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Pathological Aspects of Human African Trypanosomiasis (HAT) in Uganda

A Post-Mortem Survey of Fourteen Cases

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Summary. The pathological features of 14 cases of human African trypanosomiasis (HAT) occurring in Uganda over an 8 year period are described. Three cases were clinically proven and in all 14 cases a chronic meningoencephalitis was found. In 2 cases there was histological evidence of ganglion radiculitis and in one of these chronic choroiditis and peripheral neuritis associated with chronic myositis were present. The cardiac lesions consisted of a chronic pancarditis of varying degree in 8 cases and in 3 a generalized valvulitis was observed. In 2 cases, specially investigated, generalized lesions of the conducting system were noticed.

Previous histopathological descriptions of HAT are briefly reviewed. The present findings are compared with some of those recorded in human American trypanosomiasis and experimental African trypanosomiasis.

Key words: Trypanosomiasis – Meningoencephalitis – Neuritis – Pancarditis – Valvulitis – Myositis.

Introduction

The classical morphological studies of human African trypanosomiasis (HAT) caused by *Trypanosoma gambiense* focused exclusively on the lesions of the central nervous system (Mott, 1906; Laveran and Mesnil, 1912; Bertrand et al., 1935). The same is true of sleeping sickness caused by *T. rhodesiense* (Calwell, 1937). Recent studies in cerebral HAT are rare (Hutt and Wilks, 1971) and morphological descriptions of carditis in HAT have been reported for both strains (Lavier and Leroux, 1939; Hawking and Greenfield, 1941); but, detailed histological reports remain rare. Koten and de Raadt (1969) reported on the histological appearance of six cases of myocarditis; however, except for a brief description of the classical brain lesions, the histopathology of other organs was not mentioned.

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The World Health Organization (WHO, 1969) stated in its recommendations for research in HAT that in the absence of any comparative report involving heart and brain, further clinicopathological studies are needed. Mulligan (1970) in reviewing trypanosomiasis and Goodwin (1970) while commenting on the pathology of African trypanosomiasis insisted on the need for detailed histopathological descriptions of HAT.

Material and Methods

We report on 14 cases of HAT as recorded in the Department of Pathology, Makerere University, Kampala, Uganda, covering the 8-year period from 1967 to 1974. The tissues were formalin-fixed, and blocks for histology were paraffin-embedded and cut at 5 μ. The following stains were used: H & E, elastin-Van Gieson, Gram, Ziehl-Neelsen, periodic acid Schiff (PAS), Giemsa and Pearl's stain. The hearts of two untreated cases of trypanosomiasis were further analysed in the Department of Pathology, University of Geneva, Switzerland. The study included a systemic analysis of all valve types as well as the histology of the His bundle and its branches.

Results

Clinical Data

In the 8 year period, 7445 necropsies were carried out; the sex ratio was 7 males to 3 females. Seventy per cent were adults of 15 years and above, 30% were children. As 12 cases of trypanosomiasis were found in the adults, the incidence of trypanosomiasis in the adult necropsy population was 0.16%.

Table 1 summarises some of the main features of the 14 cases studied. Ages ranged from 10 to 45 years, 12 were males and 2 females. In the latter, the post-mortem was restricted to the brain because of family reasons and in one the exact age was not stated. In 3 patients trypanosomes were found during life and 2 of these had received trypanocidal treatment. In 5 other patients, trypanosomiasis was searched for but no parasites were found in the blood or cerebrospinal fluid (CSF). All were Africans, 7 were of northern tribes, one was a Dama of eastern Uganda, 3 were residents from the neighbouring countries (Sudan, Tanzania, Zaire) and in 3 the tribe was not indicated. Four patients were primarily hospitalised in a mental hospital and were later transferred to the New Mulago Hospital.

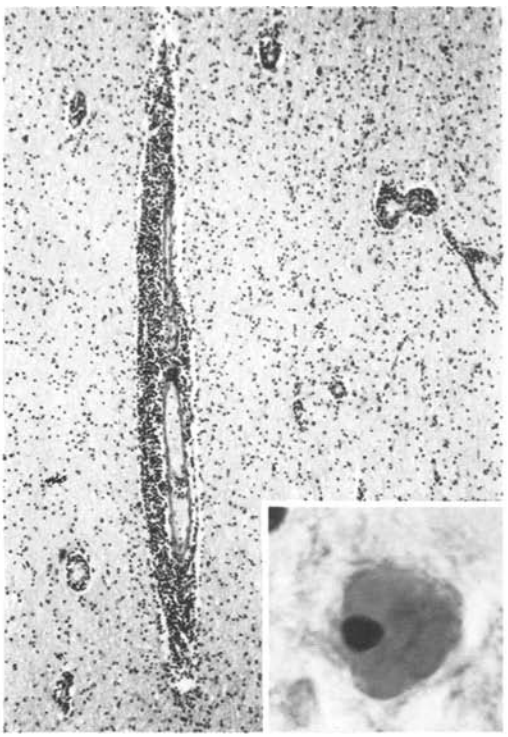
Central Nervous System

The fresh brain weight was in 12 cases above 1200 g and in 1 18-year-old it was 1160 g; in the remainder the weight was not recorded. On gross examination the following alterations were found in six brains: capillary hyperaemia in two, thickening of the meninges in two and cerebral infarctions in two. Cerebral oedema was often present.

Table 1. Some clinicopathological features in HAT

Age Sex	Brain weight (g)	Meningoencephalitis with				Heart weight (g)	Carditis affecting					Brpn	Spleen weight (g)	Liver	
		Perivascular cells	iron	Diffuse pattern	Morular cells		Endocardium	Myocardium	Epicardium	Valves	Conducting system			BSD	Schistosomiasis
40 M	1320	++	A	+	+	290	+	+	+	−	−	++	430	A	A
22 M	1380	++	P	+	+	280	+	+	+	−	−	+++	300	A	P
18 M	1160	++	P	A	+	200	A	+	+	−	−	A	1230	A	A
28 M	1420	++	A	A	+	320	−	+	−	−	−	+++	320	A	P
25* M	1400	++	P	A	+	250	+	+	+	−	−	+++	560	A	A
45* M	1240	+	−	A	+	290	A	+	A	−	−	+++	250	A	A
20 M	1200	++	P	A	++	250	−	++	+	−	−	+++	370	A	P
25* M	1340	+++	P	+	+++	380	+	++	+	+	−	++	100	A	P
36 M	1250	+++	P	++	+	240	x++	++	++	++	++	++	170	A	A
13 M	1380	+++	P	+	++	180	x++	+++	++	++	++	+++	300	A	P
39 M	1340	++	P	+	++	290	No histology					+	100	A	A
22 M	1460	+++	P	++	++	310	No histology					+++	280	A	A
10 F	1230	+++	P	++	++	Post-mortem limited to brain									
Ad F	A	+++	A	++	++	Post-mortem limited to brain									

A = absent, Brpn = bronchopneumonia, BSD = "Big spleen disease", P = present, − = no blocks or sections, + = mild, ++ = moderate, +++ = severe, x = granuloma, * = clinically proven



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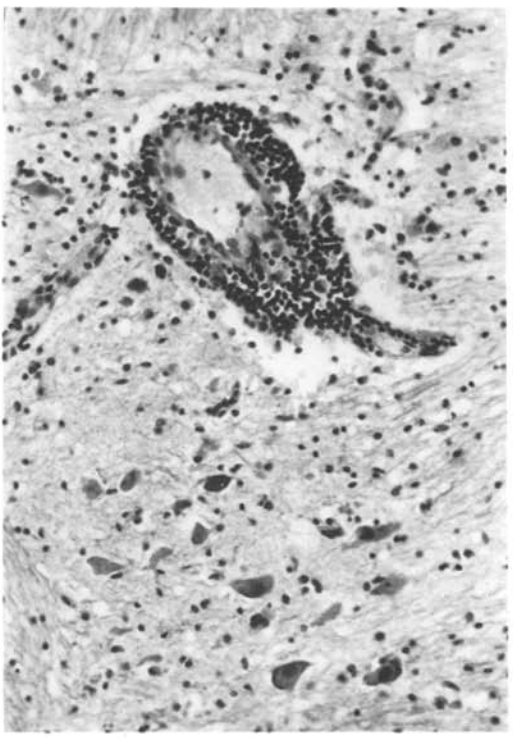

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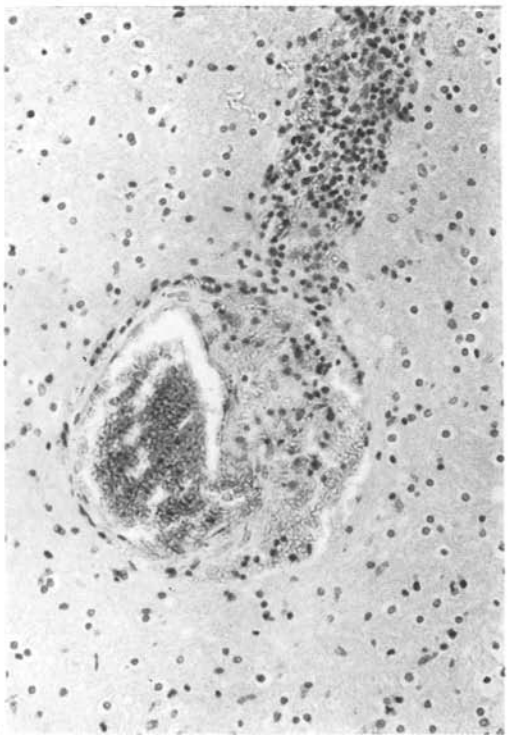

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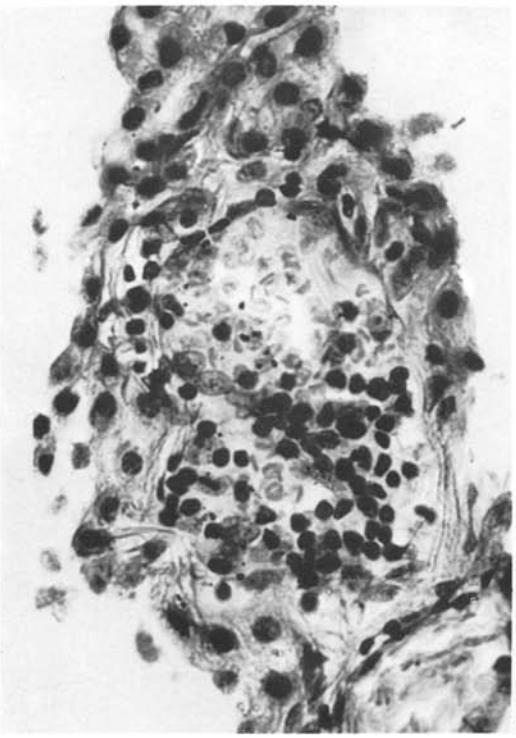

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Histologically there was perivascular cuffing (Fig. 1a, b) of the white matter with predominant histiocytic and lymphoplasmocytic infiltration and the presence of morular cells (Fig. 1a). This infiltration was severe in 6, moderate in 7 and mild in 1 case; it involved the cerebral hemispheres, the cerebellum and the pontomesencephalic structures. The white matter showed a varying degree of gliosis. The meninges were infiltrated by the same chronic inflammatory cells, especially in the Virchow-Robin spaces. This diffuse chronic meningoencephalitis was found in 9 cases. In 2 cases, mainly in the absence of inflammatory cells, perivascular erythrocytic exudation forming ring haemorrhages (Fig. 1c) was observed; in other areas foci of perivascular demyelinisation without noticeable cellular infiltrates were present. Fibrin was not apparent inside the blood vessels, the endothelium was generally not swollen. Iron deposits in or around cerebral blood vessels were observed in 10 cases; in 3 of the 4 remaining cases it was not possible to evaluate the pigment. Morular cells were mainly seen in the white matter near blood vessels; they were often associated with other inflammatory cells or occasionally isolated. In 1 case the four choroid plexuses were mildly infiltrated (Fig. 1d).

Peripheral Nervous System

In two cases the roots of the cranial nerves in the pontine region showed chronic cellular infiltration (Fig. 2a). In one case symmetrical samples of the brachial plexus and sciatic nerve were analysed and they appeared histologically normal. However, at muscular level, chronic patchy cellular infiltrations were found within small nerves (Fig. 2b).

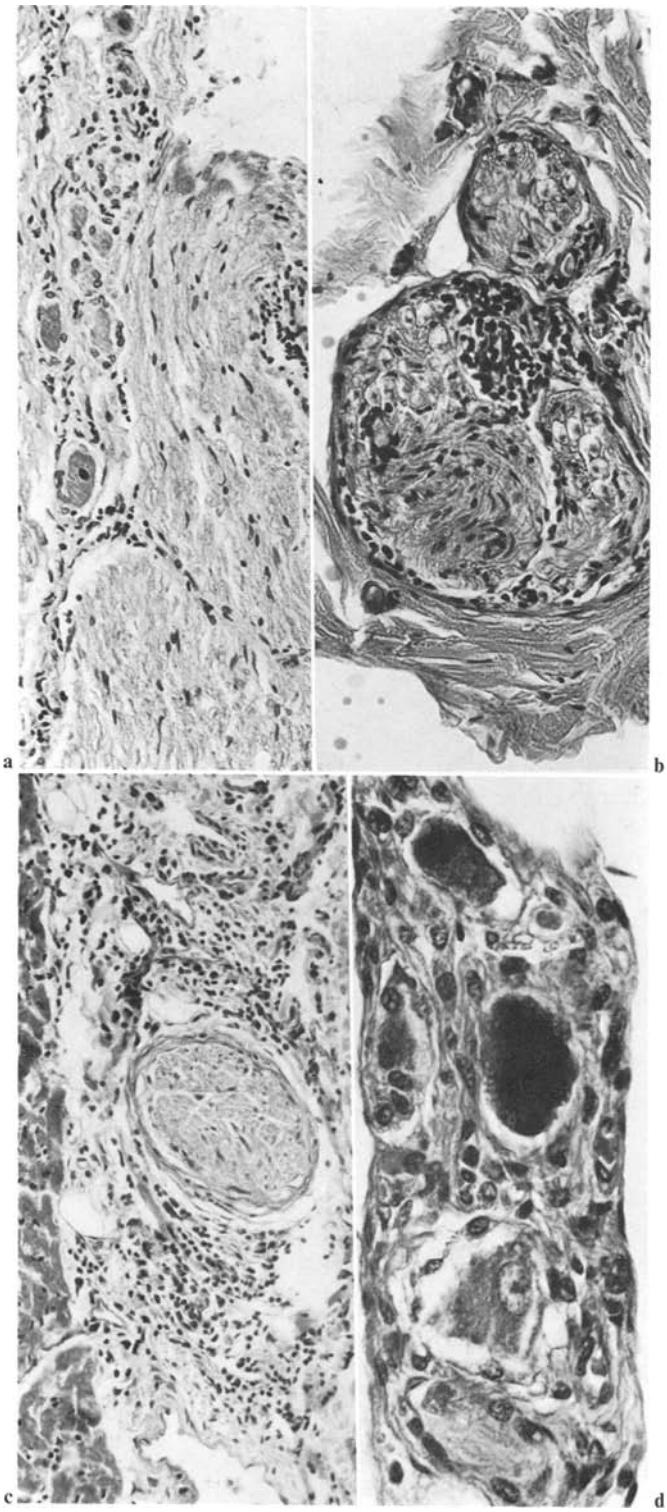
Autonomous Nervous System

Lesions of this system were found while investigating two hearts. In both, there was a chronic cellular infiltration involving the epicardial nerves (Fig. 2c) and small groups of epicardial ganglion cells (Fig. 2d). No other portions of this system were analysed.

Heart

The weight of the heart in the 12 cases examined was within normal limits except for 1 which weighed 380 g. The valves appeared macroscopically normal in all cases except in 1 where slight fibrosis of the mitral and aortic valves were noticed.

Fig. 1a–d. Lesions of central nervous system in HAT. **a** Diffuse chronic encephalitis with typical perivascular cuffing and gliosis. H & E, ×50. Inset: isolated morular cell in white matter. H & E, ×1250. **b** Lymphoplasmocytic vasculitis in pons with intact ganglion cells and some gliosis. H & E, ×160. **c** Ring haemorrhage presenting as perivascular erythrocytic exudation with few inflammatory cells. H & E, ×160. **d** Chronic inflammatory cells in choroid plexus. H & E, ×400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In 10 hearts histology was available and in all of these a chronic diffuse or focal myocarditis was present with a predominant histiolymphoplasmocytic infiltration and occasional morular cells (Fig. 3a). In 5 the changes were mild, in 4 moderate and in 1 severe. The cellular infiltrates were either interstitial or perivascular or both. In regions where the infiltration was dense the myocardial fibres were widely separated, markedly atrophied and often undergoing changes. In other regions there were many foci of fresh myocytolysis (Fig. 3b) of variable degree, with persistance of the sarcolemma and capillary network but the absence of inflammatory cells. Some of these foci led to patchy areas of scar tissue. Focal areas of lipomatosis with dense infiltrations of chronic cellular infiltration were not an uncommon finding, mainly in the right heart. Siderosis was ocassionally observed within macrophages or rarely within myocardial fibres. All four chambers were affected although sometimes the atrium appeared to be particularly involved. No clear evidence of parasites nor cyst-like structures were seen.

Endocardial oedematous thickening with patchy chronic cellular infiltration could be observed in all four chambers and the underlying muscle fibres often showed acute necrosis with contraction bands. Occasionally, a granulomatous pattern (Fig. 3c) with central eosinophilic necrosis was apparent in the endocardial lesions. Sometimes within these granulomata there were fragments of necrotic cardiac myofibrils. Parietal endocarditis was present in six cases and twice it presented with granuloma formation. Mural thrombosis of microscopic size was present in two cases.

In three cases there was a nonfibrinous, avascular chronic valvulitis (Fig. 3d) which affected all four valve types in two cases and the two examined valve types in the other. The cellular infiltrates were most often localised on the flow side of the valve but they could also be found in the retrovalvular endocardium. The valvular appendages such as the chordae tendineae and the papillary muscles showed similar patchy or diffuse chronic infiltrations (Fig. 3e).

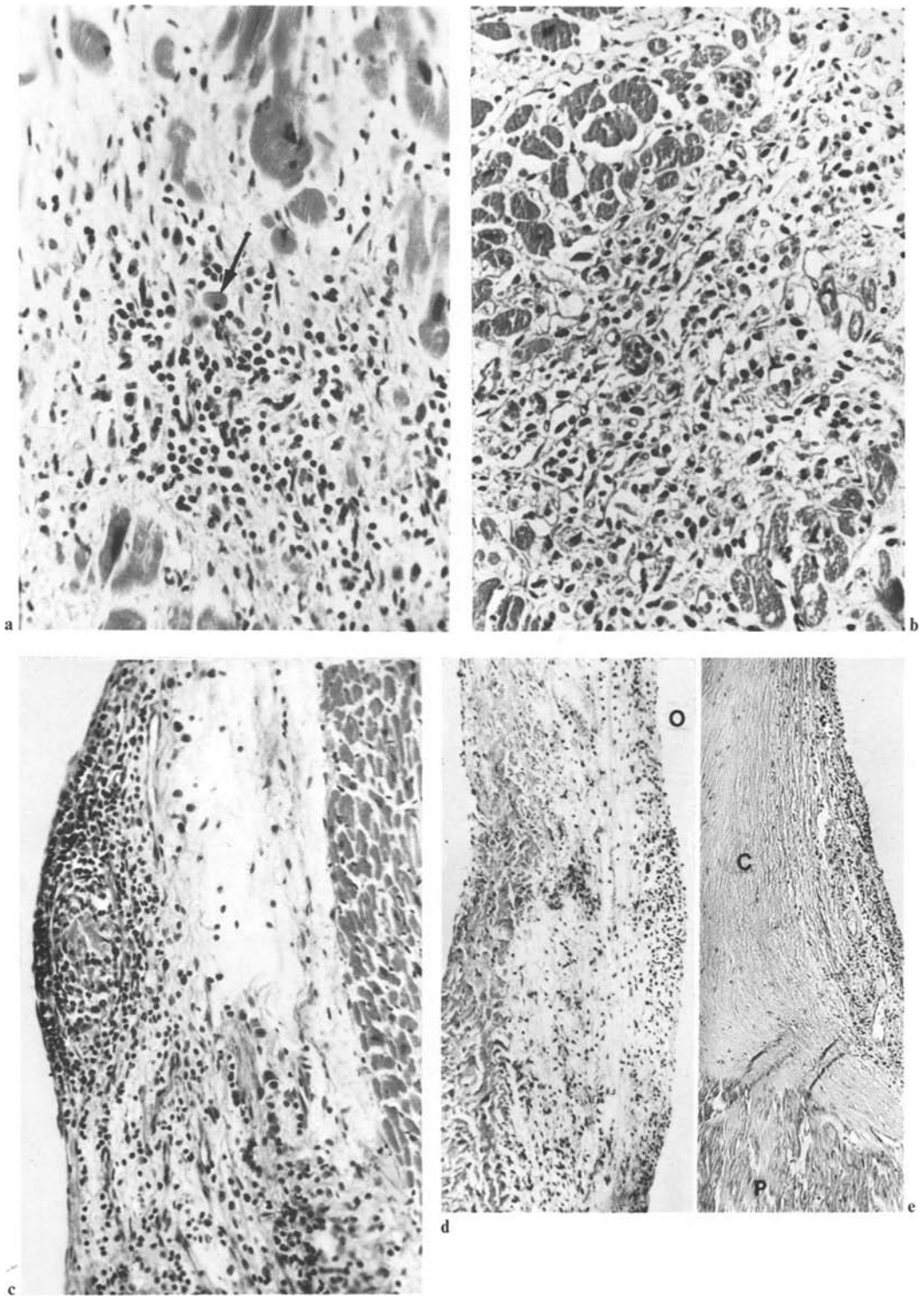
A chronic epicarditis, occasionally villous in type, was present in nine instances.

The conducting system was oedematous and showed degenerative changes of the fibres together with zones of chronic cellular infiltrations. These lesions were observed in the atrioventricular node, the His bundle as well as its branches (Fig. 4a and b). The main coronary arteries were free of lesions.

Skeletal Muscles

In one case a systemic analysis of this system was performed including samples of the upper and lower limbs, the recti abdominis and the diaphragm. The striatec

Fig. 2a–d. Lesions of peripheral (**a–b**) and autonomous nervous system (**c–d**) in HAT. **a** Cellular infiltrates in a root of a cranial nerve, containing ganglion cells. H & E, ×160. **b** Chronic cellular infiltrates of a peripheral nerve at muscular level. H & E, ×160. **c** Chronic perineuritis of an epicardial nerve. H & E, ×160. **d** Chronic cellular infiltrates of ganglion cells in the epicardium. H & E, ×400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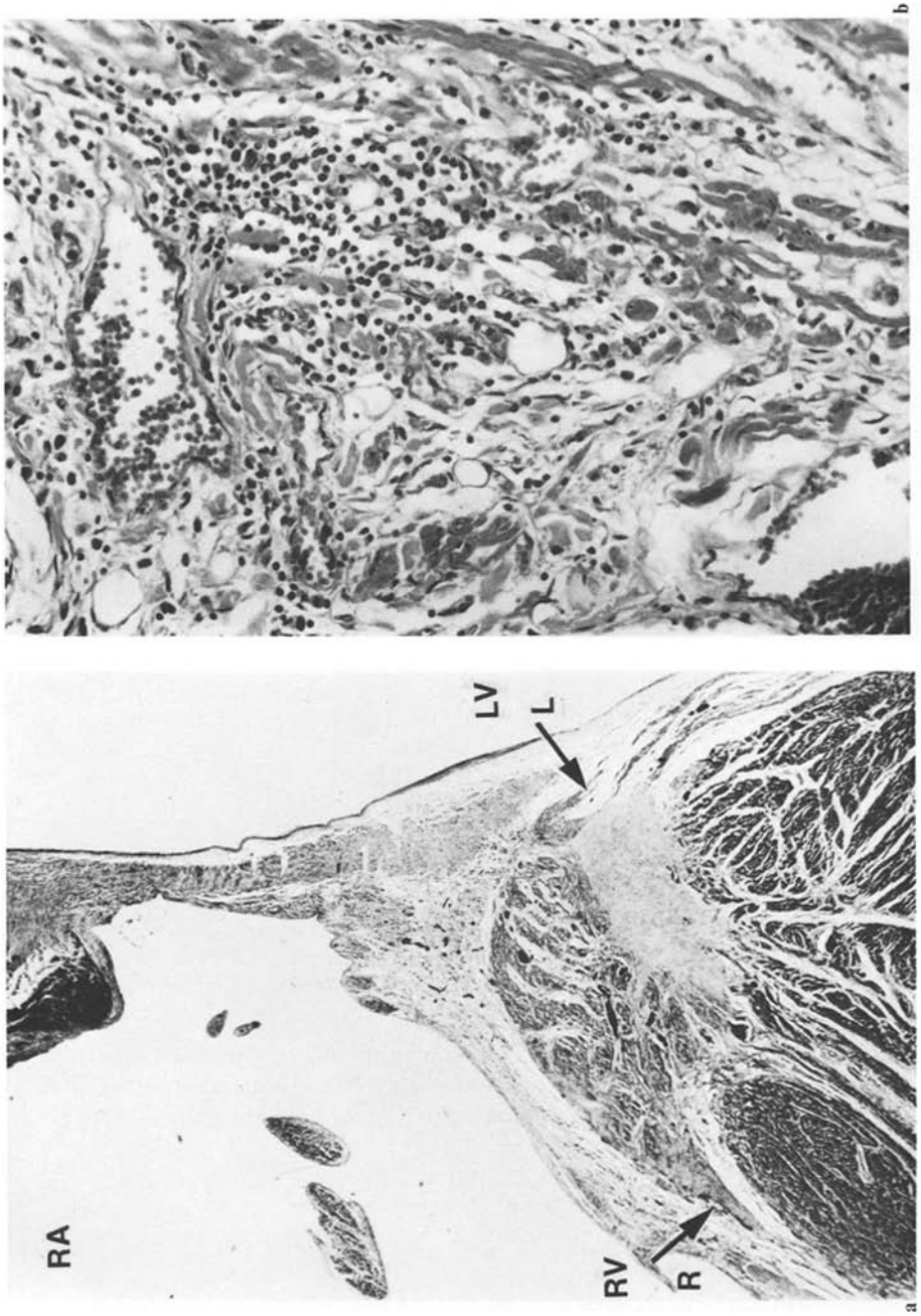

Fig. 4a and b. Lesions of cardiac conducting system in HAT. **a** His bundle and its bundle branches (*arrows*: *R*=right, *L*=left) showing signs of cellular degeneration. *RA*=right atrium, *RV*=right ventricle, *LV*=left ventricle. H & E, ×15. **b** Origin of right bundle branch with degenerating fibres and mononuclear cell infiltration and fibrosis. H & E, ×160

Fig. 3a–e. Some cardiac lesions in HAT. **a** Myocardial fibres in varying phases of destruction associated with chronic cellular infiltrates and a morular cell (*arrow*). H & E, ×130. **b** Zone of acute myocytolysis. Remaining nuclei are somewhat disorganised. There are no inflammatory cells. H & E, ×160. **c** Parietal endocarditis with granuloma formation containing degenerated muscle fibres. H & E, ×130. **d** Patchy chronic valvulitis on outflow (*0*) side of pulmonary valve. H & E, ×50. **e** Chorda tendinea (*C*) with tip of anterior papillary muscle (*P*) of mitral valve showing focal cellular infiltration. H & E, ×60.

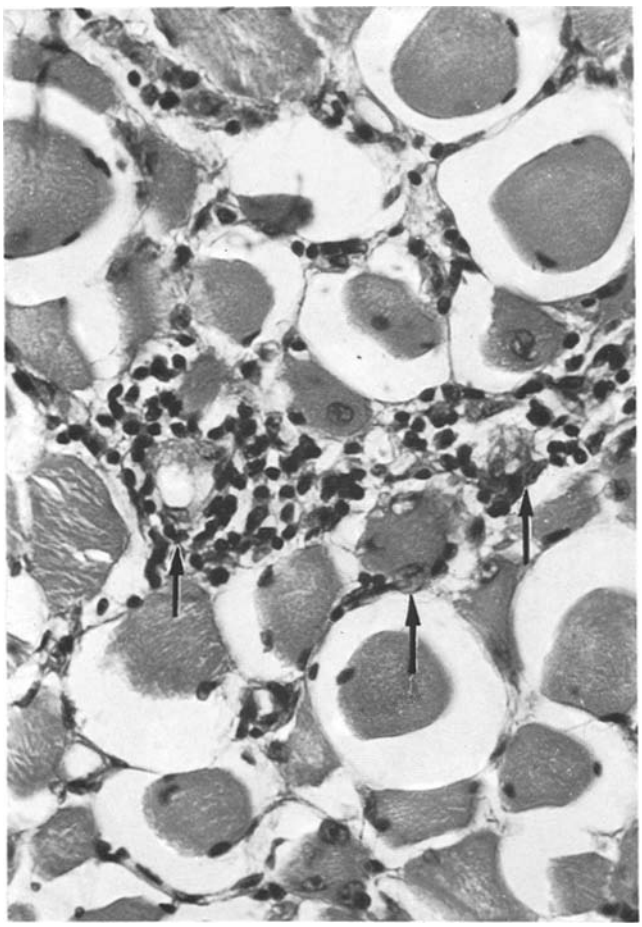

Fig. 5. Striated muscle: degenerative changes of the fibres (*arrows*) associated with chronic cellular infiltrates. (Ring formation around the muscle fibres is a fixation artefact.) H & E, ×400

muscles showed groups of atrophied fibres, sometimes accompanied by a patchy chronic cellular infiltration or with eosinophilic degenerative changes of varying degree (Fig. 5). Overall the inflammation appeared to be mild; surprisingly it was most pronounced in the diaphragm.

Other Organs

Marked bronchopneumonia was present in 7, moderate in 3 and mild in 1. In 1 case there was a pulmonary infarct. The spleen was increased in weight in the majority of cases (Table 1), 4 of which were associated with hepatic schistosomiasis. There was one spleen infarction in a case of non-valvular endocarditis. Histologically, in none of the 12 cases was there any hepatic evidence of "big spleen disease", also referred to as "tropical splenomegaly syndrome." In this

condition liver tissue shows infiltration of the sinusoids by mature lymphocytes, some Kupffer cell hyperplasia and occasional erythrophagocytosis. Lymph nodes were not available except in 1 case associated with schistosomiasis where eggs of *Schistosoma mansoni* were found in the nodes.

In the kidney no vasculitis was observed and the glomeruli did not show lesions as evidenced by routine histology in the 12 cases.

Discussion

HAT is usually diagnosed by the direct demonstration of the parasite either at the inoculation site, in lymph nodes, the peripheral blood or in the CSF according to the stage of the disease (Hutt et al., 1973). In case of diagnostic difficulties special techniques such as concentration by centrifugation, passage on sephadex column, animal inoculation, serology or immunofluorescence are needed (Willett, 1974). In sleeping sickness of the rhodesiense type the demonstration of the parasite is usually required before the toxic trypanocidal treatment is administered (Buyst, 1975).

The total number of our cases by no means reflects the epidemiology of the disease in Uganda where in 1975 at least three endemic foci were recognized in the north, northeast and southeast of the country (de Raadt, 1976). Unfortunately, no morphological studies were carried out during the epidemic outbreak near Jinja in 1972. The latter clearly indicates that although HAT has been fairly well controlled in Uganda, the disease is likely to flare up in focal epidemics. This statement is relevant for the whole trypanosome-infested areas of Africa and political disturbances and/or economic difficulties may well favour such a development as was clearly illustrated by the increase of trypanosomiasis in Zaire following independence (de Raadt, 1976).

African trypanosomes have very rarely been demonstrated in human necropsy material although the histological lesions of the central nervous system are quite consistent and considered to be characteristic. In the present series 3 of the 14 cases were proven clinically by direct evidence of the parasite while the reminder showed on histology identical lesions. Interestingly, 4 patients of the present series were referred from the mental hospital where the diagnosis was not established, a point stressed by Rwomushana (1973).

The histology of the central nervous system in all cases was consistent with the classical description of cerebral HAT (Mott, 1906; Laveran and Mesnil, 1912; Bertrand et al., 1935; Calwell, 1937; van Bogaert, 1958; Hutt and Wilks, 1971). It consisted mainly of a diffuse chronic mononuclear meningoencephalitis with marked perivascular cuffing affecting the deep areas of the white matter, particularly those in the posterior cerebral fossa. Marked gliosis was a common finding and morular cells were present in all cases. The involvement of the choroid plexus in HAT has been described (Calwell, 1937) and it was observed in one case of the present series; however there were no parasites although their occult visceral phase has been demonstrated in this tissue experimentally (Omerod and Venkatesan, 1971 a, b). The structure of the cortex appeared normal, but occasionally small perivascular zones of subcortical demyelinisation as reported

by Calwell (1937) were observed. In the majority of the present series there was an important diffuse perivascular cuffing and among the inflammatory cells were macrophages containing iron pigment. Ring haemorrhages were observed in the white matter of two cases and they were similar to those described by Hawking and Greenfield (1941). Goodwin (1970) has shown experimentally that trypanosomes were concentrated principally in the perivascular spaces with an accompanying increase in capillary permeability. Whether this iron pigment is the result of immune complex-induced haemolysis (Woodruff, 1973) or of immune complex–induced vasculitis with local tissue destruction awaits further investigation. It is interesting to note that Hawking and Greenfield (1941) did not find gross parenchymatous changes in the acute stage of cerebral HAT due to *T. rhodesiense;* similarly the encephalitis in Chagas' disease is only seen in the chronic stage (WHO, 1969). Experimental lesions of the central nervous system caused by African trypanosomes of the brucei group have been reported in a whole range of animals (Losos and Ikede, 1972) and the importance of an immune complex–induced vasculitis with perivascular deposits of immune complexes has been emphasised (Lambert and Houba, 1974).

Lesions of the peripheral nervous system in HAT have rarely been reported. Martin and Guillain (1908) and Nathan-Larrier and Sézary (1908) reported on spinal forms of HAT. Janssen et al. (1956) described extensively the morphological changes in HAT of the spinal cord, the spinal and cranial nerves as well as their respective ganglions. In the present series, ganglion-radiculitis was found in two cases and peripheral neuritis in one of these. It is noteworthy that nerve lesions such as encountered in the specimens of chronic myositis of the present series have not been described to the best of our knowledge. Experimentally myositis has been reported in *T. brucei*-infected rats (Losos and Ikede, 1972) as well as in *T. brucei*-infected mice (Castro Filho, 1975). Muscular wasting commonly known to occur in trypanosomiasis (Goodwin, 1970) can therefore be a primary muscular lesion (perhaps due to the direct action of the parasite or an immunologic reaction induced by the parasite) or secondarily induced by peripheral or central nervous involvement.

In 1941 Hawking and Greenfield found histological evidence of trypanosomal myocarditis in East Africa, and since then there have been only few reports (Bertrand et al., 1967; Koten and de Raadt, 1969; Hutt and Wilks, 1971). In the present series a pancarditis was the common finding. The myocarditis varied in intensity and various phases of evolution were observed; in general the picture was of the type described by the above-quoted authors. Morular cells were found within the cellular infiltration or isolated, a finding previously mentioned (Koten and de Raadt, 1969). A pericarditis is a common finding in HAT and this series supports this fact. In addition there was a chronic inflammation of the nerve fibres and of the ganglion cells both localised in the epicardium. The parietal endocarditis consisted of an oedematous and/or fibrous cellular thickening; in more advanced stages there was endocardial fibrosis, a fact already mentioned by Lavier and Leroux (1939). Endocardial granuloma formation often surrounding degenerated muscle fibres was observed in two instances, a finding not previoulsy described in HAT but known to occur in human *T. cruzi* carditis (Hutt et al., 1973).

In the granuloma chromatin bodies within histiocytes were observed often of bipolar shape; it could not be assessed whether they were trypanosomal in origin; similar structures had been described by Peruzzi (1928) in experimental African trypanosomiasis. Associated with the endocardial lesions were occasional microscopic thrombi. Mural thrombosis is found in human American trypanosomiasis (Koeberle, 1968; Mc Kinney, 1974), in endomyocardial fibrosis (EMF) (Shaper et al., 1968) and in idiopathic cardiomegaly (Hutt, 1974). It is possible that the macroscopically unexplained embolism in this series originated from an endocardial mural thrombus; such a mechanism of embolisation has been described for human American trypanosomiasis (Andrade and Andrade, 1971) and for EMF (Owor, 1973). A known cardiac complication of American trypanosomiasis is the formation of apical aneurysms, often with mural thrombi and this entity has to our knowledge not been reported for HAT, although idiopathic subvalvular aneurysms have been reported in Africans (Edington and Williams, 1968; Poltera and Jones, 1973).

The heart valves were said never to be involved in HAT (Hutt and Wilks, 1971) nor in human American trypanosomiasis (Mc Kinney, 1974). However, in the two hearts examined systematically there was a generalised chronic non-thrombogenic and avascular valvulitis affecting the four valve types while a third case had lesions of the available valves. The monocytic infiltration including morular cells was mainly on the flow side. The present findings are corroborated by our incidental observation in experimental *T. brucei*-infected mice in which all valves contained numerous trypanosomes[1]. It is therefore possible that in a more chronic stage the valvular and endocardial lesions will mimic EMF, particularly since the valvular appendages were equally infiltrated. Our findings suggest a possible link between trypanosomes and African cardiomyopathies of unknown origin, a hypothesis recently advanced by Bertrand (1974). The presence in this series of multiple areas of myocytolysis in the myocardium, some of which were undergoing fibrosis, may be considered as the early phases of the stellate fibrosis and scarring described in African hearts in congestive cardiomyopathy (Hutt, 1975). This myocytolysis might be the result of the direct action of the parasites on the myofibrils or perhaps simply an immunologic reaction of parasitic antigen(s) or their complexes on the sarcolemmal and subsarcolemmal sites with progressive destruction of the involved myocardial fibres. This might be so since in infected mice Lambert and Houba (1974) have shown that there are immune complexes in the blood and extravascular spaces principally in the brain, heart and kidney. Furthermore, there is clinical evidence that this might be so as patients with congestive cardiomyopathy in the Cameroons showed high serological titres for trypanosomes (Blackett and Ngu, 1976) and in Senegal where patients with such a condition had responded well to trypanocidal treatment (Armengaud and Diop, 1960). A possible relationship may also exist with EMF since histologically a pancarditis (Farrer-Brown et al., 1972) as well as the involvement of the pulmonary valve (Farrer-Brown and Tarbit, 1972) have been reported in this condition in Uganda, findings which were observed in HAT in six and two cases respectively of the present series.

[1] The material was kindly provided by P.H. Lambert to whom we are thankful (WHO Research Unit, Hôpital cantonal, Geneva, Switzerland)

In the series under discussion the conducting system of two hearts analysed showed in both multiple focal lesions either in the atrioventricular node, the His bundle or within both bundle branches. These lesions consisted either of chronic cellular infiltrates including morular cells or of zones of scarring with degenerative fibres. These findings probably explain ECG changes in HAT (Schyns and Janssen, 1955; Bertrand, 1974; Jones et al., 1975) and support two histological observations (Lavier and Leroux, 1939; Bertrand et al., 1967). Modifications in cardiac conduction and rhythm are often encountered in human American trypanosomal carditis (Rosenbaum, 1964, ; Andrade and Andrade, 1971). It is therefore possible that lesions of the conducting system in HAT might contribute as an aetiological factor to a sick sinus syndrome of unknown origin as reported in young patients from Uganda (Ikeme et al., 1975), and as it is becoming more evident that trypanosomiasis is not altogether an uncommon finding in children in endemic regions.

Among haematological disorders, anaemia is well known to occur in trypanosomiasis. Experimentally, anaemia was thought to be of the haemolytic type (Jennings et al., 1972). Immune cytolysis was found to contribute to trypanosomal anaemia in man and particularly in big spleen disease in Uganda (Woodruff, 1973; Woodruff et al., 1973). In the present series no haematological data were available, but big spleen disease was absent as evidenced by liver histology, a procedure considered to be the best diagnostic criterion of this condition (Hutt, 1971); however, splenomegaly was found in the majority of the cases and it was often associated with hepatic schistosomiasis or bronchopneumonia. Thrombocytopenia in HAT has been reported (Barrett-Connor et al., 1973; Spencer et al., 1975) and its mechanism has been explained by splenic pooling of the platelets, by possible immune damage to platelets or even platelet consumption as part of a disseminated intravascular coagulation (DIC) in some patients (Robins et al., 1975). Morphologically there was no evidence of DIC in the present series.

Experimentally much emphasis has been given to immune complex–induced glomerulonephritis in African trypanosomiasis (Sadun et al., 1973; Lambert and Houba, 1974); however, in the present series no histological abnormality of the glomeruli as seen in routine histology was observed and there were no vascular changes. Clinically reversible renal insufficiency and proteinuria prior to the specific treatment has been reported in HAT (Spencer et al., 1975). Trypanosomal antigenic variation may lead after repeated disproportionated immune response to a state of immuno-depression where infections may overwhelm (Goodwin, 1970; Murray et al., 1974). Severe bronchopneumonia has been observed repeatedly in HAT and was noticed in seven cases in this series.

To conclude, one can state from the present study that HAT is a generalised disease affecting particularly the nervous, cardiac, muscular and haemato-reticuloendothelial systems. In the nervous system there is a generalised involvement of the central, peripheral and autonomous system; likewise all layers of the heart, including valves and conducting system, are affected while the striated muscle is mildly involved. It seems now that there are more basic similarities between African and American human trypanosomiasis than formerly assumed, the main

difference being the mode of parasitic reproduction. In this regard one is eager to know more about the pathological features of Asian trypanosomiasis (Dissanaike et al., 1974).

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