

INTRACARDIAC THROMBOSIS AND EMBOLISM IN ENDOMYOCARDIAL FIBROSIS IN UGANDA

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Endomyocardial fibrosis is a common form of heart disease in Uganda. Although it has been well described and much discussed for many years, the aetiology is unknown and the relation to other cardiopathies seen in Africa and elsewhere remains undetermined. In attempting to delineate the nature of a possible relation between the several cardiopathies seen in Africa the incidence of intracardiac thrombi and of embolic phenomena have been used as criteria for differentiation. This question has recently been the subject of controversy (Thomson, 1961; Davies, 1962), and this communication details the incidence and distribution of cardiac thrombi and embolic phenomena in subjects with endomyocardial fibrosis coming to autopsy at Mulago Hospital, Kampala, and discusses the role of intracardiac thrombus formation in the pathogenesis of endomyocardial fibrosis.

SUBJECTS AND METHOD

The autopsy records for Mulago Hospital, Kampala, for the years 1950–61 inclusive were studied and all cases in which a diagnosis of endomyocardial fibrosis or necrosis had been established were included in this study. Several cases in which the endomyocardial fibrosis was of a moderate degree occur in this series and no attempt has been made to include only advanced cases. Where doubts arose as to the correctness of the original diagnosis the preserved hearts were examined. Thrombosis which was only evident on histological examination is not included in the incidence figures for intracardiac thrombosis.

Two subjects diagnosed at autopsy as endomyocardial necrosis have been included in this study as they possibly represent the more acute lesions of endomyocardial fibrosis.

There are many cases of obscure cardiopathy or myocarditis in the autopsy records of Mulago Hospital (Davies and Coles, 1959), but in these there is no evidence of endomyocardial fibrosis or necrosis. These cases may or may not be related to endomyocardial fibrosis, but since their relation to it is at present speculative they are not included in this series.

The material comprises 124 African subjects and information on cardiac thrombi was available in 123, on embolic phenomena in 124, and an age assessment had been made in 123 cases. The age distribution of the cases is shown in Table I. The incidence of endomyocardial fibrosis in the various tribal groups and the significance of the geographic distribution is discussed in a separate publication.

RESULTS

Intracardiac Thrombi. Antemortem thrombus of varying age and size was found in 57 (46%) of the 123 hearts examined. The frequency with which the various chambers of the heart were affected by thrombi was as follows: right atrium, 28; left atrium, 5; right ventricle, 11; and left ventricle, 32. Table II details the pattern of distribution of thrombi within the heart. In the Uganda series thrombi in the ventricles were always associated with the presence of underlying endomyocardial disease. Thrombi in the atria were usually situated in the atrial appendage and

TABLE I

AGE DISTRIBUTION BY SEX IN 124 SUBJECTS WITH ENDOMYOCARDIAL FIBROSIS SEEN AT AUTOPSY

Age (years)	1-4	5-14	15-24	25-34	35-44	45-54	55-64	Unknown	Total
Male	3	4*	17	31*	24	9	3	1	92
Female	0	6	6	11	7	2	0	0	32
Total	3	10	23	42	31	11	3	1	124

* Includes one subject with endomyocardial necrosis.

TABLE II

DISTRIBUTION OF THROMBI IN ENDOMYOCARDIAL FIBROSIS AND IN CRYPTOGENIC HEART DISEASE

Site of thrombi	Uganda	S. Africa*
Right atrium only	17	19
Left ventricle only	22	9
Both ventricles and right atrium	4	6
Both atria	1	3
Both atria and left ventricle	2	3
Left ventricle and right atrium	1	3
Right ventricle only	4	3
Both ventricles	1	2
All chambers	0	1
Right atrium and ventricle	2	0
Right atrium and left ventricle	1	0
Left atrium only	1	0
Left atrium and ventricle	1	0
No thrombi	57 (46%) 66 (54%)	48 (60%) 32 (40%)
Total	123	80

* From Higginson *et al.* (1960).

were sometimes associated with dilatation and hypertrophy of the atria and sometimes with underlying endomyocardial disease. As this is a retrospective study of autopsy records made by many pathologists we could not determine accurately the relative importance of these two factors in intra-atrial thrombosis.

Bacterial Endocarditis. The cardiac lesions were complicated by bacterial endocarditis in 7 of the 124 subjects (5.6%). In one case, early in the series, although no description of bacterial endocarditis is recorded in the examination of the heart, a presumptive diagnosis has been made on the presence of septic infarcts in the spleen and kidney. Cultures were not taken in these cases and the diagnosis is based on the appearance at autopsy and on histological evidence.

Bacterial endocarditis was present on the mitral valve alone in three cases, on the left ventricular wall in one, on the left atrium, mitral valve, and left ventricle in one, and affected the left ventricular wall and aortic valve in a further subject. Embolic phenomena were noted in five of the seven subjects in this group: the spleen was involved in all five, the kidneys in three, and the subject with aortic valve involvement had a cerebral infarction in addition to infarction of the spleen.

Embolic Phenomena in Subjects without Bacterial Endocarditis. Embolic phenomena in the absence of bacterial endocarditis were observed in 18 (15%) of 117 subjects with endomyocardial fibrosis. There were 4 cases of peripheral embolism in which the aorta or one of its main peripheral arteries was occluded. Splenic infarcts were present in 10 cases, being the sole embolic

feature in five of these, renal infarction occurred in three subjects, and cerebral embolism with infarction in two. Pulmonary emboli were present in 10 cases, being the sole embolic feature in five of these subjects. In one of these latter cases and in a further case with pulmonary embolism and infarcts in the spleen and kidney, there were possible venous sources of the pulmonary emboli, such as deep leg vein thrombosis in one and an ovarian carcinoma with pelvic spread in the other. In two cases with lone pulmonary embolism mitral stenosis was present. The mitral stenosis was considered to be caused by the endomyocardial fibrosis as the valvular and ventricular lesions were continuous and no histological evidence of rheumatic infection was present. Intracardiac thrombi were found in 9 of the 18 subjects with embolic phenomena and in 15 subjects there was endomyocardial disease on the side of the heart appropriate to the site of the embolus. In three cases with pulmonary embolism there were no obvious lesions of endomyocardial fibrosis in the right ventricle or atrium but in all three the atria were considerably dilated.

The four subjects with embolism affecting the aorta or one of its main peripheral arteries include three boys aged 10, 14, and 16 years and a woman of 25 years. One subject died within 24 hours of his embolic episode, two survived for periods of 21 and 14 days, and one boy died in congestive cardiac failure two years after an embolic episode which resulted in gangrene of one leg. Apart from these cases, embolism which was clinically apparent occurred in only three of the remaining subjects referred to in this section and was a terminal event.

DISCUSSION

In the original description of endomyocardial fibrosis in Uganda, Davies (1948) noted that "there may be endocardial necrosis with a layer of thrombus over the necrosed area, or more usually, there are whitish-yellow plaques of firm fibrous tissue extending over the endocardium and infiltrating widely into the subendocardium and myocardium." Splenic infarction occurred in 3 of his original 21 cases. In later reports from Kampala (Ball, Williams, and Davies, 1954; Davies and Ball, 1955) the distribution of intracardiac thrombi was noted, with the left ventricle and right atrium being predominantly affected and embolic lesions were observed in cases complicated by bacterial endocarditis. The relative infrequency of embolic phenomena despite the frequent presence of mural thrombosis has repeatedly been emphasized (Davies, 1956; Report of a Joint Seminar, 1957), and in a study of cardiovascular disorders seen at Mulago Hospital, Kampala, from 1955 to 1957 (Shaper and Williams, 1960), only one subject with a clinical episode of embolism was observed in a series of 97 patients clinically diagnosed as having endomyocardial fibrosis and in 24 of whom the diagnosis was confirmed at autopsy. In recent reviews of the reaction of the endocardium to disease (Davies, 1960, 1961) it has been stated that embolic accidents in subjects with endomyocardial fibrosis in Uganda were either associated with bacterial endocarditis or were massive terminal events affecting major blood vessels.

In West Africa, endomyocardial fibrosis appears to be a not uncommon disorder but little or no comment has been made on either the distribution of intracardiac thrombi or on embolic phenomena. In a clinical study of 50 subjects with mitral regurgitation with 13 subjects coming to autopsy Abrahams and Brigden (1961) note that mural thrombi are common but make no comment on their distribution or on the occurrence of embolic phenomena.

O'Brien (1954) has described a series of 25 cases of presumed endocardial fibrosis from the Sudan but in only two was the diagnosis confirmed at autopsy and in both of these pulmonary infarcts were present. From Southern Rhodesia, Gelfand (1957) has recorded a case of endomyocardial fibrosis in whom peripheral gangrene had occurred due to thrombus in the external iliac artery as well as pulmonary infarction. Three cases of endomyocardial fibrosis have been described in Ceylon and in two of these pulmonary infarction was present (Nagaratnam and Dissanayake, 1959).

It is extremely difficult to decide whether those cases closely resembling endomyocardial fibrosis reported from other continents are the same disease as that seen in Uganda. Many of the reported cases show gross and often well-demarcated endocardial fibrosis with overlying thrombus, and some of the cases of endocardial fibrosis or endomyocardial sclerosis reported from Europe and America

TABLE III

INTRACARDIAC THROMBOSIS AND EMBOLIC PHENOMENA IN ENDOMYOCARDIAL FIBROSIS (UGANDA) AND CRYPTOGENIC HEART DISEASE (SOUTH AFRICA)

	No. of hearts with thrombi	Right atrium	Left atrium	Right ventricle	Left ventricle	Hearts with no thrombi	Embolitic phenomena
Uganda series	57 (46%)	28 (37)*	5 (7)	11 (15)	32 (42)	66	18 (15.4%)
South African series ..	48 (60%)	34 (45)	10 (13)	8 (11)	23 (31)	32	28 (35%)

* Figures in brackets refer to percentage of total chambers involved.

do strikingly resemble endomyocardial fibrosis as seen in Uganda. Cardiac thrombi are common in these cases and embolic phenomena have occurred in about half of the cases described both in Europe (Löfler, 1936; Mumme, 1940; Edge, 1946; Gray, 1951; Hughes and Smith, 1953; Lynch and Watt, 1957; Penfold, 1957) and in the United States of America (Smith and Furth, 1943; Toreson, 1944; McKusick and Cochran, 1952; McNicol *et al.*, 1953; Hoffman, Rosenbaum, and Genovese, 1955). The nature of this group of disorders is uncertain, and their inclusion in this discussion does not imply any aetiological relation to endomyocardial fibrosis as seen in Africa, but is intended to indicate the relative frequency with which embolic phenomena complicate endomyocardial fibrosis and mural thrombosis in different populations.

The relation between the cardiopathies of South Africa and those seen in Uganda remains uncertain (Davies, 1960; Thomson, 1961), although opinion seems to favour that the two disorders described in South Africa, viz. nutritional heart disease (Gillanders, 1951; Higginson, Gillanders, and Murray, 1952) and cardiovascular collagenosis with parietal endocardial thrombosis (Becker, Chatgidakis, and van Lingen, 1953) are probably the same condition (Report of a Joint Seminar, 1957; Higginson, Isaacson, and Simson, 1960) and that endomyocardial fibrosis seen in Uganda is a separate entity (Higginson *et al.*, 1960; Abrahams and Brigden, 1961; Davies 1961). The distribution of thrombi within the heart in the cases of obscure cardiac failure seen in South African Bantu subjects ("cryptogenic heart disease") is shown in Table II, and in Table III is compared with the incidence of thrombi and embolic phenomena in cases of endomyocardial fibrosis seen in Uganda. This comparison is made to emphasize the relative frequency and distribution of thrombi in the two conditions and not in order to suggest that these conditions are related.

While there are clearly differences between the percentage incidence of thrombi in the various chambers of the heart in these two series the general pattern of involvement is similar, with predominant involvement of the left ventricle and the right atrium. Over three-quarters of the thrombi found were present in these two sites in both series. In 28 (35%) of the South African series of 80 cases there was obvious visceral infarction involving the lungs, kidneys, spleen, and brain. In 10 of these cases intracardiac mural thrombi were present.

The significance of intracardiac thrombosis in the pathogenesis of the several cardiomyopathies mentioned is not clear and it is not known whether the thrombi are primary or secondary phenomena.

In Uganda, Davies (1948) postulated that the earliest lesion in endomyocardial fibrosis is a myocardial infiltration with round cells and eosinophil cells occurring for reasons unknown, followed by necrosis of the endocardium and subendocardial myocardial fibres with mural thrombus forming over this area and subsequently becoming organized into dense fibrous tissue. In later communications (Davies and Ball, 1955; Davies, 1959; Davies, 1960) this concept of an initial subendocardial lesion has been maintained and the role of organizing thrombus in the development of the massive fibrosis has been emphasized. The cause of the postulated subendocardial muscle damage that precedes the formation of mural thrombus remains obscure. While it is recognized

that parietal endocardial fibrosis and parietal thrombus can be produced in many ways and that endomyocardial fibrosis may be an end-result common to several different causes, the Kampala workers believe that the relatively common occurrence of this strikingly consistent heart lesion points to some special ætiological factor or combination of factors (Williams, Ball and Davies, 1954).

In West Africa, Abrahams and Brigden (1961) found histological evidence of myocarditis with Aschoff nodules in association with macroscopic endomyocardial fibrosis in 3 of 13 cases of mitral regurgitation and pulmonary hypertension coming to autopsy. They do not suggest that the endomyocardial fibrosis is caused by rheumatic carditis but that in a cardiomyopathy, whether due to inflammation, nutritional deficiency, or other metabolic disorders, mural intratrabecular clots may be precipitated during an acute phase and subsequently become organized. This process may be recurrent and lead to endomyocardial fibrosis. They consider that endomyocardial fibrosis is "the final common path" resulting from many different forms of myocardial damage and that in Southern Nigeria, rheumatic carditis may be concerned with this process in some cases. In Uganda, the possibility of a relation between endomyocardial fibrosis and rheumatic heart disease has been suggested by Shaper and Williams (1960) based on the similar age incidence and on certain clinicopathological features.

In South Africa, Higginson *et al.* (1960) consider that the autopsy findings in their cases correspond most closely to the hearts described in the European and American subjects as "idiopathic cardiac hypertrophy" and that the condition is clearly different from the endomyocardial fibrosis seen in Uganda. In two of their series of 80 hearts, thick fibrous plaques were present overlying the endocardium and they present an illustration of one heart seen following the completion of their series, with features typical of endomyocardial fibrosis as seen in Uganda. They consider that the clinical and pathological features in their cases suggest that the basic lesion is a myocardial weakness, leading to dilatation and hypertrophy with secondary changes induced by the development of mural thrombi. In support of this thesis they refer to the study made by Flynn and Mann (1946) who concluded that intraventricular circulatory stasis associated with congestive cardiac failure commonly produces degenerative changes in the endocardium and subendocardial myocardium with subsequent mural thrombus formation and thrombosis of the Thebesian veins.

The South African workers regard the presence of thrombi in the atrial appendages or between the trabeculæ carneæ as supporting evidence of the role of stasis in their formation and, in their view, the final pathological picture in the endocardium is dependent on the organization of these mural thrombi. They consider that if intracardiac thrombosis is of significance in the Uganda cases, it must be of a different nature from that seen in the Johannesburg cases, being clearly a more gradual process. "It is possible that variations in the thrombotic process may partly explain the different pathological lesions reported from Africa" (Higginson *et al.*, 1960). In the cases of endomyocardial fibrosis seen in Uganda, there is no clinical or extracardiac pathological evidence of any kind to suggest that a generalized increase in the liability to thrombosis is present.

Running through all these reports is a common belief in the significant contribution of organized thrombi to the fully-developed picture of endomyocardial fibrosis. There is also general agreement that where organization of a thrombus has obscured the relation of thrombosis to endocardium, the presence or absence of pre-existing endocardial lesions is difficult to prove or disprove. Also implicit in these reports is the concept of a primary myocardial damage which produces according to some views heart failure with stasis (Higginson *et al.*, 1960; Abrahams and Brigden, 1961) and to others, a subendocardial lesion over which endocardial changes and thrombosis occur (Davies, 1960).

In support of their view that cardiac dilatation and stasis following "myocardial dysfunction" are the main factors underlying the development of mural thrombi in cryptogenic heart disease, Higginson *et al.* (1960) note that the frequency of endocardial thrombi in their series (60%) is higher than that found in hearts of patients dying in cardiac failure due to other causes. Their table indicates the frequency of intracardiac thrombi in various conditions, i.e. coronary artery disease, 58 per cent; syphilis, 27 per cent; cor pulmonale, 24 per cent; and hypertensive heart disease, 20 per cent. It is not stated whether these thrombi were predominantly in the ventricles or in the atria.

If cardiac dilatation with stasis and thrombus formation, but without some localizing endocardial or subendocardial factor, plays a significant role in the initiation of endomyocardial fibrosis, one would expect a high degree of correlation between endomyocardial fibrosis and those conditions associated with chronic heart failure. In Mulago Hospital, hypertensive heart disease accounts for 37 per cent and syphilitic heart disease for 14 per cent of cardiovascular disorders (Shaper and Williams, 1960) but endomyocardial fibrosis in association with syphilitic or hypertensive heart disease is extremely uncommon. Further, ventricular dilatation is *not* a feature of the hearts with endomyocardial fibrosis seen in Uganda. It appears that the concept of a primary myocardial failure leading to dilatation, stasis, and thrombus formation is not a significant factor in the aetiology of endomyocardial fibrosis in Uganda.

SUMMARY AND CONCLUSIONS

This communication records the incidence and distribution of intracardiac thrombi and of embolic phenomena in endomyocardial fibrosis in Uganda, and discusses the role of thrombus formation and organization in the pathogenesis of endomyocardial fibrosis and other cardiopathies. It is not an attempt to define the relation between the various obscure forms of heart disease seen in Africa and elsewhere. Whatever the ultimate nature of or relation between these various disorders, cardiac thrombi clearly play an important role in producing the typical fully-developed picture of endomyocardial fibrosis, but we consider that myocardial failure *per se* is not sufficient to account for the initiation of the condition.

From the observations made during this study we think that in endomyocardial fibrosis as seen in Kampala, Uganda, there appear to be localizing endocardial or subendocardial factors that determine the formation of intracardiac thrombosis.

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