same basic disorder?*

Pathological observations of the hearts of patients with prolonged eosinophilia have shown that both ventricles may be affected by a thrombotic endocarditis associated with eosinophilic infiltration, vasculitis, and myocardial necrosis (Brockington and Olsen, 1972; Olsen, 1975). Death may occur at this stage but more prolonged survival is followed by fibrous scarring and thickening of the endocardium, including the atrioventricular valves, and fibrous replacement of the inner myocardium. In severe cases organising mural thrombi may fill most of the cavities of the ventricles and embolism is common (Davies, 1960). The cardiac involvement may be associated with generalised eosinophilic infiltration involving other major organs (Hardy and Anderson, 1968; Shepherd *et al.*, 1971; Zucker-Franklin, 1971). Some of these cases have had a pseudo-leukaemia without abnormal myelopoiesis (Boussier, 1957) and others a genuine leukaemia, either eosinophilic or associated with eosinophilia (Bentley *et al.*, 1961; Yam *et al.*, 1972; Blatt *et al.*, 1974). Cardiac disorders may also develop with

eosinophilia in status asthmaticus (Lennox, 1948), polyarteritis nodosa (Goodwin and Oakley, 1969), sensitivity to antituberculous drugs (Gardioli and Picht, 1957), and tropical eosinophilia associated with chronic infestations including filariasis (Vakil, 1961; Johnny and Ananthachari, 1965). Chusid and colleagues (1975) found that at least 95 per cent of patients with a hypereosinophilic syndrome recorded in the published reports had clinical or necropsy evidence of myocardial disease.

Tropical endomyocardial fibrosis was first described from Uganda by Davies in 1948 after a clinical report by Bedford and Konstam (1946), and numerous further reports soon followed both from Davies and others in Uganda (Ball *et al.*, 1954; Davies, 1960) and also from West Africa (Abrahams, 1962). The characteristic sites of the endomyocardial lesions were well emphasised in these early studies. In the left ventricle the lesion, which is a scar, is strictly confined to the inflow tract. It may run from the posterior mitral leaflet to the apex where it ends abruptly in a distinctive ridge a short way up the septal wall (Davies, 1968) so sparing the anterior mitral leaflet, vestibule, and aortic valve entirely. The damage is often less extensive than this and may pick out either the apex or the region of the posterior leaflet. On the right side the process may be more massive and obliterate most of the right ventricle, but it still usually spares the infundibulum and pulmonary valve. The peculiar limitation of the left ventricular lesion may reflect the sites of maximum vortex impact on the walls of the filling ventricle (Bellhouse and Bellhouse, 1969) and suggests that the damaging agent is carried in the blood stream. The earliest manifestations of the pathological process within the heart are not well known. In Ibadan, Parry and Abrahams (1965) stressed the general constitutional illness which seemed to initiate the clinical cardiac disorder, and in the early fatal cases they found a

freshly fibrosing endocardium, active fibroblasts, engorged small blood vessels, and chronic inflammatory cells in the myocardium with areas of myofibre necrosis. Eosinophils were not mentioned but, as they noted in their paper, this initial illness had been spoken of also by French, Belgian, and Nigerian workers who had observed similar types of heart disease in West Africa and the Congo, which they had referred to as Löffler's disease or identified as a filarial cardiomyopathy. These patients had had an eosinophilia at some stage. While in tropical Africa an early constitutional illness with fever had been prominent in the Englishman with typical endomyocardial fibrosis reported by Brockington *et al.* in 1967.

In 1967, Ive *et al.* linked the geographical incidence of endomyocardial fibrosis in Nigeria with filariasis (and consequent eosinophilia) in an epidemiological study which showed that most patients came from forest areas where filariasis was common, and fell ill during the rainy season. Though their survey showed these similarities it failed to establish a cause and effect relation in Nigeria, and in Uganda the theory failed because in Uganda filariasis and endomyocardial fibrosis were not regionally associated at all.

The idea that a cardiac eosinophilia might have a pathogenetic role in African endomyocardial fibrosis came with the publication by Roberts of two cases of 'eosinophilic leukaemia' with mural endocardial sclerosis and superimposed thrombus, thrombotic valvular endocarditis, myocardial scarring, and generalised organ involvement. They predicated a spectrum of disease running from tropical eosinophilia to Löffler's disease with survival to develop Ugandan-type endomyocardial fibrosis as the end result of the endomyocardial eosinophilia (Roberts *et al.*, 1969, 1970). The next year, Brockington and associates (1970) described a further case of 'eosinophilic leukaemia' with endomyocardial fibrosis and thrombosis of the left ventricle. They considered that the cardiac lesion might have matured to typical endomyocardial fibrosis had the patient survived longer. Subsequently, fully developed typical endomyocardial fibrosis either with coexisting eosinophilia or in its absence has been described both from the U.S.A. (Libanoff and McMahon, 1976) and from this country (Faruque, 1963; Chew *et al.*, 1977). In this issue the Ugandan school report that their patients with established endomyocardial fibrosis have not shown abnormally high eosinophil counts but this observation surely cannot help elucidate whether or not the cardiac damage had been associated with an eosinophilia at its onset (Patel *et al.*, 1977).

In 1973, Brockington and Olsen compared 30

cases of Löffler's endocarditis with 6 non-tropical cases without eosinophilia and 26 cases of endomyocardial fibrosis from Nigeria, Uganda, Brazil, and Europe. They showed that the fibrous stage of Löffler's disease and endomyocardial fibrosis were indistinguishable on histological grounds.

In South Africa, Becker and his colleagues (1953) recognised that a similar clinicopathological picture to Löffler's disease could exist in the absence of eosinophilia and that if this feature were regarded as a variable phenomenon then many of the cases published under a variety of terms might all belong in the same category.

As would be necessary for a unitarian theory, endomyocardial fibrosis is now being recognised in Europeans who have never visited the tropics. Eosinophilia may be transient in Löffler's disease (Weiss-Carmine, 1957) and is inconstant in African patients with developed endomyocardial fibrosis. Since infestation with eosinophilia is much commoner in Africans than in Europeans this could account for the apparent differences in incidence between endomyocardial fibrosis, a rare disorder of the tropics, and Löffler's disease, an exceedingly rare disorder in Europe. Important circumstantial evidence is provided by non-tropical patients such as Libanoff and McMahon's and Chew *et al.*'s cases who had both typical endomyocardial fibrosis and persisting eosinophilia.

Löffler's disease with eosinophilia may present with a grave constitutional illness and often the severe right-sided failure conceals the signs of left-sided involvement until embolism occurs. If constrictive pericarditis is suspected the presence of a murmur of mitral regurgitation (which is often early to mid-systolic rather than pansystolic) should betray the endocardial site of the disorder. Apical systolic murmurs were present in 20 of 40 cases reviewed by Brink and Weber (1963).

The unitarian theory remains unproven. In endomyocardial fibrosis the scarring is usually limited to the left ventricular inflow tract while in many cases of Löffler's disease, the whole cavity may be involved and there may be a valvulitis with vegetations. But if endomyocardial fibrosis represents a milder form of Löffler's disease because it has permitted survival to the stage of scarring, surely a more restricted lesion is not unexpected? Another difficulty which was re-emphasised recently, by Bell *et al.* (1976) is the generalised arteritis which affects many organs in Löffler's disease while endomyocardial fibrosis primarily affects the heart, but since the eosinophilia may no longer persist at the stage of endomyocardial fibrosis, the general arteritis may disappear too if they had, as we suppose, been connected. A generalised arteritis may indeed never

have existed in the milder forms recognised by Hardy and Anderson (1968) and only those are likely to live to become chronic survivors. A further point in favour of the unitarian view is the high incidence of intracardiac thrombosis and embolism both in Löffler's disease with eosinophilia and in the disease which Becker described without eosinophilia. While embolism does occur in endomyocardial fibrosis (Shaper and Wright, 1963; Owor, 1973) it is fairly rare perhaps because the earlier stages of the disease are not recognised (Patel *et al.*, 1977). The apparent difference may be related to the lesser aggressiveness and greater chronicity of the process at the stage of endomyocardial fibrosis. Against the unitarian view, on the other hand, it is possible, or indeed likely, that endomyocardial fibrosis represents an end stage of any process which damages the endomyocardium, and that the eosinophil is only one of these. Carcinoid heart disease and methysergide heart disease also attack the endocardium, though neither are identical with endomyocardial fibrosis. A recent case report described endomyocardial fibrosis in a 21-year-old with acute myeloblastic leukaemia unassociated with eosinophilia but treated with daunorubicin (Wilcox *et al.*, 1976). a well-established cardiotoxic agent.

The clinical presentations of endomyocardial fibrosis are well known as a result of the comprehensive descriptions from Uganda (Shillingford and Somers, 1961; Connor *et al.*, 1967) and from Nigeria (Parry and Abrahams, 1963). The features vary greatly with the sites of the intracardiac lesions. Chronic right-sided disease may obliterate the cavity of the right ventricle almost completely without killing the patient who classically presents with proptosis and tense ascites. The condition may mimic constrictive pericarditis (Somers *et al.*, 1968) or present with pericardial effusion. Left-sided disease may simulate other cardiomyopathies and present with heart failure (Falase *et al.*, 1976). Tricuspid and/or mitral regurgitation (Clark *et al.*, 1956; Fowler and Somers, 1968) may be dominant and scar excision with valve replacement has recently been employed successfully (Cachera *et al.*, 1976). Rarely, the condition simulates primary pulmonary hypertension (Davies *et al.*, 1965) or an intracardiac tumour (Van der Hauwaert *et al.*, 1965). Clubbing and cyanosis are common with severe right-sided disease and secondary infective endocarditis is not unknown on the mitral valve (Falase *et al.*, 1976).

The main haemodynamic effect of the cardiac disorder (with or without persisting eosinophilia) is to restrict the filling and output of the ventricles, but the effect of this restriction is only felt in advanced cases and asymptomatic milder cases who do

not seek treatment would evade recognition in societies whose patients are medically less sophisticated than our own. This could, perhaps, explain the absence of descriptions of mild endomyocardial fibrosis from those centres in tropical Africa from which the 'classical' forms were described and the late appearance of endomyocardial fibrosis in temperate climes where severe forms of the disorder are rare.

The European patients with endomyocardial fibrosis have started to emerge *pari passu* with the more thorough diagnostic investigations of asymptomatic patients which are now usual. The name 'primary restrictive cardiomyopathy' was recently coined to describe British patients believed to have a mild burned out form of Löffler's disease (Oakley, 1974), but, in such cases, proof of this is dependent on cardiac biopsy or accidental death from some non-cardiac cause.

The balance of the argument suggests that endomyocardial fibrosis represents both a later evolutionary phase and a milder burned out form of the disease which Löffler described. It is probable that the eosinophil is usually though not invariably involved; the underlying pathological processes are still unknown and further study and analysis of these conditions remain to be done.

References

- Abrahams, D. G. (1962). Endomyocardial fibrosis of the right ventricle. *Quarterly Journal of Medicine*, **31**, 1-20.
- Ball, J. D., Williams, A. W., and Davies, J. N. P. (1954). Endomyocardial fibrosis. *Lancet*, **1**, 1049-1054.
- Becker, B. J. P., Chatgidakis, C. B., and Van Lingen, B. (1953). Cardiovascular collagenosis with parietal endocardial thrombosis. A clinicopathologic study of forty cases. *Circulation*, **7**, 345-356.
- Bedford, D. E., and Konstam, G. L. S. (1946). Heart failure of unknown aetiology in Africans. *British Heart Journal*, **8**, 236-237.
- Bell, J. A., Jenkins, B. S., and Webb-Peploe, M. M. (1976). Clinical haemodynamic, and angiography findings in Löffler's eosinophilic endocarditis. *British Heart Journal*, **38**, 541-548.
- Bellhouse, B. J., and Bellhouse, F. H. (1969). Fluid mechanics of the mitral valve. *Nature (London)*, **224**, 615-616.
- Bentley, H. P., Reardon, A. E., Knoedler, J. P., and Krivit, W. (1961). Eosinophilic leukaemia. *American Journal of Medicine*, **30**, 310-322.
- Blair, H. T., Chahine, R. A., Raizner, A. E., Gyorkey, F., and Luchi, R. J. (1974). Unusual hemodynamics in Löffler's endomyocarditis. *American Journal of Cardiology*, **34**, 606-609.
- Blatt, P. M., Rothstein, G., Miller, H. L., and Cathey, W. J. (1974). Löffler's endomyocardial fibrosis with eosinophilia in association with acute lymphoblastic leukaemia. *Blood*, **44**, 489-493.
- Bousser, J. (1957). Eosinophilie et leucémie. *Le Sang*, **28**, 553-580.
- Brink, A. J., and Weber, H. W. (1963). Fibroplastic parietal endocarditis with eosinophilia. *American Journal of Medicine*, **34**, 52-70.

- Brockington, I. F., Luzzatto, L., and Osunkoya, B. O. (1970). The heart in eosinophilic leukaemia. *African Journal of Medical Science*, **1**, 343-352.
- Brockington, I. F., and Olsen, E. G. J. (1972). Eosinophilia and endomyocardial fibrosis. *Postgraduate Medical Journal*, **48**, 740-741.
- Brockington, I. F., and Olsen, E. G. J. (1973). Löffler's endocarditis and Davies' endomyocardial fibrosis. *American Heart Journal*, **85**, 308.
- Brockington, I. F., Olsen, E. G. J., and Goodwin, J. F. (1967). Endomyocardial fibrosis in Europeans resident in tropical Africa. *Lancet*, **1**, 583-588.
- Cachera, J. P., Poulain, H., Menasche, P. L., Laurent, F., Loisan, D., and Chiche, P. (1976). Endocardite fibreuse d'origine filarienne. Traitement chirurgical par endocardectomie du ventricule gauche et remplacement prothétique de la valve mitrale. *Tropical Cardiology*, **2**, 79-89.
- Chew, C. Y. C., Ziady, G. M., Raphael, M. J., Nellen, M., and Oakley, C. M. (1977). Primary restrictive cardiomyopathy: non-tropical endomyocardial fibrosis and hyper-eosinophilic heart disease. *British Heart Journal*, **39**, 413-427.
- Chusid, M. J., Dale, D. C., West, B. C., and Wolff, S. M. (1975). The hyper-eosinophilic syndrome: analysis of fourteen cases with review of the literature. *Medicine*, **54**, 1-27.
- Clark, G. M., Valentine, E., and Blount, S. G. (1956). Endocardial fibrosis simulating constrictive pericarditis. *New England Journal of Medicine*, **254**, 349-355.
- Cline, M. J. (1969). Eosinophilia and eosinophilic carditis. *California Medicine*, **111**, 388-395.
- Connor, D. H., Somers, K., Hutt, M. S. R., Manion, W. C., and Darbela, P. G. (1967). Endomyocardial fibrosis in Uganda (Davies disease). *American Heart Journal*, **74**, 687-709 (Pt. 1) and (1968), **75**, 107-124 (Pt. II).
- Davies, J. N. P. (1948). Endocardial fibrosis in Africans. *East African Medical Journal*, **25**, 10-14.
- Davies, J. N. P. (1960). Some considerations regarding obscure diseases affecting the mural endocardium. *American Heart Journal*, **59**, 600-631.
- Davies, J. N. P. (1968). The ridge in endomyocardial fibrosis. *Lancet*, **1**, 631-632.
- Davies, H., Deuchar, D. C., and Missen, G. A. K. (1965). Endomyocardial fibrosis: two cases of severe pulmonary hypertension presenting in England. *Guy's Hospital Reports*, **114**, 337-362.
- Engfeldt, B., and Zetterström, R. (1956). Disseminated eosinophilic 'collagen disease'. *Acta Medica Scandinavica*, **153**, 337-353.
- Falase, A. O., Kolawole, T. M., and Lagundoye, S. B. (1976). Endomyocardial fibrosis. Problems in differential diagnosis. *British Heart Journal*, **38**, 369-374.
- Faruque, A. A. (1963). Adult endomyocardial fibrosis in Britain. *Lancet*, **2**, 331-333.
- Fowler, J. M., and Somers, K. (1968). Left ventricular endomyocardial fibrosis and mitral incompetence: a new syndrome. *Lancet*, **1**, 227-228.
- Gardiol, D., and Picht, E. (1957). Encéphalopathie et myocardite à éosinophiles. A propos d'un cas de tuberculose urogénitale traité par des tuberculostatiques. *Schweizerische Zeitschrift für Tuberkulose und Pneumologie*, **14**, 212-226.
- Gardner-Thorpe, G., Harriman, D. G. F., Parsons, M., and Rudge, P. (1971). Löffler's eosinophilic endocarditis with Balint's syndrome (optic ataxia and paralysis of visual fixation). *Quarterly Journal of Medicine*, **40**, 249-260.
- Goodwin, J. F., and Oakley, C. M. (1969). The cardiomyopathies. In *Modern Trends in Cardiology*, vol. 2, p. 280. Ed. by A. Morgan Jones. Butterworths, London.
- Hardy, W. R., and Anderson, R. E. (1968). The hyper-eosinophilic syndromes. *Annals of Internal Medicine*, **68**, 1220-1229.
- Ive, F. A., Willis, A. J. P., Ikeme, A. C., and Brockington, I. F. (1967). Endomyocardial fibrosis and filariasis. *Quarterly Journal of Medicine*, **36**, 495-516.
- Jennings, R. C., and Pengelly, C. D. R. (1968). Endocarditis parietalis fibroplastica (Löffler's disease). *Postgraduate Medical Journal*, **44**, 251-254.
- Johny, K. U., and Ananthachari, M. D. (1965). Cardiovascular changes in tropical eosinophilia. *American Heart Journal*, **69**, 591-598.
- Lennox, B. (1948). Acute parietal endocarditis in a case of status asthmaticus: a possible early stage of Löffler's endocarditis parietalis fibroplastica with eosinophilia. *Journal of Pathology and Bacteriology*, **60**, 621-628.
- Libanoff, A. J., and McMahon, N. J. (1976). Eosinophilia and endomyocardial fibrosis. *American Journal of Cardiology*, **37**, 438-441.
- Löffler, W. (1936). Endocarditis parietalis fibroplastica mit Bluteosinophilie, ein eigenartiges Krankheitsbild. *Schweizerische medizinische Wochenschrift*, **66**, 817-820.
- Nagy, Z., Bajtai, A., Bencsath, P., and Vaslaki, L. (1969). In vivo diagnosis of Löffler's endocarditis parietalis fibroplastica. *Acta Medica Scandinavica*, **185**, 409-414.
- Oakley, C. M. (1974). Clinical recognition of the cardiomyopathies. *Circulation Research*, **35**, Suppl. 2, 152-167.
- Odeberg, B. (1965). Eosinophilic leukemia and disseminated eosinophilic collagen disease—a disease entity. *Acta Medica Scandinavica*, **177**, 129-144.
- Olsen, E. G. J. (1975). Pathological recognition of cardiomyopathy. *Postgraduate Medical Journal*, **51**, 277-281.
- Owor, R. (1973). Aortic embolism in endomyocardial fibrosis. *African Journal of Medical Science*, **4**, 313-318.
- Parry, E. H. O., and Abrahams, D. G. (1963). The function of the heart in endomyocardial fibrosis of the right ventricle. *British Heart Journal*, **25**, 619-629.
- Parry, E. H. O., and Abrahams, D. C. (1965). The natural history of endomyocardial fibrosis. *Quarterly Journal of Medicine*, **34**, 383-408.
- Patel, A. K., D'Arbela, P. G., and Somers, K. (1977). Endomyocardial fibrosis and eosinophilia. *British Heart Journal*, **39**, 238-241.
- Raizner, A. E., Silverman, M. E., and Waters, W. C. (1972). Conduction disturbances and pacemaker failure in Löffler's endomyocarditis. *American Journal of Medicine*, **53**, 343-347.
- Rasche, R. F. H., Kelsch, R. D., and Weaver, D. K. (1973). Löffler's endocarditis in childhood. *British Heart Journal*, **35**, 774-776.
- Roberts, W. C., Buja, L. M., and Ferrans, V. J. (1970). Löffler's fibroplastic parietal endocarditis, eosinophilic leukemia and Davies' endomyocardial fibrosis. The same disease at different stages. *Pathologia et Microbiologia*, **35**, 90-95.
- Roberts, W. C., Liegler, D. G., and Carbone, P. P. (1969). Endomyocardial disease and eosinophilia. A clinical and pathologic spectrum. *American Journal of Medicine*, **46**, 28-42.
- Shaper, A. G., and Wright, D. H. (1963). Intracardiac thrombosis and embolism in endomyocardial fibrosis in Uganda. *British Heart Journal*, **25**, 502-508.
- Shepherd, A. J. N., Walsh, C. H., Archer, R. K., and Wetherley-Mein, G. (1971). Eosinophilia, splenomegaly and cardiac disease. *British Journal of Haematology*, **20**, 233-239.
- Shillingford, J. P., and Somers, K. (1961). Clinical and haemodynamic patterns in endomyocardial fibrosis. *British Heart Journal*, **23**, 433-446.

- Smith, J. J., and Furth, J. (1943). Fibrosis of the endocardium and the myocardium with mural thrombosis. *Archives of Internal Medicine*, **71**, 602-619.
- Somers, K., Brenton, D. P., D'Arbela, P. G., Fowler, J. M., Kanyerezi, B. R., and Sood, N. K. (1968). Haemodynamic features of severe endomyocardial fibrosis of the right ventricle including comparison with constrictive pericarditis. *British Heart Journal*, **30**, 322-332.
- Vakil, R. J. (1961). Cardiovascular involvement in tropical eosinophilia. *British Heart Journal*, **23**, 578-586.
- Van der Hauwaert, L. G., Corbeel, L., and Maldague, P. (1965). Fibroma of the right ventricle producing severe tricuspid stenosis. *Circulation*, **32**, 451-456.
- Ware, E. R., and Chapman, B. M. (1947). Chronic fibroplastic myocarditis. *American Heart Journal*, **33**, 530-537.
- Weiss-Carmine, S. (1957). Die Endocarditis parietalis fibroplastica mit Bluteosinophilie (Löffler) und ihre Stellung im Rahmen der Parietalendokardfibrosen. *Schweizerische medizinische Wochenschrift*, **87**, 890-898.
- Wilcox, R. G., James, P. D., Toghill, P. J. (1976). Endomyocardial fibrosis associated with daunorubicin therapy. *British Heart Journal*, **38**, 860-863.
- Yam, L. T., Li, C. Y., Necheles, T. F., and Katayama, I. (1972). Pseudo-eosinophilia eosinophilic endocarditis and eosinophilic leukemia. *American Journal of Medicine*, **53**, 193-202.
- Ziady, G. M., Oakley, C. M., Raphael, M. J., and Goodwin, J. F. (1975). Primary restrictive cardiomyopathy (abstract). *British Heart Journal*, **37**, 556.
- Zucker-Franklin, D. (1971). Eosinophilia of unknown aetiology: a diagnostic dilemma. *Hospital Practice*, **6**, 119.

Requests for reprints to Dr. C. M. Oakley, Department of Clinical Cardiology, Division of Cardiovascular Diseases, Hammersmith Hospital, Royal Postgraduate Medical School, Du Cane Road, London W12 0HS.