DIFFUSE ENDOMYOCARDIAL SCLEROSIS

BY

J. B. LYNCH AND J. WATT

From the Department of Pathology, University of Liverpool

Received August 23, 1956

In recent years increasing attention has been focused upon a group of cases of congestive cardiac failure that present a distinctive cardiac morphology. There is diffuse thickening of the mural endocardium of one or both ventricles and fibrosis of the myocardium which is largely confined to the inner third of the ventricular wall; the coronary arteries are normal or show minimal arteriosclerosis. Since little is known of the pathogenesis, and the morphology of the lesion is somewhat variable, we have used the general term "diffuse endomyocardial sclerosis".

From Europe, particularly Switzerland, there have been several reports of endomyocardial sclerosis, but usually of single cases only. Loeffler (1936) described two under the term "endocarditis parietalis fibroplastica with eosinophilia", and similar single case reports are those of Mumme (1940), Roulet (1944), Berblinger (1948), Lenègre and Gerbaux (1952) and others. Prior to 1948, only 22 cases had been recorded (Loeffler, 1946-47). Similarly, from America there have been very few examples described (Smith and Furth, 1943; McKusick and Cochran, 1952; McNichol *et al.*, 1953; and others). We have found only two relevant British case reports (Edge, 1946; and Lennox, 1948). A closely similar condition occurring in Africa is endomyocardial fibrosis: several detailed clinical and pathological studies on a large number of these cases have been made and Davies and Ball (1955) note that it was responsible for 33 of the 231 deaths in Uganda from cardiac failure in the period 1951-53. This curious anomaly of the geographical incidence of the condition remains unexplained.

A lesion morphologically allied to endomyocardial sclerosis occurs in infants, and has been described as foetal endomyocarditis (Farber and Hubbard, 1933), endocardial dysplasia (Prior and Wyatt, 1950), and congenital fibroelastosis (Gowing, 1953). The relationship of this condition to that in the adult remains *sub judice* at present.

We have collected four adult cases of diffuse endomyocardial sclerosis during the past four years and it is possible that the condition in this country, though rare, may escape notice. Material from cases of endomyocardial sclerosis occurring in African natives and from cases of congenital fibroelastosis in infancy has been studied for comparison. A composite clinical and pathological picture of diffuse endomyocardial sclerosis will be given and only a brief résumé of each case is presented.

CASE SUMMARIES

Case 1. A Jewess, aged 51 years, suffered from recurrent attacks of asthma sometimes with præcordial pain, for six months before admission to hospital. On examination the essential findings were diffuse bronchial spasm, a mild degree of hypertension (B.P. 170/100), and eosinophilia. The total white cell count varied from 8000 to 18,000 per c.mm., the eosinophilia fluctuating within the range 4 to 31 per cent. Her death was sudden and unexpected and was presumed to be the result of acute coronary ischæmia.

Post mortem there was a diffuse vesicular emphysema of the lungs and a moderate degree of chronic venous congestion of the abdominal viscera. The heart was enlarged, weighing 400 g. In the left ventricle there was an extensive endomural thrombus overlying a grossly thickened endocardium (Fig. 1). On histological examination the thickened endocardium consisted of granulation tissue showing numerous capillaries and a diffuse cellular infiltration comprising eosinophil leucocytes, plasma cells, lymphocytes,

FIG. 1.—Left ventricle, showing endomyocardial sclerosis, apical thrombus, and patent coronary arteries. Case 1.

FIG. 2.—Gross endocardial thickening in the apical region of the right ventricle; hypertrophy of the myocardium. Case 4.

and some hæmosiderin-laden macrophages. There was organization of the deeper layers of the overlying thrombus. The inner elastic lamina of the endocardium lying deep to the granulation tissue showed focal areas of reduplication. There were foci of fibrosis in the myocardium, almost confined to the inner third and sometimes continuous with the overlying endocardium. A scanty infiltrate of lymphocytes and plasma cells was present in several of these foci and also varying degrees of atrophy of the immediately adjacent myocardium. Occasionally there were broad connective tissue septa containing numerous sinusoidal channels. These septa were continuous with the granulation tissue of the thickened endocardium and extended inwards into the myocardium for a variable distance. Arterioles in the subendocardial region showed reduplication of the internal elastic lamina and subintimal fibrosis.

Comment. Initially this case was thought to be one of myocardial infarction with overlying thrombus. However, the coronary arteries were fully patent and showed little or no atheroma, the myocardial fibrosis was focal and limited to the inner third of the ventricular wall, and the endomyocardial sclerosis had not the distribution commonly seen in myocardial infarction.

Loeffler (1936) described two cases characterized by a progressive cardiac failure, eosinophilia, and diffuse thickening of the mural ventricular endocardium. Writing in 1947 he stated "the diagnostic clinical aspect of this condition is quite clear; it is the aspect of the so-called Fridl-Pick type of general central stasis, with this important difference that the pericardium in my cases proves to be absolutely free." It would appear that this syndrome is composed of the following triad; a clinical picture simulating constrictive pericarditis, eosinophilia, and endomyocardial sclerosis, but not all the reported cases have satisfied these criteria. If the endomyocardial sclerosis is severe, affecting the right ventricle or both ventricles, the clinical picture does closely simulate that of constrictive pericarditis (Loeffler, Case 1, 1936; Mumme, 1940; Fossel, Case 1, 1942). McKusick and Cochran (1952) were so impressed by this resemblance that they described a case under the title constrictive endocarditis. In contrast, when the lesion involves only the left ventricle, the differential diagnosis from constrictive pericarditis is not seriously in question (Buchler, 1941-42; Fossel, Case 2, 1942; Berblinger, 1948). Eosinophilia is also inconstant and Egger (1944) thought it was not an obligatory sign: to explain this Loeffler (1947) suggested that it was a phasic phenomenon related to the stage of the disease process at the time of observation. Finally, the most constant component of the triad, the endomyocardial sclerosis, also is variable in site, depth, and extent. There must, therefore, be some latitude in the identification of a particular case as an example of the syndrome.

In this patient the clinical picture of constrictive pericarditis was not present, but the findings of eosinophilia, endomyocardial sclerosis, and the morphological features of early congestive cardiac failure, we believe, warrant its inclusion as an early example of Loeffler's endocarditis syndrome.

Case 2. The essential clinical feature in this woman, aged 36, was a remittent progressive congestive cardiac failure of obscure ætiology and of three years' duration. Previous illnesses included paratyphoid and a tuberculide skin rash. On examination there was gross cardiac enlargement, and a localized soft systolic murmur at the apex. The blood pressure was 110/80; there was no anæmia or eosinophilia. Constrictive pericarditis, possibly tuberculous in origin, was considered but rejected as unlikely, and she was finally thought to have idiopathic hypertrophy of the heart.

The principal autopsy findings were cardiac enlargement (heart weight 630 g.), infarcts in the lung and spleen, œdema, ascites, and chronic passive venous congestion of the viscera. As in Case 1 there was endomural thrombus and thickening of the endocardium affecting the apex, lateral, and posterior walls of the left ventricle. The histology of the endocardium is illustrated in Fig. 3. There was a minimal fibrosis of the myocardium consisting of small finger-like extensions into the subendocardial zone, with only very occasional small foci elsewhere.

FIG. 3.—Uniform fibro-elastic thickening of the endocardium. Weigert's elastic and van Gieson; $\times 120$. Case 2.

FIG. 4.—Thickened endocardium, showing fibro-hyaline connective tissue with scanty elastic elements. Weigert's elastic, and hæmatoxylin and eosin; $\times 60$. Case 4.

Comment. Several reported cases of idiopathic cardiac hypertrophy show features similar to those found in endomyocardial sclerosis. Thus, in the endocardium small areas of necrosis, fibrinoid degeneration, an acute inflammatory infiltration, and also thickening have been reported (Norris and Pote, 1946). In the myocardium the fibrosis, though usually diffuse, may be mainly in the subendocardial region and indeed, may be restricted to this site (Reisinger and Blumenthal, 1941). In reviewing the pathology of idiopathic cardiac hypertrophy, Fowler (1947) commented on the frequent occurrence of fibro-elastic proliferation of the subendocardium, often associated with thrombus. Finally, the first case in the report of Levy and Rousselot (1933) closely simulates in its description the appearances of endomyocardial sclerosis. As we do not know the pathology of its early stages it is difficult to evaluate its relationship to these cases, especially where the idiopathic cardiac hypertrophy is associated with organizing endomural thrombus (Levy and von Glahn, 1937). To classify certain of these cases as examples of endomyocardial sclerosis is merely to change the name, and requires only a shift in the emphasis from one macroscopic

feature, hypertrophy, to another, endocardial thickening, without in any way increasing our understanding of the underlying disease process.

In the present case the uniform admixture of fibrous and elastic tissue elements of the thickened endocardium and the minimal amount of myocardial fibrosis are of interest in that these morphological features are essentially those found in congenital fibroelastosis. The possible relationship of adult endomyocardial sclerosis to fibroelastosis of infancy will be discussed later.

Case 3. A man, aged 37, suffered from an attack of diarrhoea during a dysentery epidemic while in a Polish concentration camp in 1940. Until his death in 1952, he was subject to several recurrences, each lasting a few weeks. On these occasions blood was present in the faeces, but there was no evidence of a dysenteric infection, bacillary or amoebic. With each attack a severe deficiency state, and gross anaemia developed (red cell count 1.85 million per c.mm.; haemoglobin 7.4 g. per 100 ml.) though in the interim periods his general health remained fair; therapy included a diet supplemented with vitamins and the anaemia responded to proteolysed liver extracts and folic acid. In his final illness the major clinical features were wasting, anaemia, oedema, ascites, enlargement of the liver and spleen, and a generalized brownish pigmentation of the skin, the latter having been present since 1948. In the differential diagnosis, sprue, Addison's disease and haemochromatosis were considered, but no decision was reached.

Post mortem, there was atrophy of the gastro-intestinal tract; the adrenals were small but within normal limits; the liver and spleen were enlarged and congested. The heart was small, there was much thickening of the endocardium, similar in distribution to the previous cases, but without overlying thrombus. The mitral valve cusps were slightly thickened and there was a mild degree of stenosis. The thickening of the mural endocardium was not continuous with that of the valve cusps. Microscopically, the thickening consisted of relatively acellular fibro-elastic tissue with several small foci of hyaline degeneration. There was a focal myocardial fibrosis but a striking feature was a continuous zone of fibrosis immediately beneath the thickened endocardium (Fig. 5).

FIG. 5.—Thickening of the endocardium associated with much subendocardial fibrosis. Weigert's elastic, and hæmatoxylin and eosin; $\times 4$. Case 3.

Comment. A primary cardiac disorder was not suspected and in retrospect the role played by the heart in the production of the symptom complex is difficult to evaluate. The possible aetiological relationship of malnutrition, especially vitamin B deficiency, and the cardiac pathology will be discussed in more detail with the next case.

Case 4. A woman, aged 45, enjoyed good health before detention in a Japanese prisoner-of-war camp where in 1942 she developed oedema and ascites: a diagnosis of vitamin B deficiency was made. On her return to England in 1945 she complained of dyspnoea and swelling of the legs. In 1946 she had pleurisy,

in 1950 amoebic dysentery, and in 1951 pneumonia. Thereafter her symptoms steadily increased in severity, and in 1952 there was a loud systolic murmur in the mitral area and a diagnosis of constrictive pericarditis was made. Finally, in 1955 she died a few hours after surgical intervention to relieve the constrictive pericarditis.

Post mortem, there was a moderate degree of cirrhosis of the liver, ascites, and gall stones. The heart weighed 480 g. and showed endomyocardial sclerosis involving both ventricles (Fig. 2 and 6). The histological appearance of the thickened endocardium is shown in Fig. 4. Fibrosis of the myocardium was minimal in the outer two-thirds of the ventricular walls, but in the inner third, sometimes in continuity with the endocardium, there were several focal areas of fibrosis.

FIG. 6.—Diffuse endomyocardial sclerosis of the left ventricle. Note the involvement of the posterior wall behind the mitral cusp, and shortening of the chordæ tendinæ of the posterior leaf. Case 4.

Comment. There is evidence for the thesis that malnutrition and vitamin B deficiency may, on occasion, play a part in the production of endomyocardial sclerosis. The clinical syndrome of heart failure as seen in beri-beri was first discussed by Aalsmeer and Wenckebach (1929), and subsequently by others (Keefer, 1930; Weiss and Wilkins, 1937). Gillanders (1951), however, stressed the variability of the cardiac beri-beri syndrome and cast doubt upon its specificity. The morphological findings in the heart are hypertrophy and dilatation of the ventricles associated with hydropic degeneration and interstitial oedema of the myocardium. These changes in chronic untreated cases may be progressive and irreversible, resulting in fibrosis of the myocardium (Benchimol and Schlesinger, 1951) and could well account for the failure of the clinical response to vitamin B therapy. Similar histological changes have been described in the nutritional heart disease of Bantu natives. Though these changes are not specific, they tend to be greatest in the sub-endocardial region. Further, in the ventricles of several of these cases, endomural thrombi were present which showed varying degrees of organization (Higginson *et al.*, 1952). According to Davies and Ball (1955) it is possible that these cases of nutritional heart disease represent "severe early manifestations of a process that develops more slowly and silently to severe fibrosis in Uganda-Africans." Finally, malnutrition or vitamin B deficiency were considered the possible aetiological factors in three cases of endomyocardial sclerosis described by Smith and Furth (1943). In Cases 3 and 4 of the present series, the history of the onset of symptoms during a period of malnutrition and their persistence for many years supports this hypothesis.

The adhesive pericarditis present in Case 4 was inadequate to explain the clinical features. This confirmed the opinion of the surgeon that a pericardiectomy would afford little relief for the patient. A clinical

picture closely resembling constrictive pericarditis has been reported in several cases of endomyocardial sclerosis in which the pericardium was normal (see Case 1) and the cardiac dysfunction has been attributed to the fibrosis of the endocardium (Loeffler, 1936; and others), for as pointed out by Gunnar *et al.* (1955), any lesion in any layer of the heart causing interference with diastolic expansion may simulate in its effects the clinical syndrome of constrictive pericarditis.

PATHOLOGY AND CLINICAL FEATURES OF ENDOMYOCARDIAL SCLEROSIS

Satisfactory definition of endomyocardial sclerosis as a clinicopathological entity is difficult for little is known of its proximate causation. Early examples may pass unrecognized since varying degrees of thickening of the mural endocardium, both focal and diffuse, are not uncommonly found at autopsy as an incidental finding in a variety of conditions, or in association with chronic myocardial infarction, intraventricular thrombus, syphilis, chronic dilatation of the heart, and scleroderma (Norris, 1937; Weiss *et al.*, 1943; Flynn and Mann, 1946; Becker *et al.*, 1953). At present therefore only the terminal and severe phases of endomyocardial sclerosis can be identified with any degree of certainty.

Pathology. In most cases the heart is enlarged with dilatation and hypertrophy of one or more chambers. The heart weights recorded have ranged from 300g. to 759g. There are no pronounced changes in the atria although occasionally endocardial thickening is described and thrombus may be present. The striking feature is the pearly white rugose thickening (1–4 mm.) of the ventricular endocardium. The pattern of distribution appears fairly constant: the thickening involves the trabeculated surface of the ventricles, rarely if ever affecting the smooth surface of the interventricular septum below the aortic and pulmonary valves, and the most constant site is the apex of one or both ventricles, more commonly the left, with a predilection for extension up the posterior wall. Significant lesions of the valves are not a feature though the mitral valve may show moderate degrees of scarring and/or mild stenosis. The chordæ tendineæ may be thickened, fused and shortened, and occasionally bound down to the posterior wall of the ventricle, and this occurs more commonly in relation to the chordæ of the posterior mitral cusp (Fienberg and Holzman, 1951; Case 4). Vegetations on the valves have been described but are rare (Mumme, 1940). Overlying the thickened endocardium varying amounts of thrombus are common, sometimes almost entirely filling the ventricles (Roulet, 1944; Egger, 1944). A focal and linear fibrosis of the myocardium is observed macroscopically but is usually minimal in degree. The pericardium is normal and commonly a moderate effusion is present. The coronary arteries are fully patent though a little atheroma may sometimes occur.

On microscopic examination the thickened endocardium is composed of fibrous tissue with areas of hyaline degeneration. Though elastic tissue fibrils are present, they are few in number and have no regular arrangement; focal areas of reduplication are sometimes seen. In the deeper aspect, there is a loose connective tissue often containing numerous thin-walled blood vessels and a scanty focal lymphocytic infiltration. In the myocardium there is focal fibrosis, mainly of the inner third, sometimes with a slight cellular infiltrate. In addition large tongue-shaped septa of fibrous connective tissue containing small sinusoidal vessels extend from the endocardium into the myocardium. Commonly, there are variable degrees of thickening of the walls of the small arteries and arterioles in the subendocardial zone. The histological features are those of a lesion in the chronic healed phase.

Clinical Features. Most cases of endomyocardial sclerosis occur in the third and fourth decades. There is no significant preponderance of either sex. There are no relevant findings in the family history, and no example of endomyocardial sclerosis in siblings has been recorded, although Smith and Furth (1943) mention that a sister of one of their patients died suddenly from "myocarditis" at the age of 22 years. Cases of endomyocardial sclerosis have been reported from several countries, the majority from Switzerland, but this may possibly be explained by the increased awareness of the condition in certain localities.

Although in some cases there are references to gastro-intestinal disorders, dietary insufficiency, syphilis, diphtheria, and respiratory tract infections (Case 2 and 3; Hübschmann, 1917; Levy and

Rousselot, 1933; Fossel, 1942; and others) the previous medical history is of little diagnostic value. The duration of the disease is very variable ranging from sudden and unexpected death to a history extending over ten years or more (Landau *et al.*, 1927; Comeau, 1937; Smith and Furth, 1943). Clinical assessment of the duration of the cardiac lesions must be largely guess-work, for the symptoms of the initial phases are not known—a difficulty illustrated by our Cases 1 and 3. One patient had been passed as fit for military service with a normal X-ray of the chest five years before death (Hoffman *et al.*, 1955).

Although diffuse endomyocardial sclerosis may be an unexpected finding at autopsy (Case 1), the common clinical picture is one of cardiac failure which may be predominantly right or left-sided in type. The failure may last only a few weeks, or for some years with a remittent though steadily progressive course. Not infrequently the clinical features are suggestive of constrictive pericarditis (Loeffler, 1936; Egger, 1944; and others), and indeed so close is the similarity that operation for the relief of constrictive pericarditis has on occasion been performed.

Certain symptoms and signs are considered from the diagnostic standpoint. As would be expected from the morphological finding of normal coronary arteries, the striking feature of the group as a whole is the absence of anginal pain. Occasional cases are reported with pain in the chest of possible cardiac origin (Case 1; Baumler, 1911; Loeffler, 1936) and in one case a clinical diagnosis of coronary embolism was made (Berblinger, 1948). The clinical course is afebrile; where there is a raised temperature, the cause is fairly obvious, e.g. respiratory infection, pulmonary infarction, etc. and unexplained pyrexia is rare (Buchler, 1941–42).

Although on clinical and radiographic examination the *heart* usually shows some enlargement, it may be of normal size (Case 3; Loeffler, 1936; McKusick and Cochran, 1952). There are no constant auscultatory findings in endomyocardial sclerosis, but in the severe cases when the mitral valve is sclerotic, there is commonly a loud apical systolic murmur (Case 4; Loeffler, 1936; Mumme, 1940; Fienberg and Holzman, 1951). Hypertension is rare at any time during the course of the illness, but a mild degree has been recorded (Case 1; Mumme, 1940; Berblinger, 1948).

The changes recorded in the *electrocardiogram* are non-specific and include sinus tachycardia, left axis deviation, flat or inverted T waves, and some widening of the QRS complex. In Case 4 there was RS–T depression in leads V1 and V2, V5 and V6 and RS–T elevation in aVR which may be interpreted as indicating predominant subendocardial damage, but other factors, e.g. digitalis may have been responsible. The changes of bundle-branch block have been recorded (Comeau, 1937; Toreson, 1944).

A mild or moderate degree of hypochromic *anæmia* is usually present. However, the red blood cell picture may be normal (Case 1; Deus, 1916) or there may be a very severe *anæmia* (Case 3; Buchler, 1941–42). The blood sedimentation rate may be within normal limits or may be increased; a moderate leucocytosis is not infrequent and with a raised sedimentation rate has been considered to support an infective origin (Jucker, 1946). Eosinophilia is a valuable diagnostic feature but it is not always present. It varies in degree not only from case to case but even in the same case (4 to 63 per cent Mumme, 1940; 50 to 58 per cent Roulet, 1944; 15 per cent Egger, 1944; 5 per cent Berblinger, 1948; and absent McNichol *et al.*, 1953). Apart from lung infarctions, *embolic phenomena* in other viscera are not so common as one might expect in view of the frequency of endomural thrombus. Infarctions in the kidney have been described by Smith and Furth (1943), and in the spleen by Hoffman *et al.* (1955).

ENDOMYOCARDIAL FIBROSIS IN AFRICA

This is not uncommon in the natives of certain parts of Africa. Since it was reported by Bedford and Konstam (1946) there have been several accounts of large numbers of cases with full clinical and pathological details particularly in Uganda (Davies, 1948; Ball *et al.*, 1954; Williams *et al.*, 1954; Davies and Ball, 1955) and in the Sudan (O'Brien, 1954) and in Europeans who have lived in Africa (Gray, 1951).

The clinical picture is very similar to that of endomyocardial sclerosis: a young or middle-aged adult of either sex suffers from progressive congestive heart failure of variable duration, without evidence of any of the more common causes of failure. The endocardial sclerosis may involve the mitral or tricuspid valves and cause incompetence, and when the mitral valve is affected an important diagnostic feature is a loud, high-pitched apical systolic murmur. Occasionally a syndrome simulating constrictive pericarditis occurs. The electrocardiogram is of little assistance and shows no constant pattern. Among Africans the importance that can be attached to eosinophilia is reduced in view of the frequency of parasitic infestation.

The similarity of the macroscopic appearances of the two conditions is very striking and such differences as exist are probably only those of degree. In the African series the incidence of mural thrombus and cardiac hypertrophy is lower, the sclerotic process more frequently involves the right ventricle, the mitral and the tricuspid valves, and calcification of the endocardium is more common. The histological picture is "extremely uniform despite variations in the gross appearances" (Davies and Ball, 1955). It is one of fibro-hyaline thickening of the endocardium with small amounts of elastic tissue, a deep zone with numerous small, thin-walled vessels and a septal and focal myocardial fibrosis mainly of the inner third. We received from Professor Williams of Makerere College, Uganda, for comparison with our own material, representative blocks of tissue from three typical cases of "endomyocardial fibrosis", and the histological features were very similar to those of our Case 4.

Although it is difficult to establish the identity of African and non-African cases it does appear from the present study that the clinical and morphological findings are essentially the same in the two groups.

CONGENITAL FIBROELASTOSIS: ITS RELATIONSHIP TO ENDOMYOCARDIAL SCLEROSIS

Congenital fibro-elastosis has become a well-recognized cause of death in infancy. The gross pathological findings bear some resemblance to adult endomyocardial sclerosis and for comparison we have studied ten cases.

Serious congenital anomalies of the heart were found in three cases, all infants below the age of three months, viz. a single atrium and single ventricle with a common truncus arteriosus, a rudimentary left ventricle with severe aortic stenosis, and a patent ductus arteriosus with undifferentiated aortic valve cusps. In all the hearts there was a diffuse fairly uniform, greyish-white thickening of the mural endocardium of the left ventricle (Fig. 7). A similar thickening was observed in the left atrium in one heart, and in the right ventricle in another. Ante-mortem thrombus was present in the left ventricles in two cases. There were no abnormalities of the pericardium or coronary arteries.

Major points for comparison and distinction of congenital fibroelastosis and adult endomyocardial sclerosis will be considered.

Age and Sex. A cardinal difference is of course the age incidence. In a review of 98 cases of congenital fibroelastosis, Lambert *et al.* (1953) found that 96 per cent died in the first year of life. In the present series, only one infant survived beyond that period. Of particular interest, however, are the cases recorded in children at 5, 6, and 11 years of age (Kugel and Stoloff, 1933; Dennis *et al.*, 1953), and in young adults (Toreson, 1944; Thomas *et al.*, 1954). These cases support the possibility that rarely, adult endomyocardial sclerosis may result from the persistence of congenital fibroelastosis into adult life. Occasionally congenital fibroelastosis has been reported in siblings (Ullrich, 1938; Weinberg and Himmelfarb, 1943; Greaves *et al.*, 1954); there has been no such report in adult endomyocardial sclerosis.

Heart. There are often discrepancies in the recorded incidence of heart murmurs and of heart size in congenital fibroelastosis (Adams and Katz, 1952; Lambert *et al.*, 1953). Thus, Dennis *et al.* (1953) say that enlargement of the heart is rare, while Mortensen *et al.* (1954) say that it is present in 94 per cent of cases. In adult endomyocardial sclerosis heart murmurs may or may not be heard and the size of the heart is variable and not always enlarged.

FIG. 7.—Congenital fibro-elastosis in a female infant, aged 13 weeks.

The electrocardiograms do not reveal a constant pattern of diagnostic value in either group although they may be of some value in the differential diagnosis of congenital fibroelastosis (Vlad *et al.*, 1955). Common abnormalities are left axis deviation, alteration of the P wave, and abnormalities of the T wave, usually depression. Bundle-branch block is occasionally observed; it is more common in congenital fibroelastosis. Rarely, complete heart block has been recorded in the infant, but not in adult endomyocardial sclerosis (Stadler *et al.*, 1950).

Course of the Disease and the Diagnosis. In both groups the terminal illness may be very short or may be preceded by recurrent episodes of cardiac failure. At present the diagnosis in either group is largely one of exclusion, although more recently in congenital fibroelastosis with the aid of angiographic studies, the clinical diagnosis has been made with sufficient confidence to carry out surgical treatment (Paul and Robbins, 1955). We have found no reference to eosinophilia in congenital fibroelastosis, a finding in contrast to adult endomyocardial sclerosis.

Morphology. The essential features common to both conditions are the mural thickening of the endocardium of one or both ventricles, usually the left; normal coronary arteries (except those cases of congenital fibroelastosis associated with an aberrant left coronary artery); variable though minor degrees of fibrosis of the myocardium, and no significant lesions of the pericardium. However, there are certain important differences. In the congenital group the thickening is smooth, more uniform, and more diffuse, usually involving all the mural endocardium of the left ventricle. The "outflow tract" is the commonest site and the thickening is frequently most pronounced just below the aortic valve. In contrast, in the adult case, the affected site is almost always part of the

trabeculated area of the left or right ventricle, particularly the apex. The smooth sub-aortic region of the interventricular septum is rarely if ever involved, despite the fact that focal areas of endocardial thickening occur quite frequently at this site. In the congenital group, the incidence and degree of thrombus formation is much less than in the adult group. In the infant, congenital anomalies of the heart are frequently present, e.g. stenosis or atresia of the aortic or mitral valves, coarctation of the aorta, left ventricular hypoplasia, etc.; in the adult, they are very rare, although aortic hypoplasia has been described (Bedford and Konstam, 1946). The incidence and type of valve lesion differ appreciably in the two groups. In congenital fibroelastosis, the most common lesions are those of the aortic valve. In adult endomyocardial sclerosis the most frequent finding is one of direct involvement of the posterior leaf of the mitral valve or its chordæ tendineæ by spread of the sclerotic process from the endocardium; significant lesions of the aortic valve rarely if ever occur. However, as Horley (1955) has pointed out, and as confirmed in the present series, there is a broad subdivision of congenital fibroelastosis into two groups, viz. foetal and infantile. In contrast to the foetal variety, the infantile group includes those cases that survive beyond three months and do not have associated congenital anomalies. A certain proportion of such cases persist into childhood, and it is possible therefore that on occasion they may reach adult life (Thomas *et al.*, 1954; Panke and Rottino, 1955). Support for this hypothesis is found in the histological features of certain cases of adult endomyocardial sclerosis in which the thickened endocardium shows a uniform admixture of elastic and fibrous tissue elements as found in congenital fibroelastosis. However, this histological pattern is uncommon in adult endomyocardial sclerosis, in most cases of which fibro-hyaline connective tissue is the major component of the endocardial thickening and elastic elements are only slight in amount and not uniform in distribution. Further, in Case 2 of the present series, while the histological features conform to those of congenital fibroelastosis, the macroscopic distribution of the lesion is that of adult endomyocardial sclerosis. Finally, in the usual adult case the myocardial fibrosis is more severe and is not confined as in the infant to the immediate subendocardial region. With the possible exception of rare examples of congenital fibroelastosis persisting into adult life, it would appear therefore, that adult endomyocardial sclerosis and congenital fibroelastosis should be considered as separate entities.

ÆTIOLOGY AND PATHOGENESIS OF ADULT ENDOMYOCARDIAL SCLEROSIS

Both the endocardium and the myocardium have been suggested as the initial site of the lesion in endomyocardial sclerosis. The consensus of opinion is that the myocardium is the primary site and that the diffuse endocardial thickening is secondary, resulting probably from organization of an endomural thrombus. The morphological evidence favours the latter. Support for the theory that "organized thrombus" is largely responsible for the endocardial thickening is to be found first, in the localization of the lesion to the trabeculated areas of the ventricles where mechanical factors (eddies, etc.) would predispose to the formation of thrombus, secondly, in the histological features such as areas of hyalinization and the deep vascular zone of the thickened endocardium, and thirdly, in the frequent occurrence of endomural thrombus.

In the past, individual authors on the basis of a single or very small series of cases, have sought to establish a particular concept with the result that several theories have been formulated as to the ætiological factor concerned. In the present four cases, the clinical evidence could be offered in support of different ætiological factors, e.g. allergy (Case 1), or malnutrition and vitamin B deficiency (Cases 3 and 4).

An allergic basis for the lesion is suggested by the frequent occurrence of eosinophilia (Loeffler, 1946-47) and by those cases with clinical evidence of an allergic or hyperergic state, e.g. severe urticaria (Buchler, 1941-42), rheumatoid arthritis (Egger, 1944), periarteritis nodosa (Roulet, 1944; Watt and Lynch, 1956) and asthma (Lennox, 1948; Case 1). However, eosinophilia is not a constant finding and the incidence of allergic or hyperergic states is insufficient to permit their consideration as the sole pathogenic factor.

The role of malnutrition and vitamin B deficiency in the ætiology of endomyocardial sclerosis

has been discussed (Case 4). Although malnutrition is common in Africa and may be important in African cases, the absence of dietary insufficiency in many of the patients in other countries precludes the hypothesis from explaining all examples of endomyocardial sclerosis.

In view of the frequency of gross endocardial thickening and fibrosis of the myocardium in chronic infarction, the possible role of coronary ischaemia must be considered in the aetiology of endomyocardial sclerosis. On clinical and morphological grounds most chronic myocardial infarcts are readily differentiated but the rare case of subendocardial infarction closely resembles endomyocardial sclerosis (Hughes and Smith, 1953). The state of the coronary vessels will usually identify such a case, but the occurrence of subendocardial necrosis where the coronary vessels are either normal or show minimal disease is of interest. The necrosis has been attributed to relative ischaemia of the subendocardial zone caused by a variety of factors, e.g. systemic shock, chronic anaemia, cardiac hypertrophy, etc. (Master *et al.*, 1949; Horn *et al.*, 1950; and Levine and Ford, 1951). Although the electrocardiographic findings are different in the two conditions certain examples of endomyocardial sclerosis may represent a healed phase of subendocardial necrosis, particularly if this has been associated with endomural thrombus.

Clinical and morphological features closely similar to those of endomyocardial sclerosis are found in idiopathic forms of myocarditis associated with endomural thrombus, and such cases have been reported from other countries as well as from Africa (Roque and Levy, 1914; von Bonsdorff, 1939; Dammin *et al.*, 1951). Finally there are several possible or indeed probable examples of endomyocardial sclerosis reported as some form of myocarditis, e.g. primary subacute myocarditis (Josserand and Gallavardin, 1901; Gallavardin and Gravier, 1929) myocarditis perniosa (Boikan, 1931), diffuse isolated myocarditis (Toreson, 1944) and chronic fibroplastic myocarditis (Ware and Chapman, 1947). In the toxic form of myocarditis that follows the administration of organic arsenicals, Brown and McNamara (1940), and Taussig and Oppenheimer (1936), have described damage to the endocardium, and indeed, a typical case of endomyocardial sclerosis was reported by Edge (1946).

No case of endomyocardial sclerosis directly attributable to an inflammatory form of myocarditis has been described. The focal fibrosis of the myocardium and the not infrequent association of a cellular infiltrate which may include lymphocytes, plasma cells, eosinophil leucocytes, and even giant cells (Comeau, 1937) do not necessarily indicate that the myocardial damage has an inflammatory basis. However, in his review of myocarditis Saphir (1941-42) notes that sometimes the endocardium is also involved, e.g. in trichinosis, Rocky Mountain spotted fever, and Libman-Sach's disease. Further, in diphtheria and scarlet fever, associated with an inflammatory infiltration of the endocardium there is a myocarditis in which the lesions are most marked in the subendocardial zone in the walls of the Thebesian vessels, a distribution recalling that of fibrosis in endomyocardial sclerosis. Endocardial thickening may also occur in virus infections, e.g. in rabbits (Pearce, 1954). Again, in discussing syphilis of the myocardium, Norris (1937) states that the endocardium may be white and thickened. Although the association may be fortuitous or due to yaws, a positive Wassermann reaction is not uncommon in African endomyocardial fibrosis, and a myocarditis of obscure origin, possibly syphilitic, also occurs in Uganda (Davies, 1948*a* and *b*).

It appears therefore that endomyocardial sclerosis is a terminal phase of a pathological process that has a multifactorial causation. As in chronic nephritis and cirrhosis of the liver, the identity of morphology of this terminal phase does not necessarily imply a unity of pathogenesis in all cases.

SUMMARY

The clinical and pathological features of four cases of diffuse endomyocardial sclerosis are described. In each there was fibrosis of the myocardium particularly in the inner third, much thickening of the endocardium, and little or no evidence of coronary arterial disease.

Clinically, endomyocardial sclerosis usually presents as a case of cardiac failure of obscure origin. Occasionally it may simulate the syndrome of constrictive pericarditis. Of assistance

in the diagnosis is the presence of eosinophilia, or incompetence of the mitral or tricuspid valves. Electrocardiographic changes are non-specific.

The morphological findings were compared with those in three cases of African endomyocardial fibrosis and ten cases of congenital fibroelastosis in infancy. The pathology of our four cases and that of the African material is essentially similar. Although it is possible that congenital fibroelastosis may persist into adult life and simulate endomyocardial sclerosis, it differs in its distribution and histology and must be considered a separate entity.

The hypothesis is advanced that diffuse endomyocardial sclerosis represents the terminal phase of various disease states, each of which affects a particular site, viz. the innermost layer of the myocardium. As exemplified in this small group of cases, two important factors in the pathogenesis of the condition are malnutrition and allergy.

For permission to publish these cases our thanks are due to Lord Cohen of Birkenhead and to Drs. Coope, Whitwell, and Benstead. For his invaluable assistance in the preparation of this script we are indebted to Dr. Wyn Jones.

REFERENCES

- Aalsmeer, W. C., and Wenchebach, K. F. (1929). *Wein. Arch. inn. Med.*, **16**, 193.
 Adams, F. H., and Katz, B. L. (1952). *J. Pediat.*, **41**, 141.
 Ball, J. D., Williams, A. W., and Davies, J. N. P. (1954). *Lancet*, **1**, 1049.
 Baumler, C. (1911). *Dtsch. Arch. klin. Med.*, **103**, 1.
 Becker, B. J. P., Chatgidakis, C. B., and van Lingen, B. (1953). *Circulation*, **7**, 345.
 Bedford, D. E., and Konstam, C. L. S. (1946). *Brit. Heart J.*, **8**, 236.
 Benchimol, A. B., and Schlesinger, P. (1951). *Amer. Heart J.*, **42**, 801.
 Berblinger, W. (1948). *Schweiz. med. Woch.*, **78**, 829.
 Boikan, W. S. (1931). *Virchows Arch.*, **181**, 46.
 von Bonsdorff, B. (1939). *Acta med scand.*, **100**, 320.
 Brown, C. E., and McNamara, D. H. (1940). *Arch. Dermat. Syph.*, **42**, 312.
 Büchler, H. (1941-42). *Z. klin. Med.*, **140**, 56.
 Comeau, W. J. (1937). *Amer. J. Path.*, **13**, 277.
 Dammin, G. J., Glaser, R. J., and Roberts, J. C. (1951). *Amer. J. Path.*, **27**, 695.
 Davies, J. N. P. (1948a). *E. Afr. med. J.*, **25**, 10.
 — (1948b). M.D. Thesis, University of Bristol.
 —, and Ball, J. D. (1955). *Brit. Heart J.*, **17**, 337.
 Dennis, J. L., Hansen, A. E., and Corpening, T. N. (1953). *Pediatrics*, **12**, 130.
 Deus, P. (1916). *Cor. Bl. Schweiz. Aerzte.*, **46**, 1473.
 Edge, J. R. (1946). *Lancet*, **2**, 675.
 Egger, P. (1944). *Schweiz. Path. Bakt.*, **7**, 237.
 Farber, S., and Hubbard, J. (1933). *Amer. J. med. Sci.*, **186**, 705.
 Fienberg, R., and Holzman, D. (1951). *Bull. internat. Assoc. med. Mus.*, **32**, 34.
 Flynn, J. E., and Mann, F. D. (1946). *Amer. Heart J.*, **31**, 757.
 Fossel, M. (1924). *Beitr. path. Anat.*, **107**, 241.
 Fowler, M. (1947). *Med. J. Aust.*, **1**, 672.
 Gallavardin, L., and Gravier, L. (1929). *Arch. Mal. Cœur*, **22**, 379.
 Gillanders, A. D. (1951). *Brit. Heart J.*, **13**, 177.
 Gowing, N. F. C. (1953). *J. Path. Bact.*, **65**, 13.
 Gray, I. R. (1951). *Brit. Heart J.*, **13**, 387.
 Greaves, J. L., Wilkin, P. S. W., and Pearson, S. (1954). *Arch. Dis. Childh.*, **29**, 447.
 Gunnar, R. M., Dillon, R. F., Wallyn, R. J., Elisberg, E. I. (1955). *Circulation*, **12**, 827.
 Higginson, J., Gillanders, A. D., and Murray, J. F. (1952). *Brit. Heart J.*, **14**, 213.
 Hoffman, F. G., Rosenbaum, D., and Genovese, P. D. (1955). *Ann. intern. Med.*, **42**, 668.
 Horley, J. F. (1955). *Brit. med. J.*, **1**, 765.
 Horn, H., Field, L. E., Dack, S., and Master, A. M. (1950). *Amer. Heart J.*, **40**, 63.
 Hübschmann, P. (1917). *München. med. Woch.*, **64**, 73.
 Hughes, A., and Smith, G. H. (1953). *Brit. Heart J.*, **15**, 450.
 Josserand, E., and Gallavardin, L. (1901). *Arch. Gén. Méd.*, **78**, 513.
 Jucker, P. (1946). *Schweiz. med. Woch.*, **48**, 1231.
 Keefer, C. S. (1930). *Arch. intern. Med.*, **45**, 1.
 Kugel, M. A., and Stoloff, E. G. (1933). *Amer. J. Dis. Child.*, **45**, 828.
 Lambert, E. C., Shumway, C. N., and Terplan, K. (1953). *Pediatrics*, **11**, 255.
 Landau, A., Feigin, M., Jochweds, B., and Marjanko, T. (1927). *Bull. Mém. Soc. méd. Hôp., Paris*, **51**, 481.
 Lenègre, J., and Gerbaux, A. (1952). *Arch. Mal. Cœur*, **45**, 289.
 Lennox, B. (1948). *J. Path. Bact.*, **60**, 621.
 Levine, H. D., and Ford, R. V. (1951). *Ann. intern. Med.*, **34**, 998.
 Levy, R. L., and Rousselot, L. M. (1933). *Amer. Heart J.*, **9**, 178.

- Levy, R. L., and von Glahn, W. C. (1937). *Trans. Ass. Amer. Phys.*, **52**, 259.
- Loeffler, W. (1936). *Schweiz. med. Woch.*, **66**, 817.
- (1946-47). *Bull. Schweiz. Akad. Med.*, **2**, 287.
- McKusick, V. A., and Cochran, T. H. (1952). *Bull. Johns Hopkins Hosp.*, **90**, 90.
- McNichol, C., MacMahon, E., Benenson, A. S., and Winship, T. (1953). *Circulation*, **7**, 497.
- Master, A. M., Dack, S., Field, L. E., and Horn, H. (1949). *J. Amer. med. Ass.*, **141**, 887.
- Mortensen, O., Kissmeyer-Nielsen, F., and Køeller-Jørgenson, P. (1954). *Act. Pæd.*, **43**, 87.
- Mumme, C. (1940). *Z. klin. Med.*, **138**, 22.
- Norris, J. C. (1937). *J. Amer. med. Ass.*, **108**, 169.
- Norris, R. F., and Pote, H. N. (1946). *Amer. Heart J.*, **32**, 599.
- O'Brien, W. (1954). *Brit. med. J.*, **2**, 899.
- Panke, W., and Rottino, W. (1955). *Amer. Heart J.*, **49**, 89.
- Paul, R. N., and Robbins, S. G. (1955). *Pediatrics*, **16**, 147.
- Pearce, J. M. (1954). Cited by Davies *et al.* (1955).
- Prior, J. T., and Wyatt, T. C. (1950). *Amer. J. Path.*, **26**, 969.
- Reisinger, J. A., and Blumenthal, B. (1941). *Amer. Heart J.*, **22**, 811.
- Roque, G., and Levy, L. (1914). *Arch. Mal. Cœur*, **7**, 10.
- Roulet, F. C. (1944). *Schweiz. med. Woch.*, **74**, 155.
- Saphir, O. (1941-42). *Arch. Path.*, **32**, 1000; **33**, 88.
- Smith, J. J., and Furth, J. (1943). *Arch. intern. Med.*, **71**, 602.
- Stadler, H. E., Reid, C. A., and Friedman, H. P. (1950). *J. Pediat.*, **36**, 370.
- Taussig, H. S., and Oppenheimer, E. H. (1936). *Bull. Johns Hopkins Hosp.*, **59**, 155.
- Thomas, W. A., Randall, R. V., Bland, E. F., and Castleman, E. (1954). *New Engl. J. Med.*, **251**, 327.
- Toreson, W. E. (1944). *Arch. intern. Med.*, **73**, 375.
- Ullrich, O. (1938). *Z. menschl. Vererb. Konstit. Lehre*, **21**, 585.
- Vlad, P., Rowe, R. D., and Keith, J. D. (1955). *Brit. Heart J.*, **17**, 189.
- Ware, E. R., and Chapman, B. M. (1947). *Amer. Heart J.*, **33**, 530.
- Watt, J., and Lynch, J. B. (1956). *Lancet*, **1**, 658.
- Weinberg, T., and Himelfarb, A. J. (1943). *Bull. Johns Hopkins Hosp.*, **72**, 299.
- Weiss, W., and Wilkins, R. W. (1937). *Ann. intern. Med.*, **11**, 104.
- Weiss, S., Stead, E. A., Warren, J. V., and Bayley, O. T. (1943). *Arch. intern. Med.*, **71**, 749.
- Williams, A. W., Ball, J. D., and Davies, J. N. P. (1954). *Trans. R. Soc. Trop. Med. Hyg.*, **48**, 290.