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Pancarditis with Valvulitis in Endomyocardial Fibrosis (=EMF) and in Human African Trypanosomiasis (=HAT)

A Comparadive Histological Study of Four Ugandan Cases

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Summary. The study compares the histotopographical lesions of two cases of endomyocardial fibrosis with those of two hearts in sleeping sickness, all of them from Uganda.

There was considerable overlapping of the fibrosed zones in endomyocardial fibrosis and the corresponding sites occupied by the chronic inflammatory process in trypanosomiasis. There was a tendency towards fibrosis in the hearts of trypanosomiasis while, in endomyocardial fibrosis, there were mild focal chronic cellular infiltrations. This overlapping and to some extent similarities would suggest that the two conditions may only differ in evolution in time and intensity and that they may be the result of the same inflammatory process.

Stipulating a cardiac tropism for African trypanosomes, it is suggested that some African cases of endomyocardial fibrosis may be merely burnt-out lesions of trypanosomal pancarditis.

Previous descriptions of carditis in human African and American trypanosomiasis are briefly reviewed, and the present findings are discussed in view of a possible trypanosomal aetiology in some African cardiomyopathies.

Key words: Cardiomyopathy – Conducting system – Pancarditis – Trypanosomiasis – Valvulitis.

Introduction

Pancarditis in Africans dying from sleeping sickness due to *Trypanosoma gambiense* was described by Thomas and Breinl in 1905; later Armengaud and

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Diop (1960) found trypanosomes in patients suffering from congestive cardiomyopathies of unknown origin and responding favourably to a trypanocidal treatment. Bertrand (1974) advanced the hypothesis that some of the unexplained African cardiomyopathies might be parasitic in origin, and Blackett and Ngu (1976) reported high serological titres for trypanosomiasis in congestive cardiomyopathies from the Cameroon. Histologically Poltera et al. (1976) observed a pancarditis and a generalised valvulitis in human African trypanosomiasis (=HAT) in Uganda. In addition Farrer-Brown and Tarbit (1972b) reported on the occurrence of pancarditis in endomyocardial fibrosis (=EMF) and suggested that "more attention should be directed towards investigating the concept that EMF is a pancarditis". Since the original description of EMF by Davies (1948) in Uganda, no aetiological factor has been found to explain the pathogenesis of this condition. Recently, trypanosomes have been discovered in South and South-East Asia (Shrivastava and Shrivastava, 1974; Dissanaike et al., 1974) another area where cardiomyopathies of unknown origin, similar to those described in Africa, occur (Nagaratnam and Dissanayake, 1959; Fejfar, 1968).

The present study compares some histological aspects of two hearts of EMF with those of two hearts in HAT.

Material and Methods

Two hearts presenting macroscopical features of EMF and the hearts of two cases of HAT were collected by one of the authors (A.A.P.) in Uganda (Department of Pathology, Makerere University) and were examined in the Department of Pathology, University of Geneva, Switzerland. The study consisted of a systematic analysis of all valves and their appendages, as well as all layers of the heart. The apices and the conducting system were also studied. The material was formalin fixed, paraffin embedded and cut at 5 µ. The following stains were used: Haematoxylin and eosin, elastic-van Gieson, Pearl's stain, Giemsa, Gram, PAS and Masson's trichrome.

Results

Endomyocardial Fibrosis = EMF

For convenience, the EMF hearts are labelled as 1 and 2, and their macroscopical description is reported separately.

EMF 1. The heart (225 g) was of normal external configuration. The *epicardium* showed fibrous thickening at the left apex (7 × 4 mm), on the right ventricle (30 × 10 mm) and on the posterior wall of the right ventricle (25 × 5 mm).

The *right atrium* had intact trabeculae carneae, the foramen ovale was patent with a diameter of 2 mm; there was occasional endocardial thickening, mainly in the region of the septum. The right auricular appendage was free of thrombus.

The *right ventricle* was 4 mm thick in the outflow tract. The leaflets of the tricuspid valve were not thickened. Fibrous plaques were found at the ventricular insertion of the septal leaflet (10 × 4 mm) and at the insertion of the posterior papillary muscle (4 mm in ∅). Several small fibrous zones (up

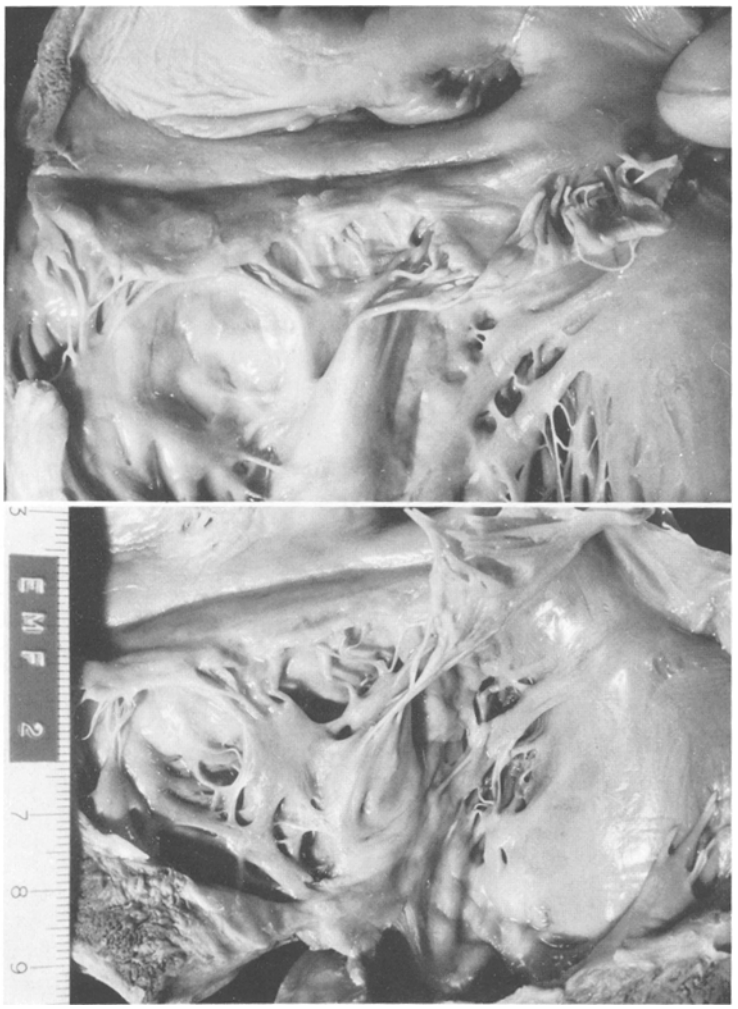

Fig. 1. a Marked fibrosis of the mitral valve and the retrovalvular region. The anterior leaflet presents only as a ridge, and the chordae tendinae are integrated into the mural endocardium, the fibrous plaque extending up to the insertion of the papillary muscle. Note left auricular hypertrophy with thickened endocardium (upper left corner). EMF 1. **b** Fibrous thickening of the anterior leaflet of the mitral valve and of some of the chordae tendinae. Note retrovalvular fibrosis. EMF 2

to 5 mm), mainly localised between the trabeculae carnae, were scattered in the retrovalvular endocardium of the posterior leaflet, between the septal papillary muscle and the apex; the latter was normal. The pulmonary outflow tract and the pulmonary cusps were also normal.

The wall of the *left atrium* measured 4 mm in thickness, and its endocardium was diffusely thickened presenting a smooth surface with loss of visible trabeculae. The left auricular appendage was free of lesions. The *mitral valve* was grossly altered, the posterior and anterior leaflet fixed to the side of the ventricle

leaving only a shrunken valvular ridge (2 mm). (Fig. 1 a). Several chordae tendineae of either leaflet and the papillary muscles were incorporated into a white fibrous plaque occupying the retrovalvular endocardium. A continuous plaque (1 mm thick) extended from both papillary muscles towards the apex involving almost all of the inflow tract.

The *left ventricle* (11 mm thick) was free of mural thrombus. On section fibrous tongues extended from the plaques of the posterior papillary muscle to half of the thickness of the myocardium; in the region of the anterior papillary muscle the tongues penetrated less deeply, and at the apex they remained superficial. The aortic outflow tract and aortic cusps were normal. The coronary ostia and the main coronary branches were free of atherosclerosis.

The macroscopical lesions were consistent with left ventricular EMF involving both mitral leaflets and to a minor degree the left apex and the left atrium; there was patchy endocardial fibrosis of the right ventricle without involvement of the apex or tricuspid valve.

EMF 2. The normal external configuration of this heart (290 g) was altered at the left ventricle where a depression or "notch" was apparent at either side of the apex with converging folds of the epicardial adipose tissue (right side $15 \times 5 \times 2$ mm; left side $7 \times 5 \times 3$ mm). A similar depression was noted at the right apex ($15 \times 7 \times 3$ mm).

The *epicardium* presented thick fibrous adhesions on the anterior wall of the right ventricle (6×4 cm) and on the posterior aspect ($3 \times 2{,}5$ cm).

The *right atrium* showed well separated trabeculae carneae without thickening of the endocardium. There was no thrombosis in the right auricular appendage. The leaflets of the tricuspid valve, the chordeae tendineae and the tip of the papillary muscles were normal. The retrovalvular endocardium of the anterior leaflet showed diffuse fibrous thickening. At the insertion of all papillary muscles, fibrous endocardial plaques were observed which extended towards the apex, the latter being free of thrombosis.

The dilated *right ventricle* had hypertrophic trabeculae carneae and a thickened wall (6 mm). The outflow tract and the pulmonary cusps were normal.

The wall of the *left atrium* appeared to be thickened. The endocardium was whitish and smooth, but no trabeculae carneae could be identified. The auricular appendage was free of lesions. The leaflets of the mitral valve appeared normal, but one portion of the anterior leaflet was slightly shortened with the corresponding chordae tendineae appearing shorter and thicker, and three being incorporated into the retrovalvular endocardium (Fig. 1 b). There was a diffuse whitish plaque covering the retrovalvular endocardium of either leaflet and permitting no distinction of the trabeculae carneae; it extended and surrounded portions of the anterior papillary muscle, the posterior being free of fibrosis at its insertion.

There were fibrous plaques starting near the papillary muscles and joining each other at a retracted apex of the *left ventricle* where the endocardium was thickened (up to 4 mm). The apical cavity was shrunken and filled at its tip with a small organising mural thrombus. The fibrous tongues penetrated the adjacent myocardium from the plaques to its inner third. The aortic outflow

tract was free of endocardial lesions and the aortic cusps were smooth. The coronary ostia and the arteries were free of atherosclerosis.

In summary, this heart had left ventricular EMF involving the mitral valve with both appendages and a fibrosed apex with superimposed mural thrombosis. There was right ventricular EMF with apical, and to a lesser extent, retrovalvular involvement.

Histology of the EMF Cases

As the histology is almost identical in the two cases, we report them conjointly.

The atrioventricular leaflets of both *valves* showed in case 1 isolated infiltrates of chronic inflammatory cells, mainly localised on the flow side or at the insertion of the leaflet on the valve ring (Fig. 2a). These cells consisted of histiocytes, lymphocytes, plasma cells, macrophages and occasional mastocytes. No parasites, bacteria or fungi were observed.

In case 2 some isolated macrophages were seen in the leaflets of both valves. There was no vascularisation of the distal portions of the leaflets. At the insertion of the tricuspid there were dilated capillaries in case 1 (septal leaflet) and a fresh haemorrhage in case 2 (anterior leaflet). The collagen fibres of the anterior leaflet of the mitral valve of case 2 were disorganised. Similarly, isolated macrophages with occasional plasma cells were seen in both types of cusps. In addition, there was in case 2 a cellular infiltration on the flow side of one pulmonary cusp; there was absence of capillaries. The chordae tendineae showed some foci of chronic inflammatory cells in both cases (Fig. 2c), in some areas the chordae were completely integrated into the mural endocardium.

The *endocardium* was thickened at the sites of macroscopical plaques and this appeared as a heavy bandlike fibrosis where hyalinised collagen was intermixed with elastic fibres and a few smooth muscle cells. Occasionally, scattered inflammatory cells could be observed in these areas. The small isolated macroscopical lesions corresponded to cushion-like thickenings of the endocardium (Fig. 2e) or trabeculae carneae showing fibrosis as described above. In areas, foci of chronic cellular infiltrates were found in the endocardium or subendocardium (Fig. 2g); these consisted of histiocytes, lymphocytes, macrophages, plasma cells and occasional mastocytes; eosinophils were rarely seen. In one instance, a plasma cell containing Russel bodies was noted. In case 1, there was a circumscribed subendocardial haemorrhage, and in case 2, macrophages loaded with iron pigment were found. In this latter case the endocardium was most thickened at the apex of the left ventricle, where there was a superimposed organising thrombus; beneath the scar, there were dilated capillaries and veins.

The *myocardium* was dissected by fibrous bands coming from the endocardium (Fig. 3a). However starlike areas of fibrosis surrounding muscle fibres in various stages of myocytolysis were observed throughout the myocardium (Fig. 3c). These areas of fibrosis were occasionally associated with chronic inflammatory cells. Another lesion observed in case 1 consisted of chronic inflammatory cells in the interstitium surrounding myocardial fibres which were in various phases of necrosis (Fig. 3e). One morular cell was observed in the

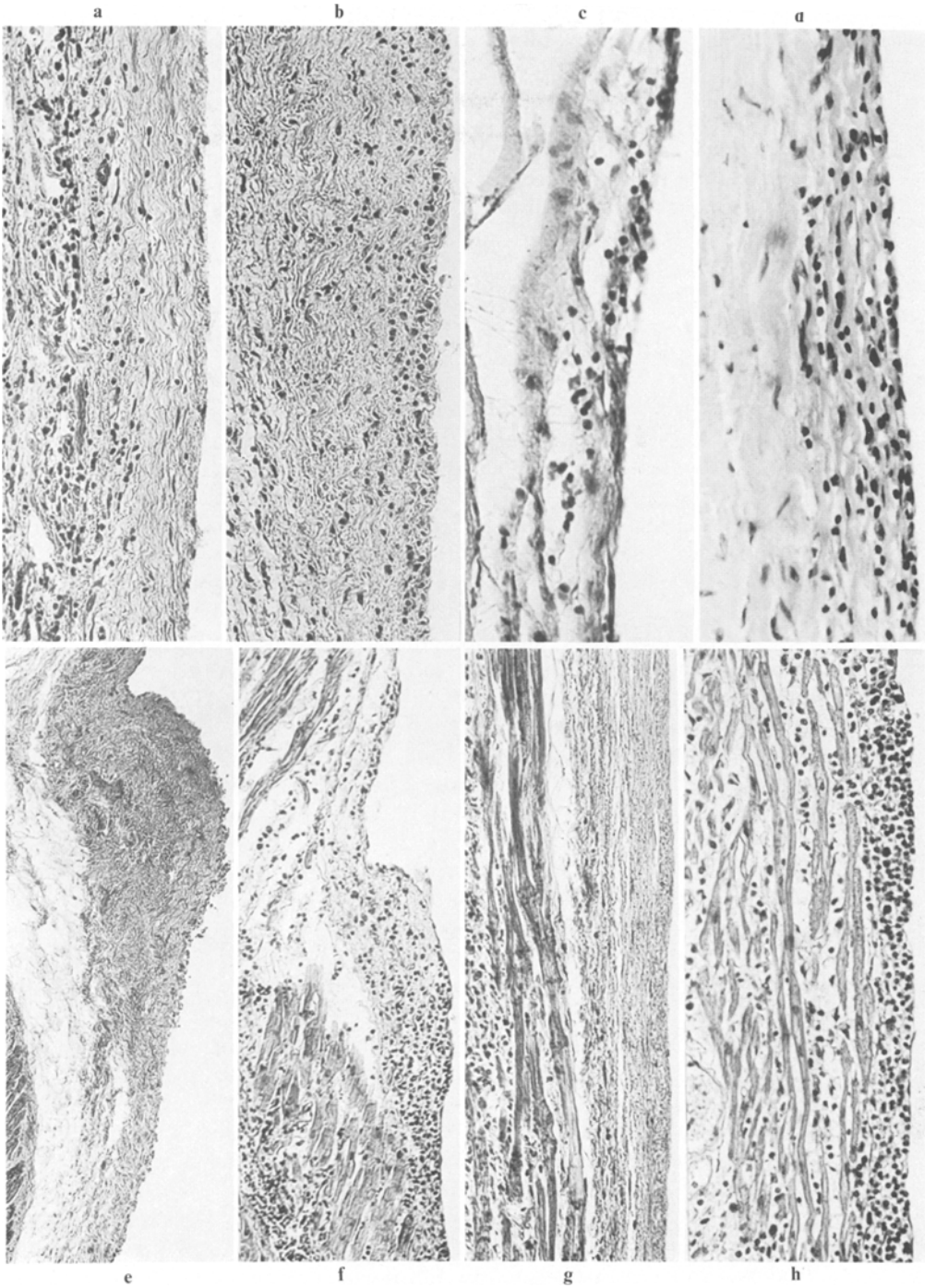

Fig. 2a–h. Comparison of histological changes in the valves, valvular appendages and mural endocardium in EMF and HAT. **a** Septal leaflet of the triscuspid valve showing several foci of chronic cellular infiltrates. EMF 1, HE, ×160. **b** Posterior leaflet of the tricuspid valve with a superficial chronic cellular infiltration on the flow side. HAT, case 1, HE×160. **c** Chorda tendinae of the anterior leaflet of the mitral valve with superficial cellular infiltration. EMF 1, HE, ×160. **d** Chorda tendinea of the anterior leaflet of the mitral valve with superficial mononuclear cell infiltration. HAT, case 1, HE, ×160. **e** Isolated cushionlike fibrosed zone of the mural endocardium with very scanty inflammatory cells. EMF 1, HE, ×63. **f** Patchy cellular infiltrates of the mural endocardium. HAT, case 1, HE, ×63. **g** Fibrous thickening of the mural endocardium with the presence of underlaying chronic cellular infiltration in the myocardium. Note thinning and contraction

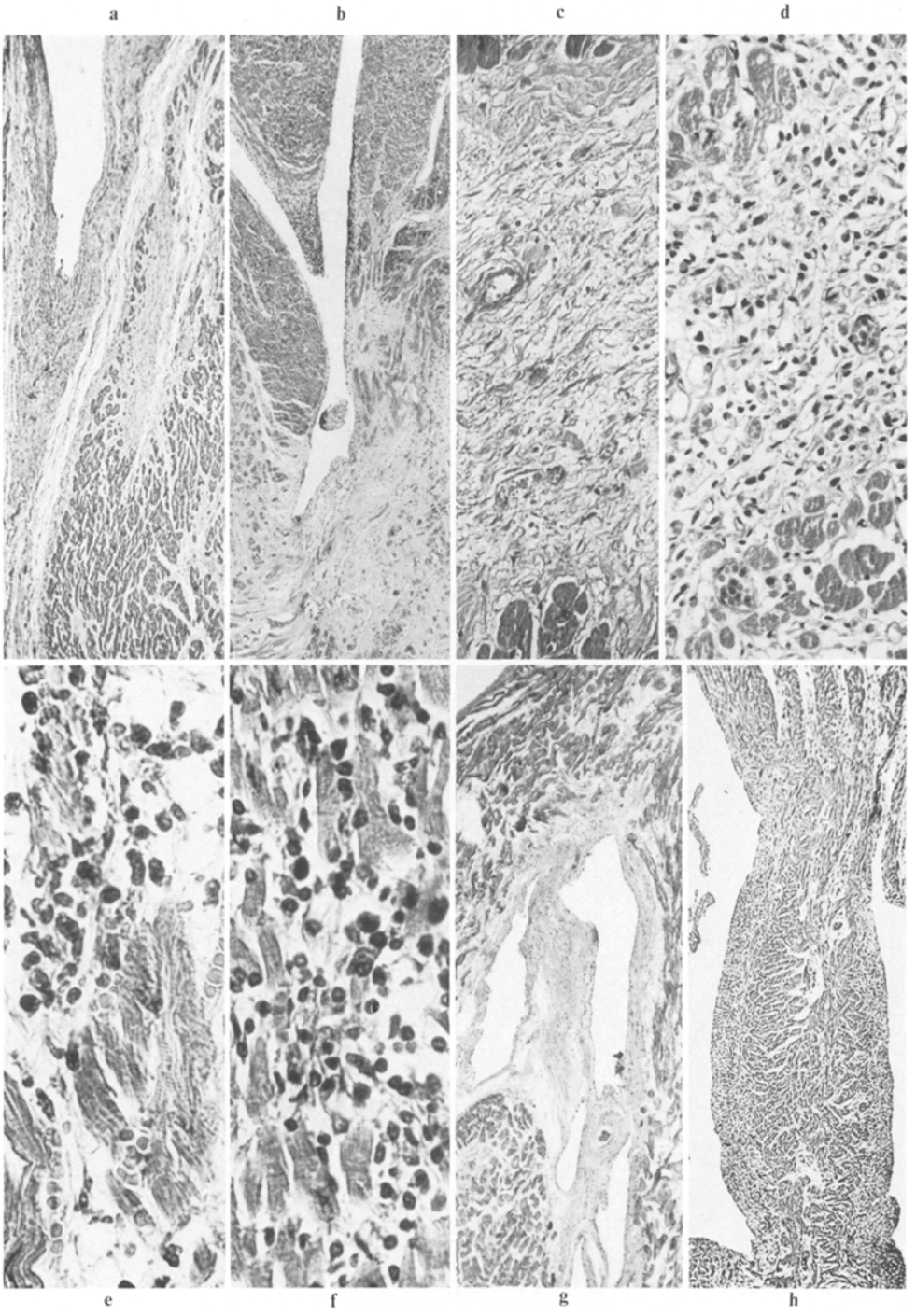

Fig. 3a–h. Comparison of histological changes in the myocardium of EMF and HAT. **a** Fibrous bands from the thickened endocardium extend into the myocardium. EMF 1, HE, ×25. **b** Mural endocarditis associated with marked subendocardial fibrosis. Note fibrous plaques containing inflammatory cells. HAT, case 2, HE, ×25. **c** Myocardial fibrosis with intact blood vessel and occasional inflammatory cells. EMF 1, HE, ×160. **d** Myocytolysis with remaining fibrillary network consisting of sarcolemn, nuclei and intact capillaries. HAT, case 2, HE, ×160. **e** Desintegrating muscle fibres sourrounded by mononuclear cells. EMF 1, HE, ×400. **f** Chronic myocarditis with muscle fibre necrosis. HAT, case 1, HE, ×400. **g** Fibrosed trabeculae carneae in the left ventricular apex. EMF 1, HE, ×25. **h** Endocarditis of the trabeculae carnae in the right ventricular apex

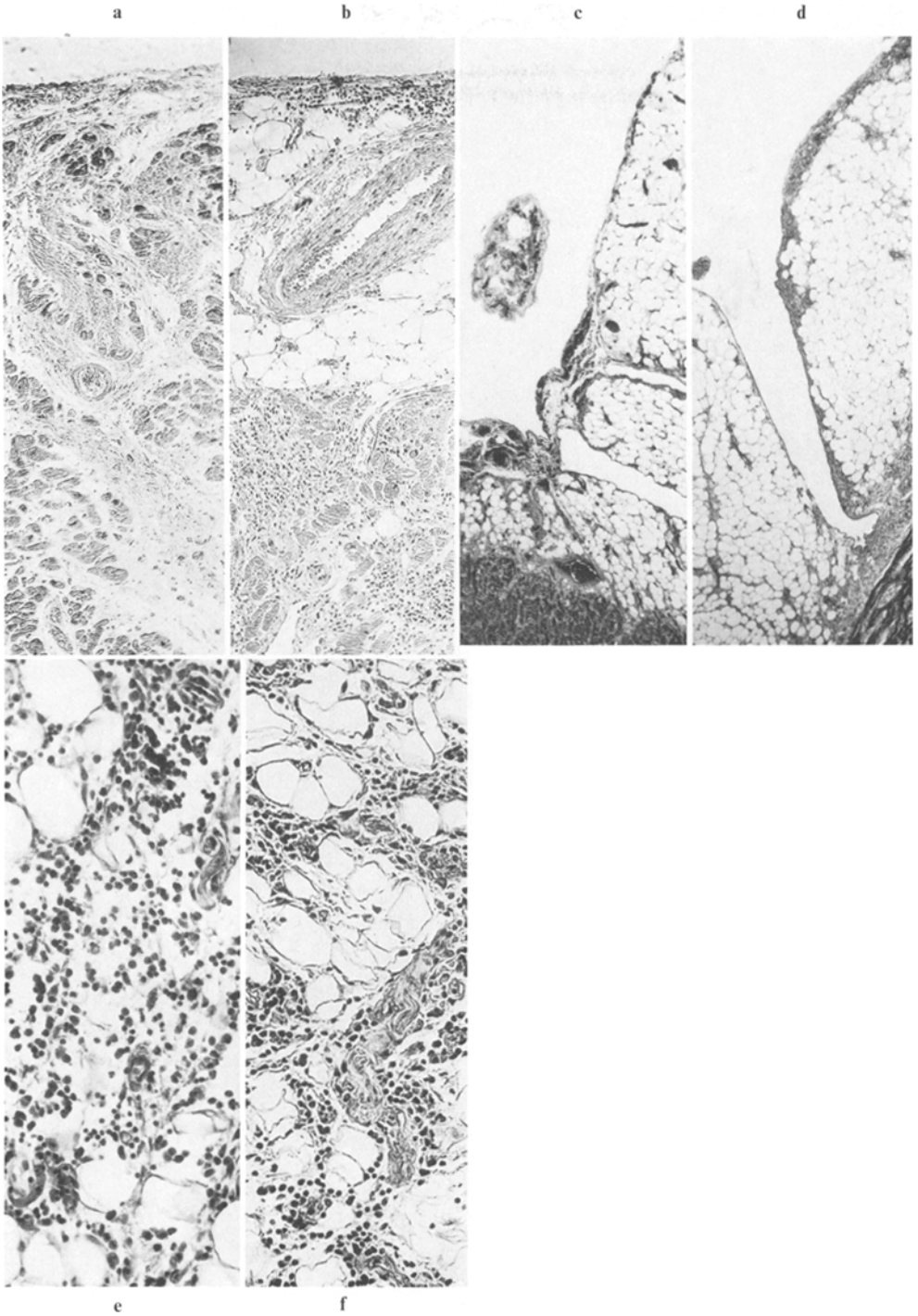

Fig. 4a–f. Comparison of histological changes in epicardial tissues in EMF and HAT. **a** Foci of fibrosis in the subepicardial ventricular myocardium. EMF 1, HE, ×63. **b** Patchy chronic cellular infiltration in the epicardium and underlaying myocardium. HAT, case 2, HE, ×63. **c** Retraction of the epicardium on the left ventricular apex which was macroscopically visible (="notch"). EMF 2, HE, ×25. **d** Slitlike retraction of the epicardium on the right ventricular apex with foci of fibrosis in the underlaying myocardium. HAT, case 2, HE, ×25 **e** Chronic cellular infiltration of the periatrial adipose tissue. EMF1, HE, ×160. **f** Chronic periatrial cellular infiltration of the adipose tissue. HAT, case 1, HE, ×160

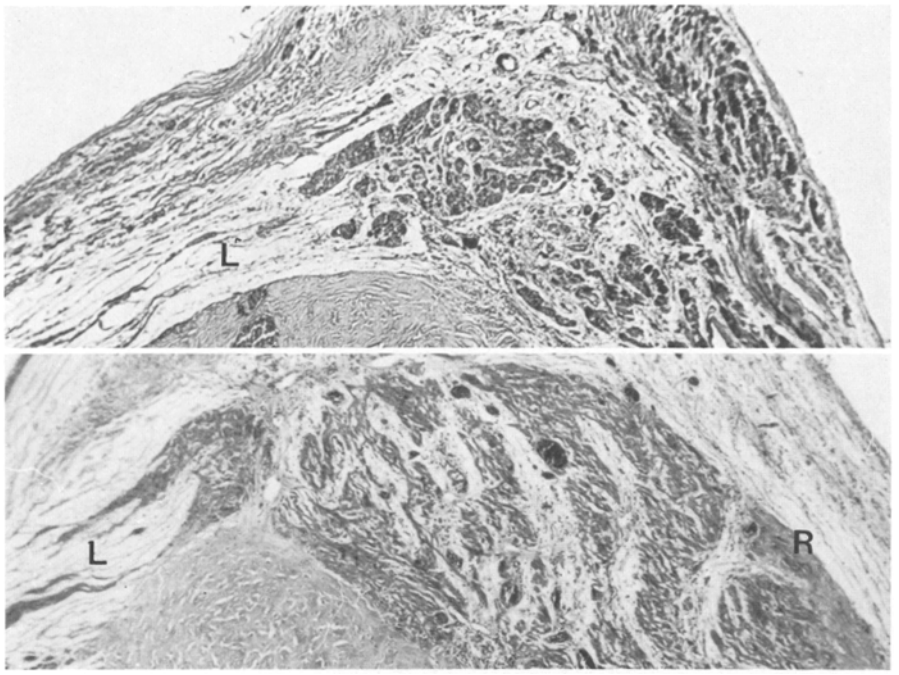

Fig. 5a and b. Lesions of the conducting system in EMF and HAT. **a** His bundle showing foci of fibrosis and partial interruption of a bundle branch (*L*). EMF 2, HE, ×25. **b** Bundle branch with incomplete fibrosis (*R*) and partial interruption (*L*). HAT, case 1, HE, ×25. *L* left bundle branch. *R* right bundle branch

myocardium of case 2. In the subendocardium of case 1, contraction bands of the muscle fibres could be observed. The fibrosis was particularly marked in the atria, involving the whole layer. No Aschoff nodules were noted. The smaller arteries were free of lesions. Papillary muscles showed similar lesions to those described in the endo- and myocardium. In both ventricular apices (Fig. 3g) of case 2 and in the left apex of case 1, there was marked or almost complete fibrosis of the trabeculae carneae. Inflammatory cells were scattered throughout the layers of the right apex in case 1 and were also present in both apices of case 2.

The *epicardium* was marked by circumscribed areas of fibrosis (Fig. 4a) or chronic mild cellular infiltration. The epicardial nerves showed little cellular infiltration in case 1, but no lesions in case 2. Ganglion cells were only observed in case 1, and they showed a few surrounding inflammatory cells. At the site of the apical notches (Fig. 4c) of case 2, localised subepicardial fibrosis extended into the myocardium; inflammatory cells were also present.

The *adipose tissue* showed either perivascular or interstitial fibrosis or chronic inflammatory infiltrates (Fig. 4e).

The *conducting system* was normal in case 1.

Case 2 showed marked fibrosis at the level of the His bundle with destruction of the left bundle branch (Fig. 5a). At the site of fibrosis inflammatory cells

were not a conspicuous finding however several foci of such cells were found inside the conducting system either in the His bundle or its branches. The portion containing the sinus node was not available but in its vicinity zones of chronic cellular infiltration alternating with zones of fibrosis were observed.

Human African Trypanosomiasis (=HAT)

The two hearts of HAT have already been reported in detail (Poltera et al., 1976). Both hearts were of normal weight and the first case appeared macroscopically normal; the second case showed a flabby myocardium with patchy yellowish discoloration. There was no endocardial thickening nor fibrosis, and the chordae tendineae appeared normal.

Histology of the HAT Cases

All *valves* showed in both instances a nonfibrinous, avascular chronic valvulitis (Fig. 2b). The monocytic infiltration, including occasional morular cells, was linear or patchy, and mainly localised on the flow side of the valves. There was also oedema and a various degree of ballooning with disorganisation of the collagen fibres. The chordae tendineae of the atrioventricular valves were similarly infiltrated (Fig. 2d).

The *endocardium*, including the retrovalvular portions, showed patchy or diffuse oedematous thickening in all four chambers with chronic cellular infiltrations (Fig. 2f+h). Occasionally, there was fibrosis (Fig. 3b). The inflammatory cells included lymphocytes, mastocytes, plasma cells, morular cells and histiocytes. Occasional Russel bodies were seen. The underlaying muscle fibres showed acute necrosis with well defined contraction bands. Granuloma formation, surrounding degenerated muscle fibres, was apparent in the endocardial lesions. In some of the granulomata histiocytes contained cytoplasmic bipolar inclusion bodies whose nature could not be assessed.

The myocardium showed focal or diffuse interstitial or perivascular cuffing with a predominantly histioplasmocytic infiltration and occasional morular and Antischkow cells. In densely infiltrated areas the myocardial fibres were widely separated, markedly atrophied and often undergoing degenerative changes (Fig. 3f). In other regions there were foci of fresh myocytolysis (Fig. 3d) of variable degree with persistance of the sarcolemna and capillary network. There were also patchy areas of scar tissue (Fig. 3b). Focal areas of lipomatosis were associated with chronic cellular infiltrates; siderosis was occasionally observed within the macrophages or rarely within myocardial fibres. All four chambers were affected, although sometimes the atrium appeared to be particularly involved. The papillary muscles showed the same lesions as described in the myo- and endocardium, except for granulomata.

In the apices of both cases, the cellular infiltration of the endo- and myocardium was severe; in case 2, the inflammatory cells were less dense and the

Table 1. Degree of cellular infiltration and fibrosis of some cardiac lesions in HAT and in EMF

Site of the lesion	HAT 1		HAT 2		EMF 1		EMF 2	
	C	F	C	F	C	F	C	F
Atrioventricular valves	++	0	++	0	+	+	(+)	+
Semilunar valves	++	0	+	0	(+)	0	+	0
Chordae tendineae	+	(+)	++	0	(+)	++	(+)	++
Mural endocardium	++	+	++	(+)	+	++	(+)	+++
Apex	+++	+	+++	(+)	(+)	++	(+)	+++
Myocardium	++	+	+++	(+)	+	+++	(+)	+++
Epicardium	++	(+)	++	+	+	++	+	++
Adipose tissue	++	(+)	++	+	+	+	+	++
Atrioventricular node	+	++	+	++	0	0	–	–
His bundle and branches	++	++	++	++	0	0	(+)	++
Ganglion cells	(+)	0	(+)	0	(+)	0	(+)	0
Epicardial nerves	++	(+)	++	(+)	(+)	(+)	0	(+)

(+)=very mild, +=mild, ++=moderate, +++=severe; 0=no change, –=not investigated, C=cellular infiltration, F=fibrosis

endocardium showed slight fibrosis. The process was particularly pronounced in the trabeculae carneae (Fig. 3h).

The *epicardium* had also a similar chronic cellular inflammation (Fig. 4b). In case 2, there was focal epicarditis on the right apex forming a small notch (Fig. 4d). In both cases, there was a chronic cellular infiltration involving the epicardial nerves and small groups of epicardic ganglion cells.

The *adipose tissue* showed patchy chronic cellular infiltration of variable degree, the apical and atrial portions being particularly involved (Fig. 4f).

The *conducting system* was oedematous and showed degenerative changes of the fibers together with zones of chronic cellular infiltrations and fibrosis. These lesions were observed in the atrioventricular node, the His bundle and its branches (Fig. 5b). The sinus nodes were not available for examination; however, there was a marked chronic cellular infiltration in their neighbourhood.

Conclusions

This study shows a predominantly cellular response in HAT in all sites examined, with signs of fibrosis in some areas. In contrast fibrosis is well developed in most of the sites examined in EMF; but in the majority of these sites there was also a mild or chronic cellular infiltration (Table 1). It is of importance that the same sites are affected by these two processes, and there seems to be an overlap of these in case 2 of HAT and case 1 of EMF, the latter probably representing an early phase of this condition. The outcome of any cellular granulation tissue is a scar. From the present findings, it is tempting to consider that at least certain cases of EMF represent a burnt-out phase of trypanosomal carditis.

Discussion

To the best of our knowledge, no comparative studies have been undertaken in Africa to investigate a possible relationship between the pancarditis of *HAT and African cardiomyopathies* of unknown origin (EMF and idiopathic cardiomegaly = IC). Although chronic Chagas' disease can present with endocardial fibrosis, mural thrombosis and pancarditis involving the conducting system (Andrade and Andrade, 1975), EMF and IC are usually either regarded as separate entities (Hutt, 1974), as a varietion of the same disease (Edington and Jackson, 1963; McKinney, 1970), or even a particular form of arterial hypertension in Africans (Brockington and Edington, 1972). Köberle (1968) also pointed out the difficulty in differentiating IC anatomically from Chagas' disease, if there is a positive serology for *Trypanosoma cruzi*. Davies and Coles (1959) reviewed cases of idiopathic myocarditis in Uganda and suggested a viral aetiology, but did not mention trypanosomes. Connor et al. (1967) had only one heart from a case of HAT in their comparative study of EMF from Uganda but they did not report the histological findings of that case (Connor et al., 1968). However, in HAT of the gambiense type, Bertrand et al. (1974) reported macroscopic fibrosis of the endocardium and dissecting fibrosis of the myocardium; the latter has also been described histologically (Lavier and Leroux, 1939; Collomb and Bartoli, 1967).

Heart valves have been said never to be involved in Chagas' disease (McKinney 1974; Prata et al., 1974) although Ferreira and Rossi (1972) described denervation of the tricuspic valve in human Chagas' disease. Similarly, valves were considered to be free of lesions in HAT (Hutt and Wilks, 1971), EMF (Davies, 1957; Edington and Gilles, 1969; and McKinney, 1974) and IC (Fejfar, 1968). However, Poltera et al. (1976) have described generalised valvulitis in HAT. Clinically, cardiac murmurs have been heard in severe cases of HAT (Bertrand et al., 1974) and these might be clinical indications of valvular lesions. In the present study, similar valvular lesions, although less pronounced, were found in all valves of the two EMF cases. EMF was classically shown to involve only the atrioventricular valves, but it has recently been reported that the semilunar valves may also be involved (Farrer-Brown and Tarbit, 1972a; Brockington and Edington, 1972). This study demonstrates that not only the valves but also the chordae tendineae and the papillary muscles were infiltrated by chronic inflammatory cells in HAT and in EMF.

Although chronic cellular infiltrates are known to occur in all layers of the heart in EMF, their importance has usually been underestimated; it was Farrer-Brown and Tarbit (1972a, 1972b) who emphasised the fact that there exists a *pancarditis* in EMF. The aetiology of EMF still remains obscure, however in view of the rather striking histological similarities with HAT we have observed, one can postulate that in trypanosome infested areas EMF might represent a burnt- out trypanosomal pancarditis. This statement does not exclude the possibility that hypersensitivity reactions may lead to a similar macroscopical pattern and further investigations are necessary before affirming that EMF and parietal fibroplastic endocarditis as described by Löffler (1936) are one and the same disease (Brockington and Olson, 1973; Roberts and Ferrans, 1974).

The release of kinins in HAT (Boreham, 1970) and the formation of granuloma (Poltera et al., 1976) would favour a hypersensitivity reaction in this condition. The cellular, and/or fibrosing process has been shown to affect all cardiac layers including valves and their appendages as well as the conducting system. Lesions of the latter might explain some of the pathologic electrocardiographic findings in HAT (Bertrand et al., 1974; Jones et al., 1975) and in EMF (Williams and Somers, 1960; Shillingford and Somers, 1961). In Chagas' disease, Andrade (1974) found a good correlation between ECG changes and anatomo-pathological lesions.

Trypanosomes are readily recognised in the heart muscle fibres in acute Chagas' disease, but were only found in about a third of the cases in the chronic form and almost never seen in the "indeterminate form of the chronic phase" (Prata et al., 1974). In HAT however it is difficult to find individual trypanosomes in formalin fixed material, where no cysts have ever been observed. *Experimentally,* African trypanosomes have been shown to invade the cardiac interstitium (Peruzzi, 1928; Höppli and Regendanz, 1930; Lambert and Houba, 1974). In *T. brucei* infected mice an immune complexe induced vasculitis has been reported (Lambert and Houba, 1974) and the type of general histological reaction depends largely on the immune status of the infected mouse (Castro Filho, 1975). However, we observed that in *T. brucei* infected mice trypansomes did penetrate avascular structures such as the mural and valvular endocardium, causing lesions.

It has been shown in acute experimental *T. cruzi* carditis that trypanosomes have a tendancy to cause *apical aneurysms* (Anselmi et al., 1971). In the present study, apical lesions in the form of severe cellular infiltration were found in HAT and healing would presumably result in scaring, equivalent to that seen in EMF. Shaper and Bellhouse (1973), using a model ventricle, to study ventricular flow patterns, found a low wall shear stress in both systole and diastole near the apex and behind the atrioventricular valves. They explained the distribution of the lesions in EMF in this way suggesting they were confined to regions of low wall shear stress. Our findings, together with the aneurysms observed in Chagas' disease, rather suggest that trypanosomes might take advantage of this pecularity. A possible complication of this apical lesion is the occurrence of mural thrombosis as observed in chronic, and more rarely in acute Chagas' disease (Prata et al., 1974), in HAT (Poltera et al., 1976) and in EMF. Incidentally, the association of EMF with subvalular aneurysms has been recorded (Robertson and Jackson, 1960; Poltera and Jones, 1973), but its signification remains as yet unclear.

Although myocarditis is known to occur histologically in both types of HAT (Lavier and Leroux, 1939; Hawking and Greenfield, 1941), the clinical report of Armengaud and Diop (1960) suggesting a *cardiac tropism* for African trypanosomes in the absence of central nervous lesions has largely passed unnoticed. They had successfully and specifically treated congestive cardiomyopathies in proven *T. gambiense* cases. Recently, Blackett and Ngu (1976) confirmed this observation, demonstrating high serological titres for trypanosomes in congestive cardiomyopathies of unknown origin in Cameroon. Increased values of serum glutamic-oxalacetic transaminase and lactic dehydrogenase in Ameri-

cans with imported African trypanosomiasis (Spencer et al., 1975) equally points to a possible myocardial damage. Since "healthy carriers" are known to occur in HAT (Willett, 1974), one can stipulate an indeterminate cardiac phase in chronic HAT similar to that observed in Chagas' disease (Prata et al., 1974). This would suggest that in certain instances there will be an interval before a patient presents with cardiac symptoms.

In rheumatic heart disease (=RHD), an autoimmune mechanism has been postulated (Read and Zabriskie, 1967). Heart *autoantibodies* have also been demonstrated in EMF (Shaper et al., 1967). Several autoantibodies have been demonstrated in rabbits infected with *T. brucei* (Mackenzie et al., 1972). It is possible that cross reacting antibodies are present in HAT, in particular since only a small portion of the overwhelming antibody response is specific trypanosomal antibody (Greenwood, 1974) and even the specific antibody is dependent upon the antigenic variation (Lambert and Houba, 1974; Vickerman, 1974).

Immunoglobulin changes in EMF have been reported from Uganda (Van der Geld et al., 1966; Shaper et al., 1967). Shaper et al. (1967) speculated on the reasons of the presence of high malarial antibodies (=IgM) advancing the hypothesis that an antibody cross reactivity rather than malaria was the cause (Shaper et al., 1968b). In this connection, the poor socioeconomic status of the "immigrant Rwandans"—in whom the incidence proved to be higher than in the local population—was particularly emphasised (Shaper et al., 1968a). However no exact data on these "Rwandans" were given: one does not know the exact region from where they had come nor the exact time they had migrated to Uganda (Shaper and Coles, 1965; Connor et al., 1967). Interestingly Rwanda still has several endemic foci of HAT (de Raadt, 1976) and unfortunately for our hypothesis we have not found data indicating the incidence of trypanosomiasis in immigrant "Rwandans" in Uganda. Immunoglobulins and particularly IgM, are known to be increased in either type of HAT (Mattern et al., 1961; Binz, 1972a), and their production has been related to local morular cells in the cerebral form (Greenwood and Whittle, 1973). These cells have been found to occur in the hearts of HAT and EMF in this study. It might be possible that trypanosomal immunoglobulin fractions have been missed by previous workers on EMF while reporting on the total amount of immunoglobulins. In Nigeria, the immunoglobulins in EMF were also investigated in correlation with Loa loa antibody titres, and the Ig fraction was shown to be particularly increased (Carlisle et al., 1972); but the results were too small to be conclusive. French (Gerbaux et al., 1957) and Nigerian authors (Ive et al., 1967; Brockington and Edington, 1972) favour the hypothesis of a filarial aetiology for EMF; however certain authors from Uganda have rejected this hypothesis on the basis that Loa loa does not occur in Uganda. In contrast Nnochiri (1971) and Poltera (1973) have shown that a Loa parasite does exist in a widespread manner in Uganda. It might well be that filariasis is only a concomitant disease in EMF.

Why the lack of a "trypanosomal approach" towards the aetiology of African cardiomyopathies?

Firstly, the exact extent of the disease is not known.

Secondly, the possibility has not been considered frequently enough. In two recent large series on pericarditis in Africans (Diop, 1972; D'Arbela et al., 1974), trypanosomes were not mentioned. Focusing on cardiology, one can only repeat Armengaud and Diop's (1960) statement that in each case of cardiopathy of unknown origin in trypanosome infested Africa, one has to search for trypanosomes.

Thirdly, the demonstration of trypanosomes in the blood or the cerebrospinal fluid remains a hazardous diagnostic procedure in the chronic stage of HAT. One can therefore presume that HAT is likely to be underdiagnosed and hope that recent immunological tests for the detection of trypanosomal infections—if used in a widespread way—will provide a higher yield in the diagnosis of HAT (Binz, 1972b; Bone and Charlier, 1975; Voller et al., 1976).

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