THE PATHOLOGY OF ENDOMYOCARDIAL FIBROSIS IN UGANDA

BY

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Rare examples of heart failure due to extensive endocardial sclerosis have been reported from various countries in the last half century; in Uganda, however, this is one of the commonest causes of heart failure. The first indication that this condition was prevalent amongst Africans was given by Bedford and Konstam (1946), who had seen it in African troops. Independent pathological observations were made in Uganda and reported shortly afterwards (Davies, 1948, *a* and *b*).

In this paper a detailed description is given of the pathology of the disease, based on 32 necropsies. Over 100 have been performed on this condition since 1946 at Mulago, but unfortunately much of the collected material was destroyed in an explosion in the Medical School in 1951. Nineteen of the 32 necropsies analysed here were found in the 550 necropsies performed in 1953 (i.e. 3·5 %). Endomyocardial fibrosis was responsible for 33 of the 231 deaths from cardiac failure in the period 1951–53 (i.e. 14 %). Only hypertension, and that mainly renal, caused a higher proportion of heart failure. The third common cause of heart failure was syphilitic aortitis. Rheumatic heart disease is less common than in European series (though the pathological lesions do not differ), atheromatosis and essential hypertension are much less common, and coronary thrombosis in Mulago is very rare indeed (Williams *et al.*, 1954).

The 32 hearts on which the following description is based come from patients of both sexes and all ages (Table II). All were native Africans. The essential pathological lesion to be described in detail below is a *fibrosis of the endocardium of the ventricles*. On this, thrombus may be superimposed. The auriculo-ventricular valves are often involved by an extension of the lesion upwards from the apices of the ventricles (Table I).

TABLE I

MAIN ANATOMICAL AND CLINICAL SUBDIVISIONS OF ENDOMYOCARDIAL FIBROSIS

Region	Lesion	Clinical result
(1) L. ventricle	Endo- and myo-cardial fibrosis	Bilateral heart failure
(2) Mitral valve	Adherence of posterior cusp to ventricle	Mitral incompetence
(3) R. ventricle	Obliterative fibrosis	Pure right heart failure
(4) Tricuspid valve	Adherence of posterior cusp to ventricle	Tricuspid incompetence

The *pericardium* itself showed no abnormality. A small excess of pericardial fluid was common and a very large collection was found on one occasion (over 1500 ml.). In all these cases the fluid was clear and contained few cells, and only 2–4 g. of protein per 100 ml.

A depression over the apex of the right ventricle was visible in 16 hearts (Fig. 1); as this was associated with lesions of the endocardium in the right ventricle, it will be described in the section on that subject.

Heart Weight. The heart weight varied over an extraordinary range from atrophy to extreme hypertrophy. Adult male hearts ranged from 205 to 680 g. (mean 370 g.); adult female hearts from 185 to 260 g. (mean 212 g.); children's hearts were all greatly enlarged (Table II).

Muller's index (heart weight × 1000 ÷ body weight) was calculated and compared with normal indices for different ages and sexes in Europe (Rossle and Roulet, 1932). It was found that three hearts were atrophic (10–22 % below the normal mean). Of the rest one-third were normal in weight (±10%), one-third were moderately hypertrophied (10–30% above normal), and one-third were considerably hypertrophied (40–180% above the normal mean). These figures tend to be

TABLE II

A SUMMARY OF THE FINDINGS IN THE 32 NECROPSIES

No.	Sex	Age	B. W. (Kg.)	H.W. (g.)	Anasarca (graded 1, 2 or 3)	Duration of H.F. (months)	Chambers with E.F. (in order of severity)	Site of antemortem thrombus	Site of calcification	Valves involved
1	F	24	—	185	0	0	*RV*	0	RV	T
2	—	—	—	170	—	—	LV *RV*	LV RV	0	M T
3	—	—	—	370	—	—	LV RV	LV	0	M (pap.)
4	—	—	—	325	—	—	LV RV	0	LV (hist.)	M T
5	M	—	—	300	0	0	LV *RV* LA RA	LV LA RA	0	T (pap.) M (pap.)
6	M	35	54·4	240	3	4	LV RV	LV	0	M
7	M	35	47·6	524	2	3	LV *RV*	0	0	M T
8	M	40	52·3	445	1	½	LV RV	0	0	M T
9	M	30	59·9	640	2	9	LV LA	RV RA (hist.)	0	M
10	M	4	13·5	120	1	1	LV RV	LV	0	M
11	M	25	48·5	680	2	3	*RV* LV	RA LA LV	0	0
12	M	25	57·2	325	1	84	*RV* LV	RA	RV	T M
13	F	5	16·4	210	0	12	RV LA	0	0	M T
14	F	29	38·2	210	2	11	*RV* LV RA LA	0	0	M T
15	M	45	76·3	510	3	32	LV RV	RA LV RV	0	M
16	M	35	41·5	275	1	? 1	LV *RV*	0	0	M (steno sis) Aortic
17	M	30	38·3	230	0	0	LV *RV*	0	LV	0
18	M	60	60·0	355	2	1	LV *RV* RA	RA	0	M T
19	M	32	50·4	315	1	? 1	LV RV	LV	LV M	M T
20	M	30	42·9	320	3	5	LV *RV* RA	LV	0	M T
21	M	35	48·1	400	2	33	*RV* LV RA	RA	LV RV	T M (pap.)
22	M	60	54·0	320	0	0	LV *RV*	LV (hist.)	M	M T (pap.)
23	M	30	50·5	425	0	0	LV RV RA LA	RA	LV (hist.) LA (hist.)	T M (pap.)
24	M	55	33·0	205	3	9	*RV* LV	RV LV	LV (hist.)	T M
25	M	45	73·5	400	1	1	LV RV	0	LV	M T
26	M	47	55·0	270	2	44	*RV* LV RA	RA	0	T M
27	M	50	36·7	210	0	0	LV RV LA	0	M	M T
28	M	50	46·0	330	0	0	LV *RV*	LV	LV	M T (pap.)
29	F	35	44·0	260	3	1	*RV* LV RA	RV RA LV	RV (hist.)	M T
30	F	26	50·6	210	3	7	*RV* LV	RV M	0	T M (stenosis)
31	F	9	37·5	230	2	1	LV *RV* LA RA	LV (hist.)	LV	M T
32	M	30	65·6	435	3	3	LV *RV* LA	RA	M	M T

B.W.=Body weight. H.W.=Heart weight. H.F.=Heart failure. E.F.=Endocardial fibrosis. *RV*=Italic type shows that the RV lesion has produced obliteration. T=Tricuspid valve. M=Mitral valve. — =Unrecorded. pap.=papillary muscle only involved. hist.=lesion only visible histologically.

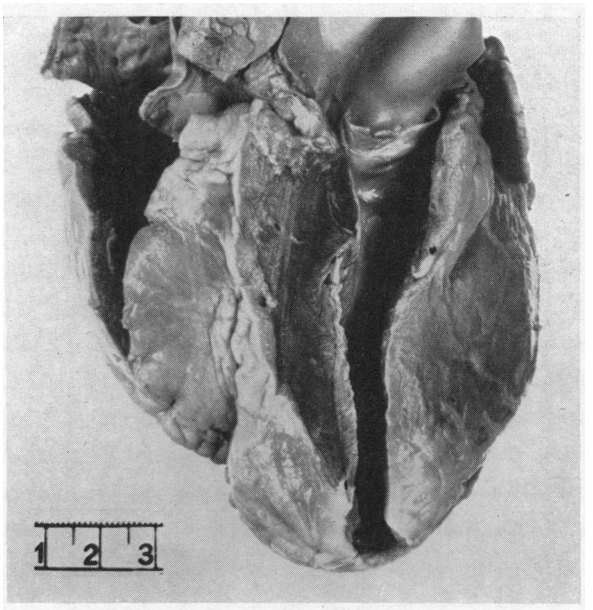

FIG. 1.—Deep depression over apex of right ventricle (Case 14).

lower than they should be as the presence of œdema adds false body weight and lowers Muller's index. Unfortunately we are ignorant of the normal heart weight for the different ages and sexes in the African.

No correlation with such factors as duration of heart failure or valve lesions has been found to suggest an explanation for these wide differences.

NAKED EYE APPEARANCES OF THE LESIONS OF THE LEFT SIDE OF THE HEART

The fibrotic endocardial lesions in the left ventricle will first be described; then the complications of thrombosis on the surface and calcification in the depths of the endocardium. It is logical to describe next the mitral valve as it seems that the lesions of this valve result from a spread of the ventricular lesions on to the chordæ and cusps, particularly the posterior. The result is usually incompetence, rarely stenosis. Finally, the minor left atrial lesions are described.

Left Ventricle. The endocardium of the left ventricle showed naked-eye lesions in 30 out of 32 hearts. In twelve all four walls and the apex showed fibrosis. The region most commonly involved was the posterior wall (29/30 cases), closely followed by the apex and lateral wall (both 25/30 cases); the septal wall was less frequently affected (15/30), and when it was the fibrosis was less in area and depth than on the other walls (Fig. 2 and 3). In the few cases where slight lesions were incidental findings in patients who had died of some other condition, they commonly took the form of a small patch of fibrosis at the extreme apex (Fig. 4). These were of pearly white fibrous tissue, often with a rugose surface, and with edges raised above the surrounding endocardium. More extensive lesions may also show this raised, rolled edge, beyond which there may be a filmy thickening of the endocardium. The maximal thickness of the endocardium was usually 2–3 mm., but it was occasionally as much as 10 mm. thick. Once or twice it showed a layered appearance in some areas, like agate. It was sometimes very firm at the raised edges and on the ventricular surface, but softer in the deeper layers where there was usually a thin layer of visible engorgement. Fibrous strands extended from the endocardial fibrous tissue into the myocardium in about

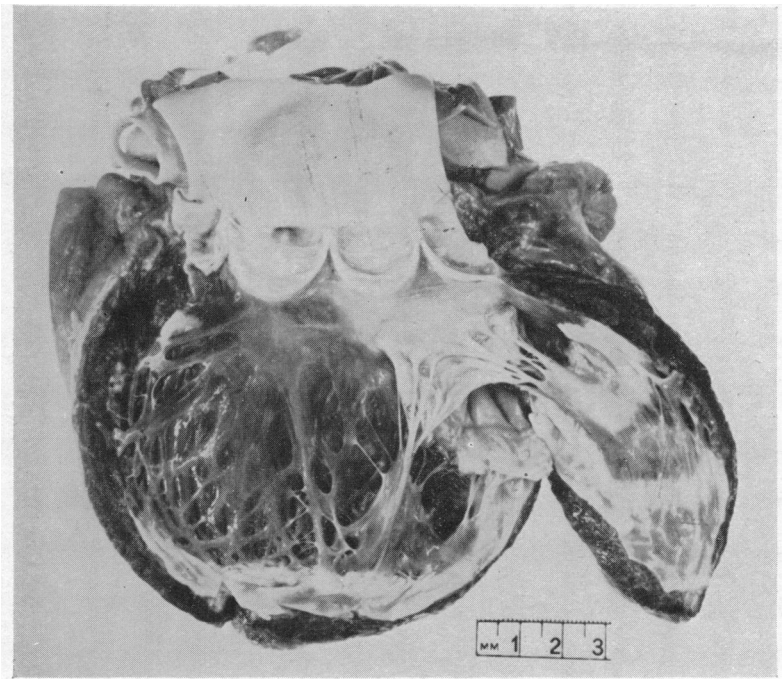

FIG. 2.—Left ventricle: smooth white fibrous tissue extending from apex up the posterior wall to the posterior mitral cusp, and also on to antero-lateral wall. The septum is characteristically spared (Case 26).

FIG. 2

FIG. 3.—Left ventricle: rugose fibrotic endocardium covers the apex, posterior, lateral, and anterior walls. Posterior mitral cusp completely adherent. Chordæ of anterior cusp thickened.

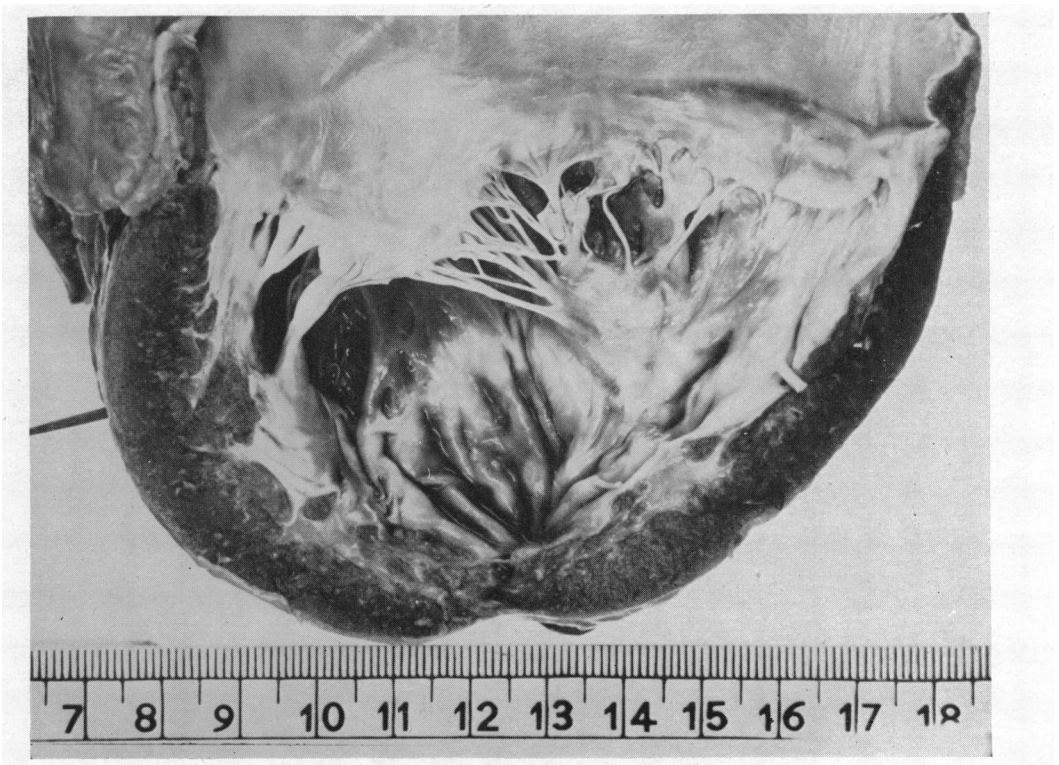

FIG. 3

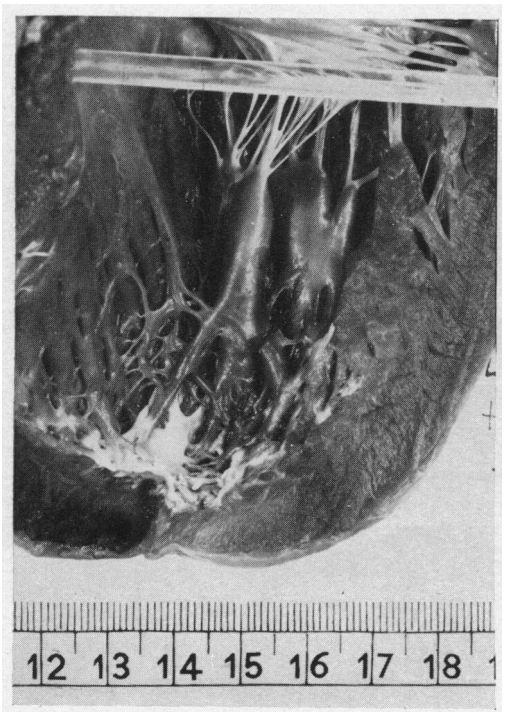

FIG. 4.—Left ventricle: small patch of fibrotic endocardium at extreme apex, found in a patient who died from uræmia (Case 23).

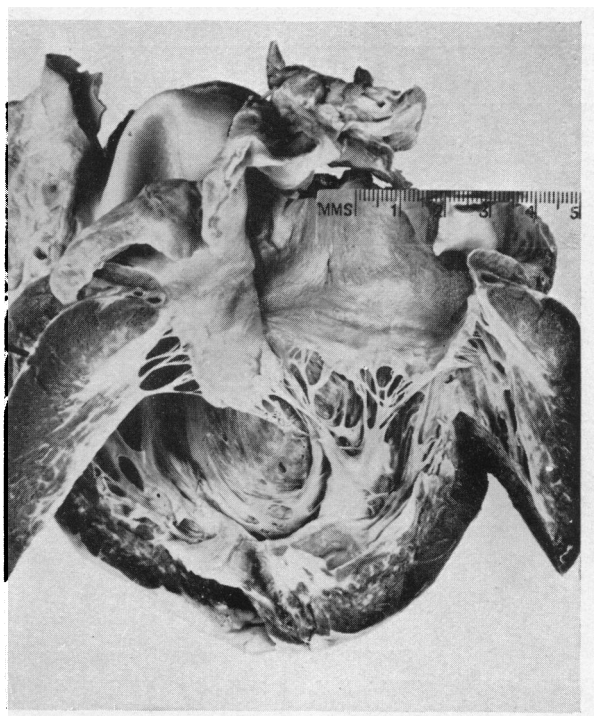

FIG. 5.—Left ventricle: note the flecks of fibrous tissue in the myocardium, and the way the papillary muscle has been surrounded and largely replaced by white fibrous tissue (Case 25).

one-third of the cases (Fig. 5). These were usually confined to the inner third but occasionally penetrated more deeply. The 30 left ventricular lesions were arbitrarily classified as follows.

(1) Mild in 7 (less than one-quarter of the endocardial surface being involved).

(2) Moderate in 11 (one-quarter to one-half being fibrotic).

(3) Severe in 12 (with fibrosis of more than half of the endocardial surface (Table III).

In 13 hearts the smooth white surface of the endocardial fibrosis was covered in part by mural thrombus in various stages of organization (Table IV). In nine the thrombus was only a thin layer varying from reddish-brown to yellow-green. In four there were masses of clot varying from 4 to 20 mm. in depth. The largest of these almost filled the ventricle, greatly reducing the cavity; such cases had been noted in a previous series (Davies, 1948, *b*). Mural thrombosis was much commoner when the endocardial fibrosis was extensive.

In nine left ventricles there were areas of calcification in the endocardial fibrous tissue, mostly as small granules, but in one case as a calcified plaque 2–3 mm. thick and 20×30 mm. in area (Fig. 6 and 7). Bacterial endocarditis was superimposed on the apical fibrosis in one heart.

In about one-third of the hearts the maximal thickness of the left ventricle lay between 15 and 18 mm.; this is slight hypertrophy on the criteria of Pagnoni and Goodwin (1952). This does not include three large hearts weighing 524, 640, and 680 g., whose maximal thicknesses were 8, 12, and 13 mm. respectively.

Mitral Valve Apparatus. The papillary muscle endocardium was more commonly involved than that over the chordæ or cusps (Table V). In 10 this was only slightly thickened, but in 9 one

TABLE III

INCIDENCE OF ENDOCARDIAL FIBROSIS IN THE DIFFERENT REGIONS OF 32 HEARTS

Region	Number	Percentage	Sub-divisions
Left ventricle	30	94	Mild 7 Moderate 11 Severe 12
Right ventricle	31	97	Mild 16 Moderate 6 Severe 9
Mitral valve *	25	78	Incompetence (i.e. posterior cusp adherent) 16 Stenosis as well 2 Minor lesions 9
Tricuspid valve *	23	72	—
Left atrium	7	22	—
Right atrium	9	28	—

* Excluding valves in which the papillary muscles only were affected.

TABLE IV

INCIDENCE OF VISIBLE MURAL THROMBUS IN THE FOUR CHAMBERS OF 32 HEARTS

Chamber	Number	Percentage	Sub-divisions
Left ventricle	13	41	Thin layer 9 Thick clot 4
Right ventricle	5	16	Thin layer 2 Thick clot 3
Left	2	6	—
Right	11	34	

TABLE V

INCIDENCE OF FIBROTIC LESIONS IN VENTRICLES AND A-V VALVES ARRANGED TO SHOW THE DIMINISHING INCIDENCE FROM VENTRICLE TO VALVE CUSP

Mitral valve	Cusp	Posterior 21	Anterior 15	
	Chordæ	,, 23	,, 12	
	Papillary muscles	28		
Left ventricle		30		
Tricuspid valve ..	Cusp	Posterior 14	Anterior 2	Septal 2
	Chordæ	,, 20	,, 8	,, 7
	Papillary muscles	,, 18	,, 16	— –
Right ventricle ..		31		

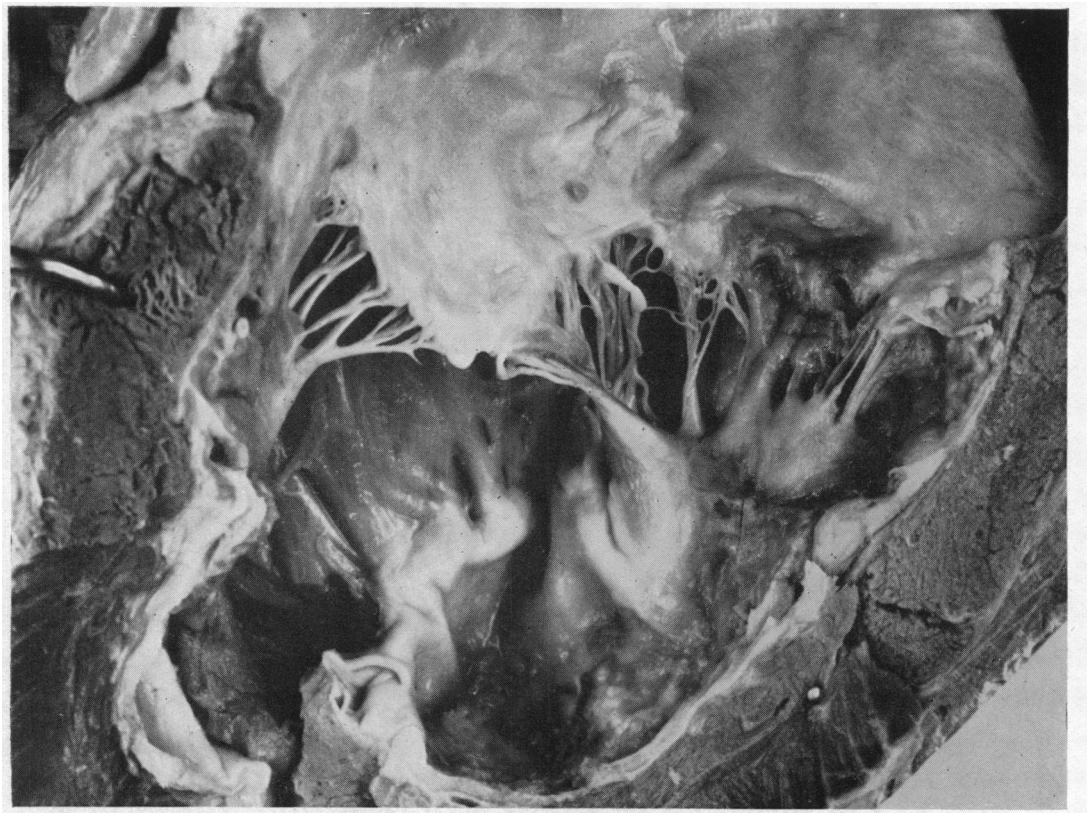

FIG. 6

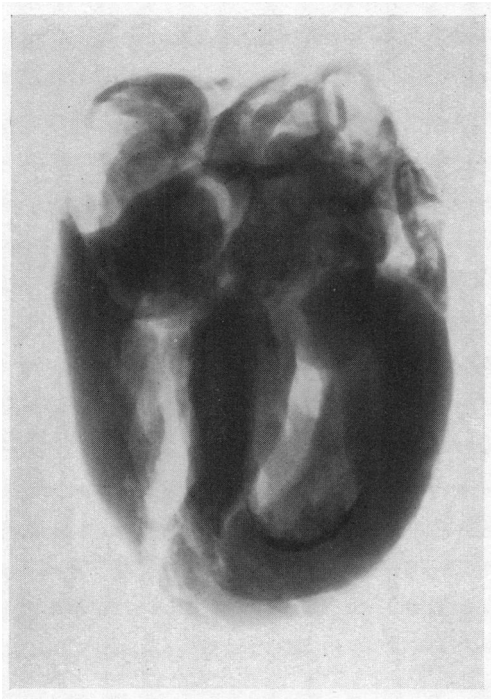

FIG. 6.—Left ventricle: extensive, thick and calcified endocardial fibrosis; posterior mitral cusp adherent (Case 19).

FIG. 7.—X-Ray of isolated heart to show plate of calcium at the apex of the left ventricle (Case 19).

or both papillary muscles were more or less completely buried in white fibrous tissue. In 4 the muscular tissue of the papillary muscle was almost entirely replaced by fibrous tissue (Fig. 5).

When the chordæ are involved in the process, they become thickened and apparently shortened, with adhesion to each other and to the ventricular wall (Fig. 8). In the advanced lesion the chordæ of the posterior cusp may become completely embedded in a mass of fibrous tissue and both become functionless (Fig. 3, 6, and 9). The anterior group of chordæ, like the anterior cusp is less frequently affected, and although they fuse together they cannot for anatomical reasons adhere to the ventricular wall. In four instances chordæ had ruptured, and in three vegetations of bacterial endocarditis were found.

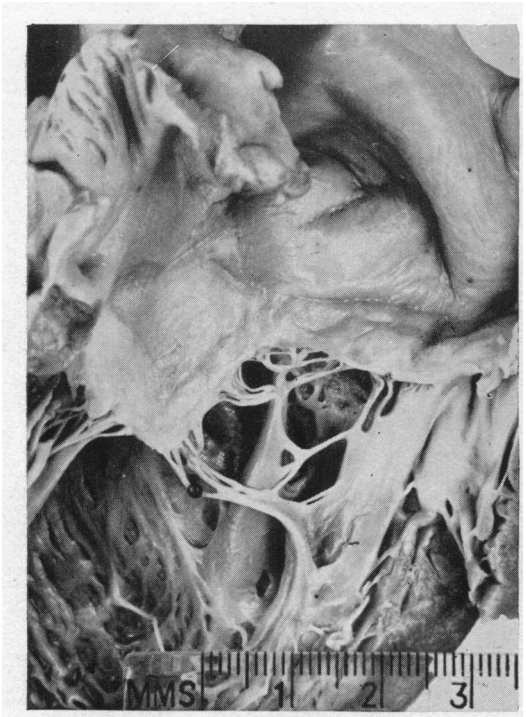

FIG. 8.—Mitral valve: posterior chordæ are fused to each other in a band and to the area of fibrotic endocardium beneath (Case 14).

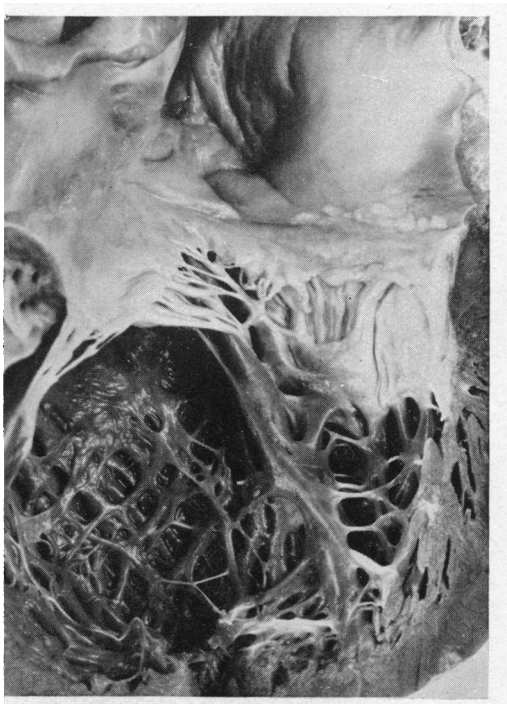

FIG. 9.—Mitral valve: complete adhesion of posterior cusp and chordæ to thick underlying fibrous plaque. Margin of anterior cusp and some of anterior chordæ are thickened. The lesion in the lower part of the ventricle is unusually slight (Case 8).

Abnormalities of the cusps were usually associated with abnormalities of the chordæ. The posterior mitral cusp was abnormal in 21 hearts (Table V); in 12 of these it was completely immobilized by adherence to the posterior wall of the ventricle. Sometimes the end-result was a fibrous surface running straight down from the atrium to the ventricle and broken by no more than a slight irregularity where the cusp had become embedded (Fig. 3 and 9). In others the remains of the cusp projected as a short thick shelf. In four cases there was only partial adhesion of the cusp, and in five the cusp showed slight thickening without being adherent. The anterior cusp was less frequently and less severely affected, the usual lesion being a band of fibrous thickening along the free margin. Vegetations were present on four of these cusps, and microscopy demonstrated the presence of a superimposed bacterial endocarditis.

Four mitral valves showed slight calcification.

Mitral Incompetence. Incompetence was thought to have been present in 12 of the patients during life, as the entire cusp (in seven) or the greater part of it (in five) was found to be adherent; a further four with slighter adherence may have had some incompetence. The importance of the short posterior cusp in closing the mitral ring has been stressed by Brock (1952), and support is given to this view by the close correlation that we found in a previous study between clinical signs of incompetence and posterior cusp adherence (Ball *et al.*, 1954).

Mitral Stenosis. Two of the valves were stenosed, having maximal circumferences of 4 and 5 cm. respectively. In one of these a scarred and thickened aortic valve gave rise to a suspicion of rheumatic heart disease, as the aortic valve is almost always normal in endomyocardial fibrosis. Both these hearts showed characteristic endocardial fibrosis with typical histological lesions and no other evidence of rheumatism.

Left Atrium. Small patches of thickened endocardium with well defined edges were seen in the left atrium in seven hearts, three being in the appendage and three close to the posterior mitral cusp. The former are thought to represent completely organized thrombi. The latter three resembled MacCallum's patches; these three had all been diagnosed in life as having mitral incompetence, and this was confirmed in each by the nature of the valve lesions discovered. We concur with Brigden and Leathem (1953) in thinking that this lesion is due to the regurgitant stream of blood. Mural thrombosis was rare in this chamber, being found in only two hearts; in both the site was the appendage.

The maximal thickness of the wall in eight atria was 4 mm. or more; these were regarded as undoubtedly hypertrophied. A further ten were 3 mm. thick, a borderline measurement. There was a tendency for the hypertrophied atria to be associated with mitral incompetence, but there were many exceptions. Dilatation of the atrium was obvious in seven hearts.

Lesions of the Right Side of the Heart

The lesions in the right heart were in general similar to those in the left. The main difference was the development of obliteration of the cavity of the right ventricle when the endocardial lesion became extensive.

Right Ventricle. Endocardial fibrosis was present in the right ventricle in 31 out of 32 hearts; these could be divided into three groups of ascending severity.

(1) Mild in 16 cases (in which less than one-quarter of the endocardium was covered by visible fibrosis).
(2) Moderate in 6 cases (in which one-quarter to one-half of the surface was covered).
(3) Severe in 9 cases (in which more than half of the surface was covered).

The smallest lesions were invariably found between contiguous surfaces; in the crevices between adjoining trabeculæ carneæ or where a papillary muscle, chorda, or cusp touched the ventricular wall (Fig. 10). The sharply-defined plaques of fibrosis that characterize the early left ventricular lesion were rarely seen.

A striking feature of most of the moderate and all the severe lesions was the obliteration of the cavity produced by the advancing fibrosis. This is presumably at least partly due to the different anatomical configuration of the right ventricular apex, where most of the lesions started. In the most advanced cases the process had gone on to virtual obliteration of the inflow tract. The position of the apex thus moved progressively nearer to the tricuspid valve (Fig. 11, 12, 13, and 14). The lesion is best demonstrated by a series of coronal sections made at right angles to the plane of the septum. These usually reveal obvious penetrating strands of white fibrous tissue which indicate the position of the obliterated cavity. Sometimes a small, blind crypt, lined with endocardium, is left behind at the site of the original apex. When occasionally the fibrous strands are inconspicuous, the apposition of the septum and lateral wall produces a massive wedge of muscle (Fig. 16). Such an appearance was seen by Fienberg and Holzman (1951) in a heart that also had extensive endocardial fibrosis.

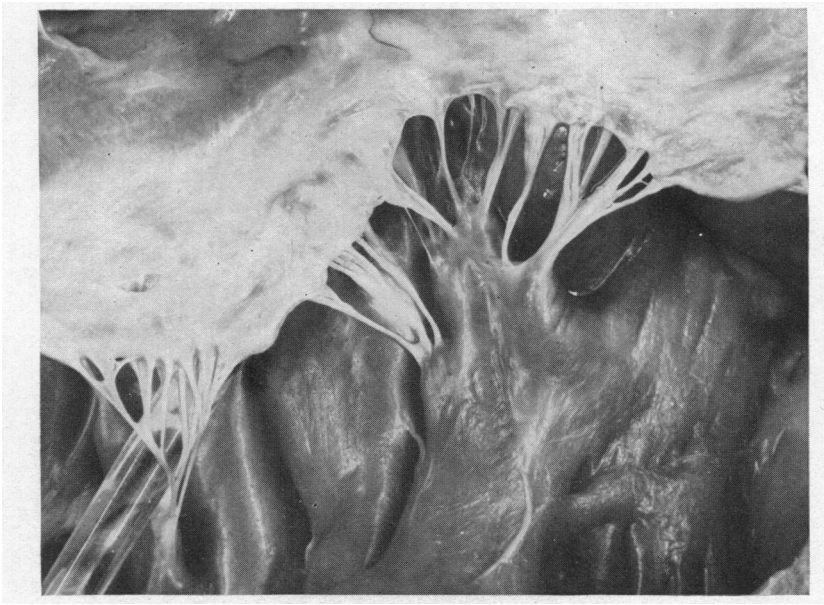

FIG. 10.—Tricuspid valve, medial end of posterior cusp and septal cusp. One of the chordæ has become completely adherent to a small patch of white fibrous tissue at a point where it crosses one of the trabeculæ carneæ (Case 23).

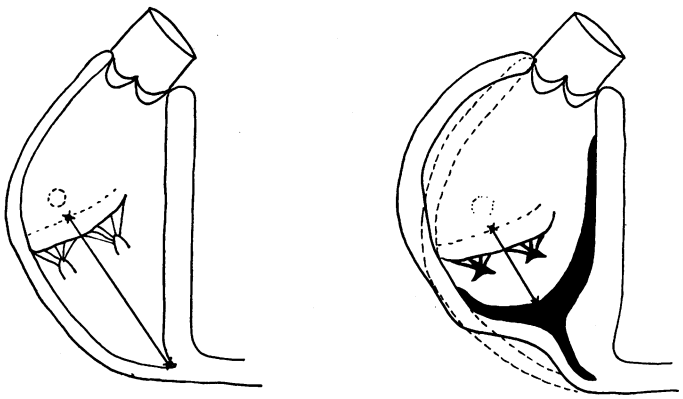

FIG. 11.—Diagram to show the main features of the obliterative fibrosis of the right ventricle. The relative length of the inflow tract is reduced from about 5–7 cm. in normals to about 2–6 cm.

One effect of this obliterative process was the drawing in of the anterolateral wall of the ventricle to produce the external depression previously mentioned (Fig. 1). This may be a deep crease, a saucer, or a triangular depression. It was always present when the right ventricular lesion was a severe one. It appeared that this indrawing of the myocardium was due to the approximation of the walls of the inflow tract with partial obliteration of the cavity. No external depression was seen at the apex of the left ventricle, even when there was extensive fibrosis of this chamber.

A means of measuring this obliterative process was devised; the distance was measured from the mid-point of the posterior tricuspid cusp at its attachment (a point just below the coronary sinus orifice), to the " apex," the point on the endocardium nearest to the lower end of the septum.

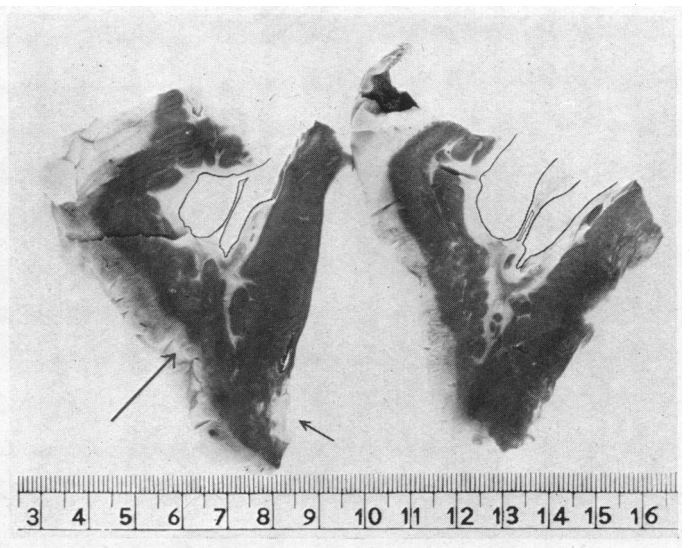

FIG. 12.—Sections through the apex of the right ventricle and septum. Fibrous tissue has filled up the apex and embedded the papillary muscle. The left-hand arrow indicates the characteristic external depression (covered by thick layer of epicardial fat) and the right-hand arrow points to a plaque of fibrous tissue at the apex of the left ventricle (Case 12).

In 16 normal hearts, the length of the inflow tract, thus defined, varied from 5·0 to 7·6 cm. In 17 hearts with obliteration of the right ventricle, the distance varied from 2·2 to 6·1 cm. These findings are shown in relation to the heart weights in Fig. 15.

Obliterative fibrosis was not always apical; in three hearts such a lesion was found on the septum, level with the tricuspid valve, producing an hour-glass constriction of the ventricle (Fig. 17). One of these lesions had caused an external depression.

Mural thrombosis, present in five instances, was relatively uncommon in this chamber. In two of these the thrombosis was massive, almost filling the inflow tract with greenish-yellow, fibrin thrombus, lightly attached to the endocardium. Calcification was also less frequent than in the left ventricle, occurring in four patients; one of these showed the most extensive calcified lesion found in this series, the calcium being deposited as numerous, bulky, granular masses, up to 15 mm. thick (Fig. 16 and 18).

Hypertrophy and dilatation were very common. As the apex was distorted, measurements were made at the infundibulum, and this showed mild hypertrophy in 18 hearts (5–7 mm.), moderate in 7 (8–10 mm.), and severe in 4 (over 10 mm.) (Pagnoni and Goodwin, 1952). It seemed possible that right ventricular hypertrophy might be related to mitral or tricuspid incompetence, but there was no correlation with adherence of the cusps of either valve. The isolated dilatation and hypertrophy of the right ventricle seen in cardiac beri-beri was not found.

Tricuspid Valvular Apparatus. Minor lesions of the papillary muscles, chordæ, or cusps were found in 26 hearts. The papillary muscles were involved in 19. The muscle may simply be surrounded at its base, or covered by a thin layer of fibrosis; or it may be engulfed in a mass of fibrous tissue, a mere nodule projecting to give rise to the chordæ (Fig. 12). The milder lesion is commoner in the anterior muscle, the severer in the posterior.

The tricuspid chordæ were abnormal in 20 valves, the common lesions being shortening, thickening, and adhesion to each other or to underlying patches of endocardial fibrosis (Fig. 10 and 19).

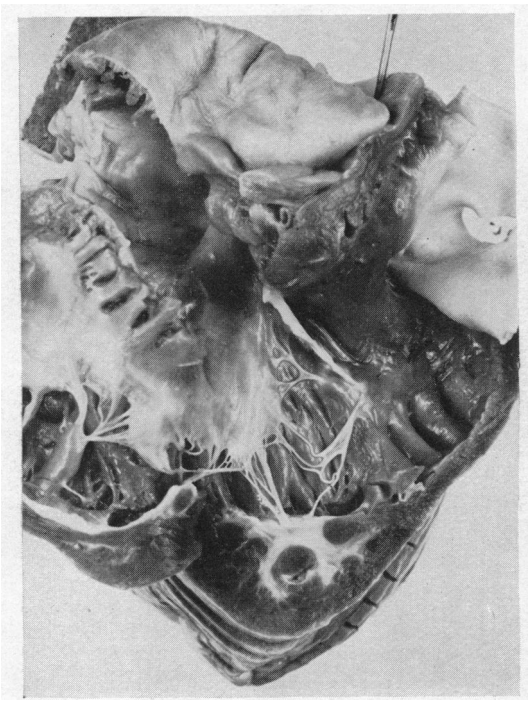

FIG. 13.—Right ventricle and tricuspid valve. The lesion is confined to the lower part of the inflow tract, which has become completely filled up with white fibrous tissue (Case 28).

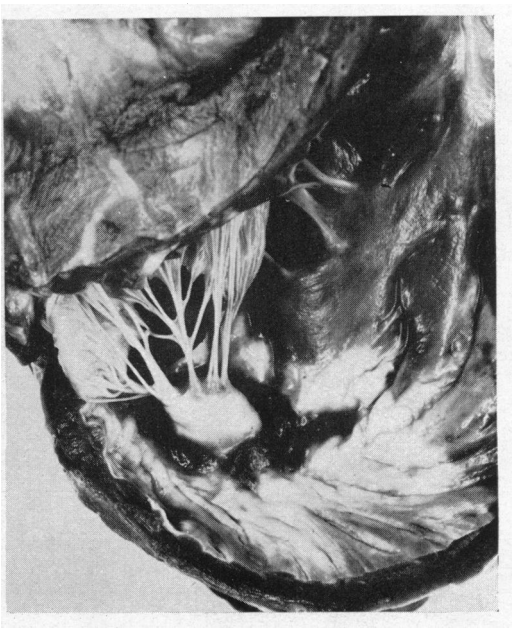

FIG. 14.—Right ventricle: apex seen from above. The apex is obliterated and the large anterior muscle surrounded and covered with fibrous tissue. A dark layer of ante-mortem thrombus can be seen.

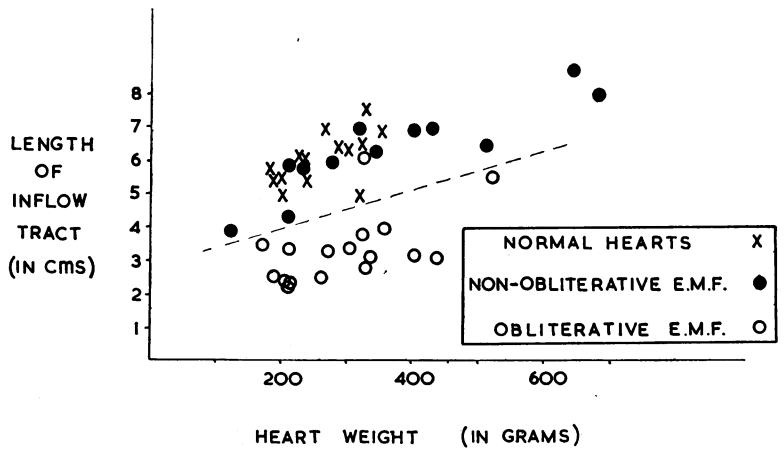

FIG. 15.—Right ventricle: length of inflow tract (as defined in the text), plotted against heart weight, in hearts showing obliterative fibrosis. The comparison with normal hearts shows that the obliterative fibrosis can halve the length of the inflow tract.

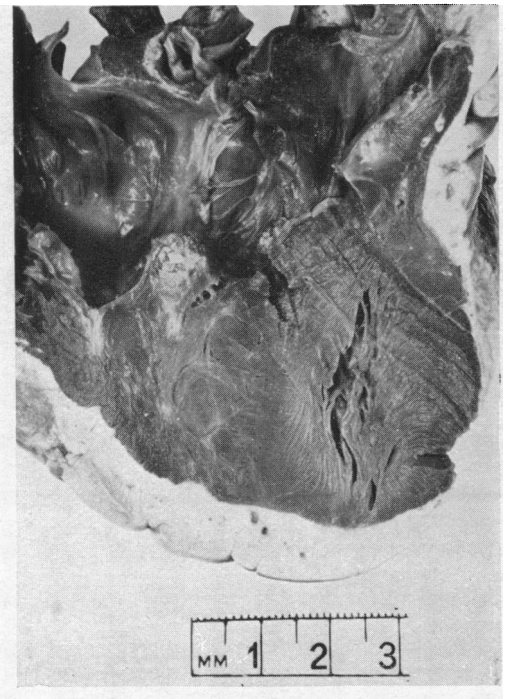

FIG. 16.—Section through the apex of the right ventricle, showing extreme obliteration of the inflow tract, deposits of calcium below the endocardium, which is only moderately thickened, and the massive wedge of muscle which has resulted from apposition of the walls of the right ventricle. The section has just gone into the left ventricle, the cavity of which is seen on the right of the picture. Thick layer of epicardial fat (Case 1). See Fig. 18 for X-ray of this heart.

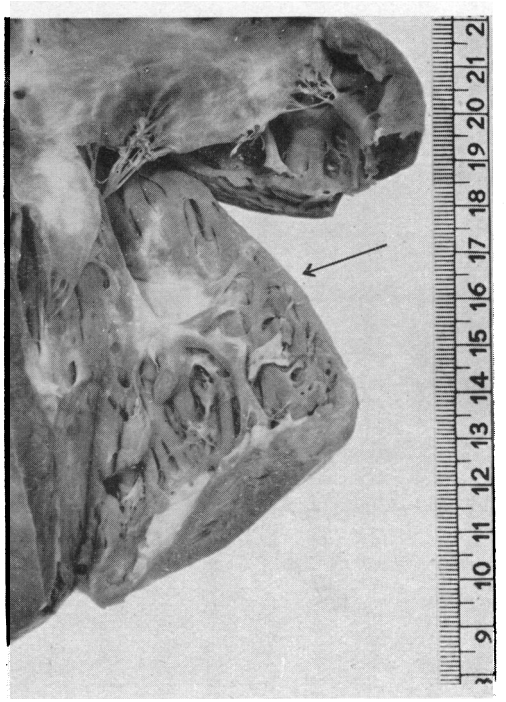

FIG. 17.—Right ventricle, showing three patches of thickened endocardium. The largest, to which the arrow is pointing, is causing obliteration at the waist of the ventricle, between the inflow and outflow tracts (Case 11).

FIG. 18.—Radiograph of isolated heart, showing extensive granular deposits of calcium beneath the endocardium of the right ventricle, which has undergone advanced obliteration (Case 1).

Combinations of these lesions were common. The posterior chordæ were more frequently and more severely involved than the anterior and septal groups.

A common lesion in the cusps, which showed some abnormality in 14 cases, was adhesion of the posterior cusp to the ventricular wall; in the present series this was never so completely immobilized as the posterior mitral cusp. Since closing the series, however, we have seen two tricuspid valves in which the posterior cusp had completely disappeared beneath a sheet of white fibrous tissue; in both of these tricuspid stenosis was present, along with extreme obliterative fibrosis of the right ventricle and characteristic lesions of the left. In a smaller number the cusp was moderately thickened towards the free margin. Such thickening was less common in the anterior cusp and least of all in the septal.

Neither calcification nor bacterial endocarditis was found as a complication of the tricuspid lesions. Tricuspid incompetence can occasionally be diagnosed in life (Ball *et al.*, 1954).

Right Atrium. The endocardium showed focal areas of thickening with clear-cut edges in nine atria. Seven of these were close to organizing thrombus, and it is believed that they were the result of complete organization of small thrombi. In seven further cases there were ill-defined patches of slightly thickened endocardium of doubtful significance.

Ante-mortem thrombus was attached to the right atrial wall in 11 of the hearts. In some it was dark red and lightly attached, in others it was mottled yellow-red on section and partly organized, and in two it was covered with a layer of white fibrous tissue, the result of complete organization. The commonest site was the appendage.

FIG. 19.—Tricuspid valve and right ventricle. The posterior cusp of the valve is thickened and in places adherent to the underlying fibrotic endocardium. The chordæ are short, thick and fused. The lower part of the right ventricle is filled up with dark friable ante-mortem clot (Case 24).

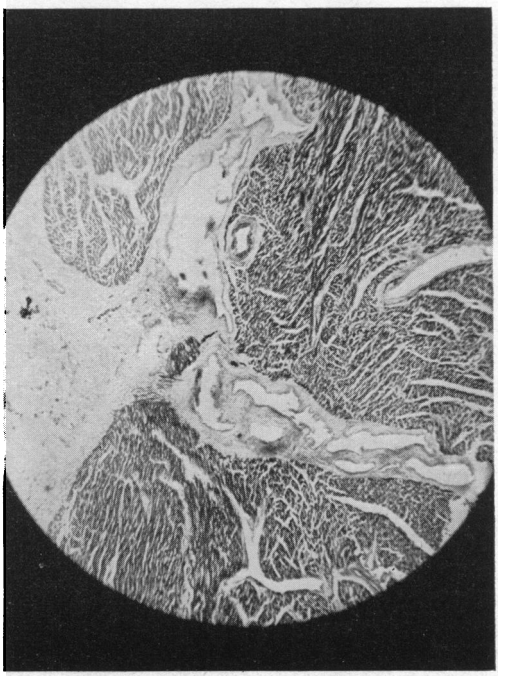

FIG. 20.—Dilated thin-walled blood vessels in the myocardium under a patch of endocardial fibrosis. The deeper part of the fibrous endocardium is seen on the left.

Hypertrophy and dilatation were both present in some two-thirds of the series. Two of the three atria that showed these changes most severely were associated with marked obliterative fibrosis of the right ventricle.

Semilunar Valves and Great Vessels. The pulmonary valve escaped completely and so did the aortic, except for the one case mentioned above. The great veins entering the atria showed no lesions.

The pulmonary arteries were normal save for occasional slight atheroma, and the same is true of the aorta. While we have not always made full measurements of the aortic calibre, our observations have not led us to associate this disease with aortic hypoplasia; this is common in East African natives (Dick, 1947). The major coronaries were normal; obliterative changes in the small branches are described below. No vascular defects have been noted in other regions of the body.

Histopathology of Ventricular Changes

The histological changes are extremely uniform despite variations in the gross appearance.

Mural Thrombus. This, consisting of fibrin alone or of all the components of a blood clot, was superimposed on the fibrotic endocardium in 21 of the 61 abnormal ventricles; in 18 of these it was visible to the naked eye (Table IV). It was often covered at its edges by endothelial cells and there was evidence of organization at the edges. Sometimes a ball of old thrombus completely encapsulated by fibrous tissue has been seen.

Endocardium. The greatly thickened mass of endocardial fibrosis showed three zones (Fig. 21). The superficial zone beneath the thrombus was usually acellular and often hyalinized. Deposits

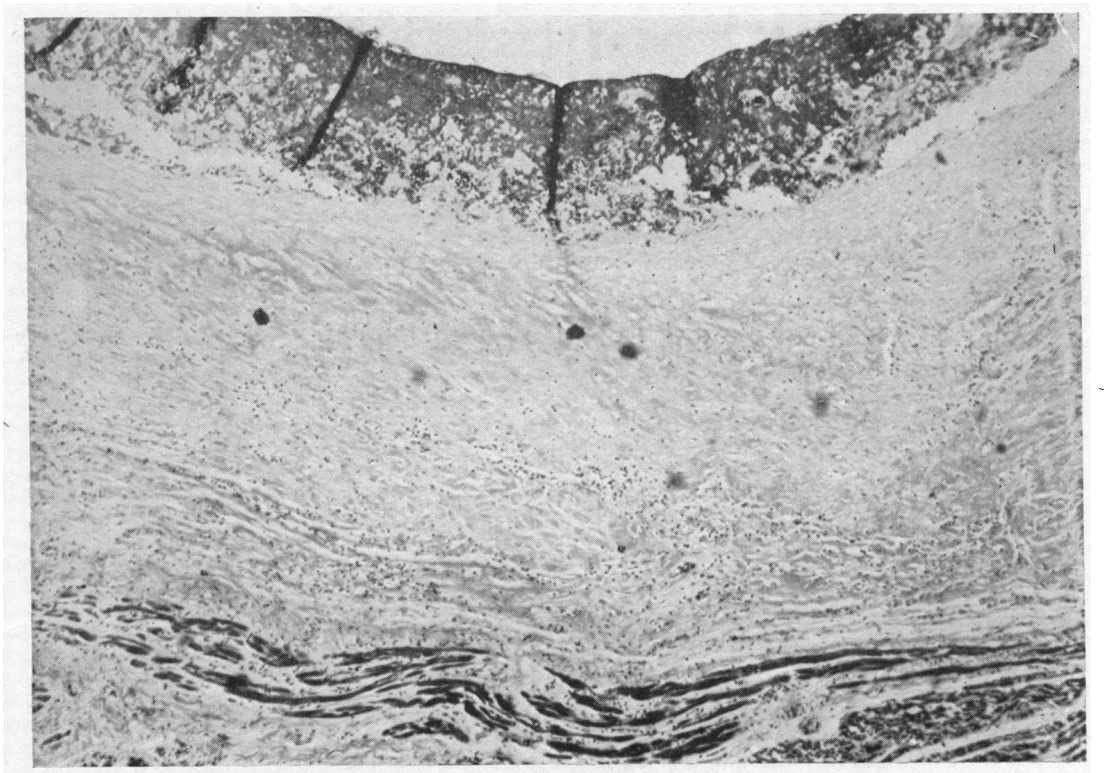

FIG. 21.—Section showing greatly thickened ventricular endocardium. Note the thin layer of mural thrombus, the layer of acellular fibrous tissue and the deeper zone of moderately cellular fibrous tissue. Fibrous tissue is invading the myocardium. Magnification, ×37. Case 6.

of calcium when present were in this layer. Deep to this was an intermediate zone of loosely-textured fibrous tissue containing an occasional macrophage, lymphocyte, or plasma cell, but rarely polymorphonuclear leucocytes or eosinophils. Next to the myocardium there was invariably a zone of small blood vessels, often with a few chronic inflammatory cells; we have called this the granulation tissue layer (Fig. 22). In this layer and in the layer above it, surviving degenerate muscle fibres were seen on occasion, usually in bundles but sometimes in isolation. Areas of irregular elastosis were rarely seen and when present were scanty and irregular in contrast to the picture in congenital fibro-elastosis.

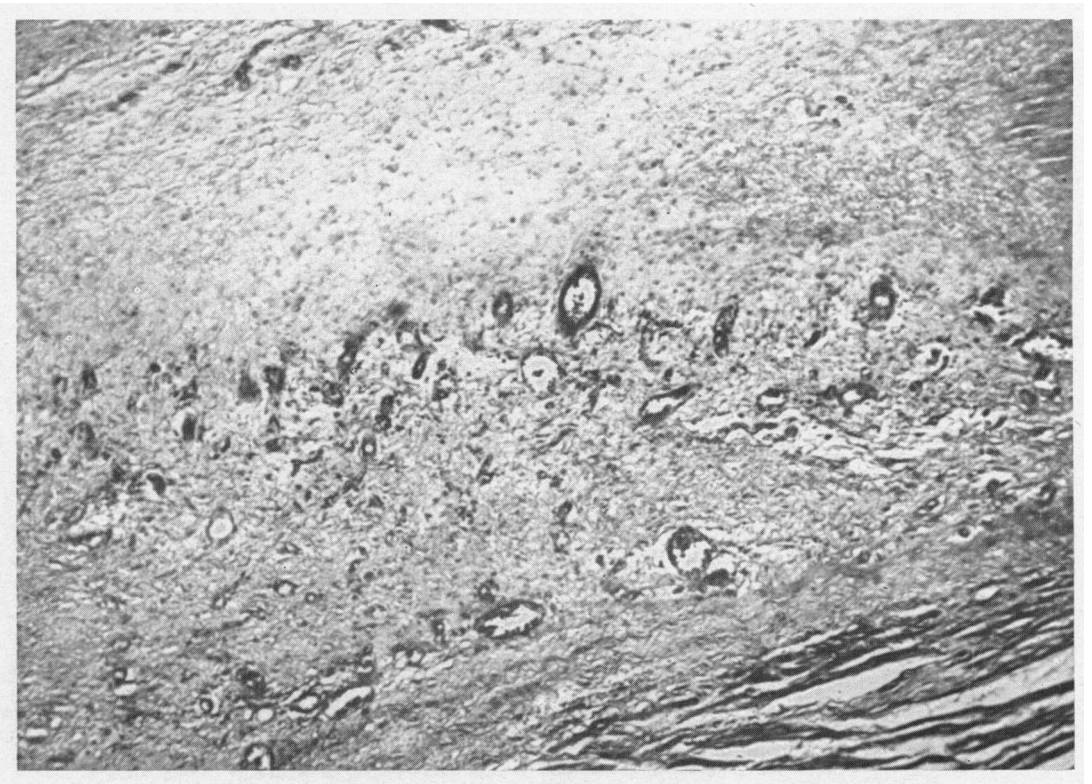

FIG. 22.—Granulation tissue layer, between the fibrous endocardium and the myocardium; many small blood vessels are present and some chronic inflammatory infiltration.

Myocardium. The inner third of the myocardium showed the greatest abnormality both in its interstitial cells and parenchyma. Bands of fibrous tissue extending inwards from the fibrosed endocardium penetrated this region of the myocardium, cutting off bundles of myocardial fibres which showed degenerative changes. All hearts showed more or less fibrosis in the myocardium, and it is for this reason that we use the term endomyocardial fibrosis. In these fibrous bands many small blood vessels were seen but also numerous thin-walled, dilated vascular channels. We take these to be thebesian veins and arterio-luminal vessels (Wearn, 1941) which had become dilated from obstruction by endocardial fibrosis (Fig. 20). The myocardial fibrosis seems to develop around these vessels. The myocardial fibres themselves showed a combination of the following changes, atrophy with wavy loss of sarcoplasm, hyalin changes, interfibrillary œdema (" moth-eaten " fibres), and interstitial œdema. The nuclei were commonly enlarged and hyperchromatic and were often sharply rectangular or cigar-shaped; such nuclear changes were present in 27 of the 32 hearts. Special stains did not show fat or excess of glycogen. These muscle fibre abnormalities were found

in all chambers irrespective of the presence or degree of endocardial fibrosis, but were always most marked in the subendocardial region. Despite these degenerative changes acute necrosis of fibres and evidence of their removal was not seen.

A mild infiltration of the myocardium with lymphocytes and macrophages was common; it was abundant in 5, but absent in 18 ventricles. Polymorphonuclear infiltration was very unusual and pigmented macrophages were not seen. There was no evidence of Aschoff bodies, fibrinoid necrosis, or verrucose angeitis, nor of parasitic infestation.

Coronary Arteries. No abnormalities have been seen in the major coronary vessels but, where the endocardial fibrosis was extremely advanced, obliterative changes were sometimes seen in the smaller vessels.

Histopathology of Valves and Atria

Valvular Apparatus. Abnormalities were only found in the atrioventricular valves with one exception in which there was some thickening of an aortic cusp. The papillary muscles showed the same changes as in the ventricular walls, save that replacement of the muscle fibres by fibrous tissue was commonly more severe. Sometimes the papillary muscle was found to have become a cone of pure white fibrous tissue. The thickening of the chordæ was due to an increase of fibrous tissue on the surface; the deeper portion was cemented to the mural endocardium by organizing fibrous tissue. The valve cusps were similarly affected, being sealed to the mural endocardium by organizing fibrous tissue with deposition of fibrous tissue on their surface.

The characteristic vegetations of a bacterial endocarditis were found on cusps and chordæ in 5 of the 23 damaged mitral valves. Two of the thrombi in the right auricle had become terminally infected. One case had extensive bacterial endocarditis super-imposed on a patch of left ventricular endocardial fibrosis.

Atria. The myocardial changes described in the ventricular walls were also found in the atria, but often extending through the whole thickness of the muscle; such changes were seen in the absence of endocardial changes. Adherent organizing thrombus commonly filled the interstices of the musculi pectinatæ of the right atrium and occasionally covered the smooth muscle layer in the left atrium. Endocardial fibrosis was less frequently seen in the atria as compared with the ventricles and when present was smaller but might still show a granulation tissue layer.

To summarize, there is fibrosis of the endocardium often with thrombus formation, and underneath this fibrous tissue is a vascular layer with a few chronic inflammatory cells. Fibrous bands invade the myocardium, particularly in relation to thin-walled blood vessels. There is atrophy and degeneration of muscle especially in the sub-endocardial region. No arterial occlusion or parasitic invasion is seen, nor is there any clear evidence of infection.

Extra-cardiac Pathology

Study of the extra-cardiac lesions in these necropsies has thrown no light on the cardiac condition. A variety of lesions was seen that might be found amongst any thirty necropsies at Mulago Hospital. Pyelo-nephritis, nephritis, or some renal scarring was present in five cases. Septic renal and splenic infarcts were found in the organs of a patient who had died of bacterial endocarditis; but apart from this and one old infarct in a spleen, infarction was not seen. Two spleens showed nodules of uncertain ætiology of a type often found in Africans. Sickling of the red blood corpuscles was seen at necropsy in three cases only. Active tuberculosis was found in two cases and pneumonia in seven. Cirrhosis was present in four and an excess of periportal fibrous tissue was present in the livers of the others. The adrenals, thyroid, and pituitary glands were usually atrophic by European standards, but these findings, as well as liver fibrosis, are common in Uganda Africans. Subcutaneous œdema was almost invariable and often there were large serous effusions. Syphilis was no more frequent than it is in other patients and was specifically excluded in many. Lesions due to past malnutrition were common, but no more than in other Africans in this hospital.

In summary, the only lesions commonly observed outside the heart were those of congestive cardiac failure and terminal infections.

Summary of Clinical Findings

The clinical picture has been found, not unexpectedly, to depend on the site of the major lesion (Table I). When this is in the left ventricular endocardium, left and right heart failure appear without murmurs or other distinguishing features; diagnosis can be made only by exclusion. When the left ventricular lesion is more advanced, the mitral valve is involved and mitral incompetence results. This is the most easily diagnosed form of endomyocardial fibrosis and probably the commonest. These patients have a loud, commonly high-pitched, apical systolic murmur and thrill, and a moderately enlarged left atrium which may show systolic expansion.

When the main lesion is in the right ventricle the patient develops ascites and œdema without dyspnœa, and is found to have a loud third heart sound but no murmurs. When the tricuspid valve is involved in the fibrosis, the signs of tricuspid incompetence are added. Combinations of these clinical patterns are often seen. A detailed description of the clinical picture was the subject of an earlier paper (Ball *et al.*, 1954).

Cause of Death. Thirteen patients died as a direct result of their endomyocardial fibrosis; eight from heart failure alone, four with heart failure and bacterial endocarditis, and one from bacterial endocarditis alone. Ten patients died from intercurrent infection (pneumonia in six) during the course of chronic heart failure. The remaining six died from various causes, but without any obvious signs or symptoms of heart disease. Three of these had such advanced lesions, both macroscopically in the left ventricular endocardium and the mitral valve and microscopically in the muscle fibres, that it is difficult to understand why gross heart failure had not followed.

Pathogenesis

The provocative agent or agents and the site and character of the initial lesions in this disease are alike unknown. Possible ætiological factors have been discussed elsewhere (Williams *et al.*, 1954). It is clear, however, that there is no great loss of muscle tissue such as would follow severe necrosis of muscle, and the presence of a granulation tissue layer indicates that a process of organization has been going on. It is difficult to believe that this could be anything else but the organization of thrombotic material such as can sometimes be seen in progress in the centre of a nodule of fibrous tissue. Such a process is more commonly seen in the atria. Thrombosis in the ventricles is seen to be more frequently superimposed on the mural surface of an extensive fibrous plaque. It seems likely, therefore, that thrombosis occurs in two stages, at an early stage and at a much later stage as a result of ventricular immobilization. This indication of a vicious circle fits in with the slow inexorable nature of the disease. One probable effect of the endocardial thrombosis and fibrosis is obstruction of the thebesian and arterio-luminal vessels, and dilatation of these vessels is a feature of the histological picture. If such obstruction does develop, and this may be a crucial factor, the lesion will be self-aggravating, the hypoxia of obstruction adding its insult to the injuries already received by the myocardium.

If thrombosis is the factor that initiates the endocardial fibrosis, one must ask what could have caused the mural thrombus. It is generally held that mural thrombus will only be deposited on abnormal endocardium, and with this we agree. In what way could such initial endocardial damage be produced? It might be the result of some direct injury. The relative delicacy of the endocardium of the inflow tract (Nagayo, 1909) the region predominantly involved, suggests that some factor operates directly on the inflow tract endocardium that spares the coarser outflow tract endocardium. Direct mechanical injury to the endocardium has been held responsible for the fibrotic patches of endocardium associated with congenital defects (Taussig and Semans, 1940) and with valvular incompetence (Schmincke, 1908; Saphir, 1930); but there is no evidence that such

factors are operating in endomyocardial fibrosis, save perhaps in some of the left atrial lesions associated with mitral incompetence.

Alternatively the endocardium could be damaged as a result of spread from an initial myocardial lesion. Support for this view comes from the existence of lesions in the subendocardial muscle in chambers and regions that show no endocardial fibrosis, as well as in those that do. Another supporting observation is that in the valves, where the endocardium is not in contact with the heart wall, isolated lesions are not seen; valvular fibrosis is always in continuity with lesions of the adjacent mural endocardium.

It seems likely, therefore, that the sequence of events is as follows: initial damage to the subendocardial muscle, spread of process to the endocardium, primary mural thrombosis, organization of the thrombus to fibrous tissue, obstruction of communicating vessels by thrombus and fibrous tissue causing increased myocardial damage, and finally secondary mural thrombus when the fibrotic lesion is extensive. It is not suggested that this chain of events is complete or that it is proved, and there are certain puzzling discrepancies.

One feature of our cases has been the extraordinary infrequency with which embolic lesions have been encountered, despite much mural thrombosis, even in late cases. If mural thrombosis is an early lesion, we can only suppose that the thrombi become speedily and firmly attached and perhaps because of the lack of cardiac hypertrophy, the feebleness of the heart's action, or because of the rapidity with which endothelium can grow over fibrin thrombi (Duguid, 1949), they are infrequently dislodged. Our search for early cases in acute heart failure or in accidental deaths has not so far revealed evidence of the squence of changes we have postulated. While mural thrombosis has been reported in South Africa to be frequent (Higginson *et al.*, 1952), the lesions of advanced endomyocardial fibrosis are very rare (Gillanders, 1954).

Discussion

The recurring pattern of lesions that we have encountered in these hearts fits into none of the accepted varieties of heart disease. In reviewing the literature we find reports of some conditions that are very similar; they would, indeed, have been accepted by us on our criteria of selection, " the presence of mural endocardial fibrosis, easily visible to the naked eye and due to none of the recognized causes." This does not of course presuppose pathogenetic or ætiological identity. We are reviewing these reports under three headings.

(1) *Reports of Hearts Closely Similar to Endomyocardial Fibrosis*

These reports fall into two groups—those reported from Africa, and those from Europe and America, the latter mainly reports of isolated or small groups of cases.

African Cases. Bedford and Konstam (1946) described 40 cases of unexplained heart failure in East and West African soldiers, and in 17 necropsied cases they report " some had an obvious and extensive subendocardial fibrosis . . . adherent to which was organized ante-mortem clot." O'Brien (1954) has described 25 patients with heart failure from the Sudan with necropsy evidence of endomyocardial fibrosis in two; in one of these there was involvment of the tricuspid valve such as we have described.

Personal communications have revealed that similar cases are fairly common in Southern Rhodesia (Gelfand, 1954) and Northern Rhodesia (Buck, 1954). Reports of three white patients who contracted the disease have come from West Africa (Edge, 1946; Gray, 1951) and one of us has seen a typical case there, in an African from the Gambia. Although we have not full details about many of these cases, there is strong cumulative evidence that the disease is widespread in Africa.

Non-African Cases. From outside Africa have come a small number of case reports, mainly from the United States and from Switzerland. American reports include those of Smith and Furth (5 cases, 1943), McNicol *et al.* (2 cases, 1953), Fienberg and Holzmann (1951), and McKusick

and Cochran (1952). In the last two reports there was striking obliteration of the right ventricle, close in its resemblance to the lesion we have described.

The reports from the European continent have come mainly from Switzerland. In 1936 Löffler described two patients with extensive endocardial fibrosis: both had a high blood eosinophilia. Somewhat similar cases, sometimes without the eosinophilia, have been described from Switzerland (Egger, 1944; Roulet, 1944; and Berblinger, 1948); from Germany (Mumme, 1940); from France (Landau *et al.*, 1927; Lenègre and Gerbaux, 1952); and from Austria (Fossel, 1942). The identity of these lesions with each other and with endomyocardial fibrosis is not easy to establish, and the significance of the eosinophilia is not certain. In some of the Swiss cases it disappeared during certain stages of the disease. It was common but not constant in our Uganda cases, but some of these had helminthic infestations capable of causing high degrees of eosinophilia. Personal conversations with Swiss colleagues has shown that they have doubts as to Löffler's disease and endomyocardial fibrosis being identical diseases. Pending further observations, we therefore reserve judgment on this matter.

(2) *Reports of Hearts that Show only Some Similarity to Endomyocardial Fibrosis*

Certain conditions have been reported from other parts of the tropics in which the cardiac abnormalities include mural thrombus and some degenerative myocardial lesion. A slight degree of endocardial fibrosis, usually beneath the thrombus, is present in some. Normet (1937) in his description of the lesions in the disease which had been called Bouffissure d'Annam, and which is now thought to be adult kwashiorkor (Trowell *et al.*, 1954), described mural thrombosis of the ventricles with vacuolation of the myocardial fibres but without fibrosis. It was seen in patients with fatty livers and with atrophic pancreatic lesions. The disease described from South Africa by Gillanders and his associates (Gillanders, 1951; Higginson *et al.*, 1952) was also seen in patients who had liver disease presumed to be due to malnutrition. Their descriptions of the changes in the myocardial fibres are similar to those we have described; there was marked mural thrombosis, in some cases with minor degrees of subjacent fibrosis. Embolic phenomena were common and severe degrees of endocardial fibrosis with valvular involvement were not seen. It is possible that these were severe early manifestations of a process that develops more slowly and silently to severe fibrosis in Uganda Africans. We have seen similar cases to these in Uganda (Davies, 1950), but as previously remarked there are some obscurities which further observations may resolve. In Uganda embolic phenomena are very unusual and severe liver disease, while often present, is not so evident as in the South African natives.

The report of Becker *et al.* (1953) is not easy to evaluate. They do not refer to the cases described by Gillanders. They have reported a heterogenous group of patients, of different races, who died of heart failure with mural thrombosis in the ventricles. There was little evidence of fibrosis and no mention of valvular lesions. From their studies, and from the use of histochemical methods, they concluded that they were dealing with a cardiac collagenosis. We would interpret their findings rather differently and can see nothing in our own specimens to suggest that they fall into the collagenosis group.

The cases of mural thrombosis in South Africans and in Annamites may well be related to endomyocardial fibrosis, but we think it is premature to insist at this stage that there is an association.

(3) *Reports of Cardiac Conditions that though Distinct Show Endocardial Fibrosis of some kind*

Congenital Endocardial Fibroelastosis. This condition is predominantly a disease of early childhood (Craig, 1949; Gowing, 1953), but can also occur in adults, and most writers believe that it is congenital in origin. Macroscopically there are certain resemblances to endomyocardial fibrosis but aortic and pulmonary valve lesions are common and the process is one that predominantly involves the out-flow tract endocardium.

Histologically there are distinct differences, as has been shown by Thomas *et al.* (1954). In

endomyocardial fibrosis there is a lack of the characteristic elastosis, thrombosis seems to be an integral part of the lesion, and there is evidence of a destructive type of lesion rather than a proliferative lesion such as is seen in fibroelastosis. In both diseases it seems that the thickened endocardium obstructs the arterio-lluminal circulation (Weinberg and Himmelfarb, 1943).

Rheumatic Carditis. This condition is not uncommon in Africans and, pathologically at least, it resembles the disease as seen in Europe. The endocardial fibrosis is usually confined to the valves but it may spread to involve to a minor degree the mural endocardium, particularly in the left atrium and ventricle. In endomyocardial fibrosis, the spread is in the reverse direction, from the mural endocardium to the valve. The mitral lesions of one disease can to some extent mimic those of the other disease, especially those rheumatic valves showing pure incompetence and the " endomyocardial " valves showing stenosis. The aortic valve, so frequently affected in rheumatism is rarely affected in endomyocardial fibrosis. No histological evidence of past or present Aschoff bodies has been found in endomyocardial fibrosis. The two diseases would seem to resemble each other in the slow relentless progression of the fibrosis, and the mechanism of fibrin deposition on a damaged surface described by Magarey (1951) may well operate in both diseases.

Ischæmic Heart Disease. Cardiac infarction may heal with endocardial scarring, but in endomyocardial fibrosis no lesions have been found in the major coronary arteries, and the distribution of the endocardial and of the myocardial fibrosis is unlike that found to result from cardiac infarction. The subendocardial distribution of the muscle lesions recalls the acute coronary insufficiency of severe anæmia (Master *et al.*, 1950) but anæmia has not been marked in our cases nor has it figured prominently in their past histories. The possible effects of the endocardial fibrosis and thrombosis on the arterio-luminal vessels has been mentioned. An isolated patient with extensive endocardial fibrosis associated with multiple infarcts was recently described (Hughes and Smith, 1953).

Diffuse Collagen Diseases. The cardiac lesions that have been described in diffuse lupus erythematosus (Gross, 1940) and scleroderma (Weiss *et al.*, 1943; East and Oram, 1947) sometimes show a slight degree of fibrosis extending to the endocardium, but the myocardial fibrosis predominates. A recent African patient with scleroderma heart disease showed lesions no different from those reported in Europeans.

Virus Myocarditis. Although many viruses are known to cause myocarditis in man (Saphir, 1953; Lyon, 1947) the endocardium is not particularly attacked. In rabbits myxoma virus causes a myocarditis in which there is " striking thickening of the endocardium of the ventricles with obliteration of all the crevices between the trabeculæ " (Pearce, 1954). Other experimental virus infections cause thickening of valve cusps and myocardial calcification (Pearce, 1950). Whether viruses can produce such lesions in man is not known, but they point to the possibility that virus infection may be an ætiologic factor in endomyocardial fibrosis.

Heart Disease from Malnutrition. One or two reports suggest that malnutrition may be responsible for endocardial fibrosis (Smith and Furth, 1943; Brinkman and Prior, 1950). There are many nutritional disorders in man and animals that can cause myocardial lesions, but endocardial fibrosis is a feature in none. Prominent among these is beri-beri, which is exceptionally rare in Uganda, and our patients with endomyocardial fibrosis have shown no response to vitamin B1. The conditions described in South Africa and Annam have been mentioned above.

Comment. This review of the different types of endocardial fibrosis indicates that virus infection, some antigen-antibody reaction, and malnutrition are possible ætiological factors in the form of endocardial fibrosis common in Uganda.

SUMMARY

Endomyocardial fibrosis is one of the commonest causes of heart failure in Africans in Uganda. A description of the pathology, macroscopic and microscopic, is given, based on a series of 32 necropsies.

The lesions of the left heart consist essentially of fibrosis of the endocardium and underlying myocardium at or near the ventricular apex. Thrombus is commonly deposited on the surface of the abnormal endocardium and calcification is not infrequent in its depths. This fibrous tissue tends to spread up to involve the papillary muscles, chordæ, and cusps of the mitral valve; the process is particularly liable to involve and immobilize the posterior mitral cusp. Incompetence is the usual result of the mitral lesion; stenosis follows occasionally. Bacterial endocarditis of this valve is not uncommon terminally. The left atrial endocardium sometimes shows small patches of fibrosis.

The right heart lesions are in general similar to those on the left. Ventricular endocardial fibrosis is as constant as it is on the left, but usually the lesions are less extensive. When the fibrosis does extend to involve more than one-third of the ventricle it produces an obliteration of the in-flow tract which has no parallel on the left side. The tricuspid valve lesion is similar to the mitral but less extensive. It also produces incompetence and occasionally stenosis. The right atrium commonly contains ante-mortem thrombus; some of the small fibrotic patches of the atrial endocardium are directly connected with organizing thrombus.

Histological studies show massive thickening of the endocardium, the major part of which consists of acellular fibrous tissue; the deepest layer contains many small blood vessels with some chronic inflammatory cells. Strands of fibrous tissue penetrate the myocardium to a varying depth. Degenerative changes are nearly always present in the myocardial fibres even in regions and chambers that show no endocardial lesions.

No significant lesions are found outside the heart, except for those resulting from heart failure or terminal infection.

The clinical features and the cause of death are briefly reviewed.

The nature of the pathogenesis is discussed, and reasons are given for thinking that the lesion may start in the sub-endocardial muscle with subsequent spread to the endocardium. The causative agent is unknown. Organization of thrombus is thought to play an important part in the development of the massive fibrosis.

Reports of similar conditions occurring in Africa, North America, and Europe are surveyed. The other causes of fibrosis of the endocardium are also briefly reviewed.

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REFERENCES

Ball, J. D., Williams, A. W., and Davies, J. N. P. (1954). *Lancet*, **1**, 1049.
Becker, B. J. P., Chatgidakis, C. B., and van Lingen, B. (1953). *Circulation*, **7**, 345.
Bedford, D. E., and Konstam, G. L. S. (1946). *Brit. Heart J.*, **8**, 236.
Berblinger, W. (1948). *Schweiz. med. Wschr.*, **78**, 829.
Brinkman, G. L., and Prior, I. A. M. (1950). *N.Z. med. J.*, **49**, 266.
Brigden, W., and Leathem, A. (1953). *Brit. Heart J.*, **15**, 55.
Brock, R. C. (1952). *Brit. Heart J.*, **14**, 489.
Craig, J. M. (1949). *Bull. Internat. Assoc. med. Mus.*, **30**, 15.
Davies, J. N. P. (1948*a*). *E. Afr. med. J.*, **25**, 10 and 454.
—— (1948*b*). M.D. Thesis. Bristol.
—— (1950). Liver Injury. *Proc. 9th Conference, Josiah Macy Foundation*, New York.
Dick, G. W. A. (1947). *Ann trop. Med. Parasit.*, **41**, 48.
Duguid, J. B. (1949). *Lancet*, **2**, 925.
East, T., and Oram, S. (1947). *Brit. Heart J.*, **9**, 167.
Edge, J. R. (1946). *Lancet*, **2**, 675.
Egger, P. (1944). *Schweiz Z. Path. Bakt.*, **7**, 237.
Fienberg, R., and Holzman, D. (1951). *Bull. internat. Assoc. med. Mus.*, **32**, 34.
Fossel, M. (1942). *Beitr. Path. Anat.*, **107**, 241.

Gillanders, A. D. (1951). *Brit. Heart J.*, **13**, 177.
—— (1954). *Lancet*, **2**, 657.
Gowing, N. F. C. (1953). *J. Path. Bact.*, **65**, 13.
Gray, I. R. (1951). *Brit. Heart J.*, **13**, 387.
Gross, L. (1940). *Amer. J. Path.*, **16**, 375.
Higginson, J., Gillanders, A. D., and Murray, J. F. (1952). *Brit. Heart J.*, **14**, 213.
Hughes, A., and Smith, G. H. (1953). *Brit. Heart J.*, **15**, 450.
Landau, A., Feigin, M., Jochweds, B., and Marjanko, T. (1927). *Bull. Mém. Soc. Méd. Hôp., Paris*, **51**, 484.
Lenègre, J., and Gerbaux, A. (1952). *Arch. Mal. Coeur*, **45**, 289.
Löffler, W. (1936). *Schweiz. med. Wschr.*, **66**, 817.
Lyon, E. (1947). *Medical Record*, **160**, 403.
McKusick, V. A., and Cochran, T. H. (1952). *Bull. Johns Hopk. Hosp.*, **90**, 90.
McNichol, C., MacMahon, E., Benenson, A. S., and Winship, T. (1953). *Circulation*, **7**, 497.
Magarey, F. R. (1951). *Brit. med. J.*, **1**, 856.
Master, A. M., Dack, S. Horn, H., Freedman, B. I., and Field, L. E. (1950). *Circulation*, **1**, 1302.
Mumme, C. (1940). *Z. klin. Med.*, **138**, 22.
Nagayo, M. (1909). *Beitr. Path. Anat.*, **42**, 283.
Normet, C. (1937). *Bull. Soc. sci. Hyg. aliment.*, **25**, 153.
O'Brien, W. (1954). *Brit. med. J.*, **2**, 899.
Pagnoni, A., and Goodwin, J. F. (1952). *Brit. Heart J.*, **14**, 451.
Pearce, J. M. (1950). *Pathogenesis and Pathology of Viral Disease*. Ed. by Kidd, J. C., Columbia University Press, N.Y.
—— (1954). Personal communication.
Roessle, R., and Roulet, F. C. (1932). *Mass und Zahl in der Pathologie*. Springer, Berlin.
Roulet, F. C. (1944). *Schweiz. med. Wschr.*, **74**, 155.
Saphir, O. (1930). *Amer. J. Path.*, **6**, 733.
—— (1953). *Pathology of the Heart*. Ed. Gould, Thomas, Springfield.
Schmincke, A. (1908). *Virchows. Arch. path. Anat.*, **192**, 50.
Smith, J. J., and Furth, J. (1943). *Arch. intern. Med.*, **71**, 602.
Taussig, H. B., and Semans, J. H. (1940). *Bull. Johns Hopk. Hosp.*, **66**, 156.
Thomas, W. A., Randall, R. V., Bland, E. F., and Castleman, E. (1954). *New Engl. J. Med.*, **251**, 327.
Trowell, H. C., Davies, J. N. F., and Dean, R. F. A. (1954). *Kwashiorkor*. Arnold, London.
Wearn, J. T. (1941). Harvey Lecture. New York Acad. Med., Series 36.
Weinberg, T., and Himelfarb, A. J. (1943). *Bull. Johns Hopk. Hosp.*, **72**, 299.
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.