Afr. J. Med. med. Sci. (1976) 5, 125–130.

The histopathology of early hepatic schistosomiasis[1]

S. B. BHAGWANDEEN

Department of Pathology, University of Zambia

Summary

The late stages of hepatic schistosomiasis (pipe-stem portal fibrosis) were first described from hyper-endemic areas of *Schistosoma mansoni* in Egypt and South America.

More recently all grades of hepatic schistosomiasis have been reported from endemic areas of *S. mansoni* as well. There is, however, a discrepancy in the histopathological descriptions of hepatic lesions.

This paper presents the author's experience with hepatic schistosomiasis in an endemic area of *S. mansoni* in Zambia. The unit of the schistosomal lesion is the pseudo-tubercle which develops around the individual eggs. Confluence of these granulomata has a role in the subsequent development of the more severe chronic stages of portal fibrosis.

The late stages of pipe-stem portal fibrosis of the liver due to schistosomiasis are well documented from the major endemic areas of *Schistosoma mansoni* in Egypt and South America. This clinico-pathological entity of schistosomal pipe-stem portal fibrosis of the liver, after initial debate and scepticism (Higginson & de Meillon, 1955; Prates, 1961; Gelfand, 1962) is being more frequently reported from endemic areas of Africa as well (Manson-Bahr, 1958; Bhagwandeen, 1964, 1968, 1973; Gelfand, 1964).

The entire spectrum of liver disease as described by the author in an endemic area of *S. mansoni* in South Africa (Durban) is also being seen in Zambia (Bhagwandeen, 1973). Zambia also is an endemic area of schistosomiasis with focal endemicity of both *S. haematobium* (Bhagwandeen, 1970) and *S. mansoni* (Henderson, 1969).

[1] Paper read at the First International Conference on Basic Medical Sciences in Africa, Lusaka, 7–14 March 1973.

Correspondence: Professor S. B. Bhagwandeen, Department of Pathology, School of Medicine, P.O. Box R.W. 110, Lusaka, Zambia.

Although schistosomal pipe-stem portal fibrosis of the liver is now accepted as a pathological entity, there is still some discrepancy in the histopathological descriptions of the liver lesions (El Gholomy *et al.*, 1955; Carter & Shaldon, 1959; Bogliolo, 1967; De Paola & Winslow, 1967; Winslow, 1967).

This study is an account of the early hepatic lesions produced by *S. mansoni* and their natural history as observed in liver biopsies. It is an account of the lesions produced by mature, apparently viable eggs of *S. mansoni* (as judged by the presence of a recognizable miracidium in the egg). Although other factors have been incriminated in the production of hepatic lesions (Gillman, 1957; Andrade, Paronetto & Popper, 1961) it is generally accepted that mature, viable eggs of *S. mansoni* are the main etiologic agents responsible for the subsequent hepatic lesions (Fairly, 1920; Dew, 1923; Meleney *et al.*, 1952; Cameron & Ganguly, 1964; Bhagwandeen, 1968).

Early stage of hepatic lesions around S. mansoni *eggs*

The earliest stage of hepatic involvement is the appearance of the egg (Fig. 1). Although it has been claimed that the site of eggs in the hepatic lobule is variable (Carter & Shaldon, 1959) in my experience they are always present in the portal radicles. Occasionally when they do appear to be in parenchyma, distant from portal tracts, serial sections have always demonstrated their true relations within portal tracts. In the earliest stage no reaction is immediately apparent except for an occasional mononuclear cell, which is a non-specific reaction.

Soon after the egg is trapped in the peripheral portal radicle, there is a pronounced infiltration of cells with eosinophil leucocytes predominating (Fig. 2). Contrary to the experience of Koppisch (1943),

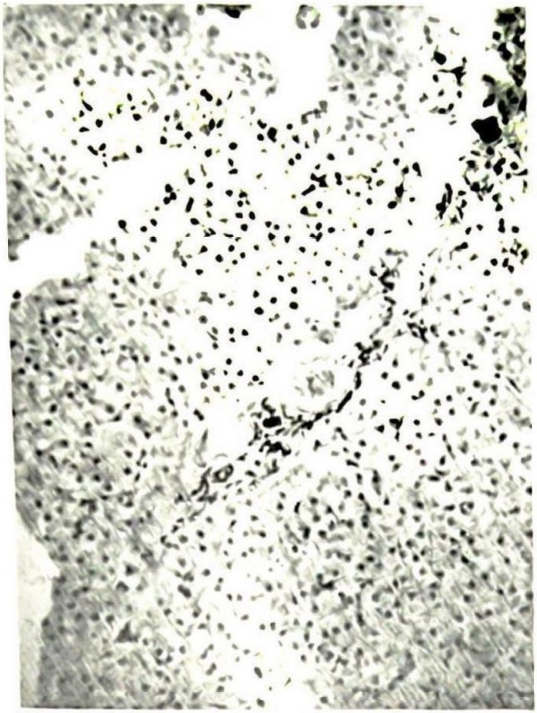

FIG. 1. Schistosome egg in portal tract. Schistosomal pigment is noted and a few mononuclear cells. The miracidium within the egg can be just recognized. H & E. × 70.

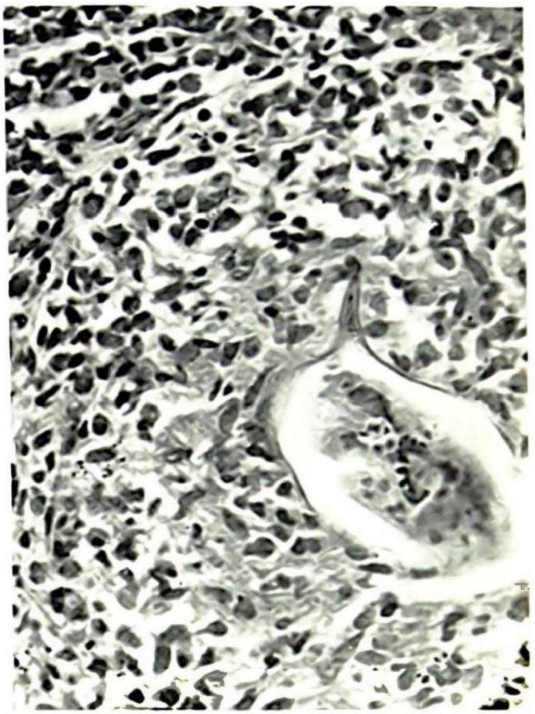

FIG. 2. *S. mansoni* egg surrounded by intense cellular reaction with eosinophils predominating. The miracidium inside the egg is clearly visible. H & E. × 525.

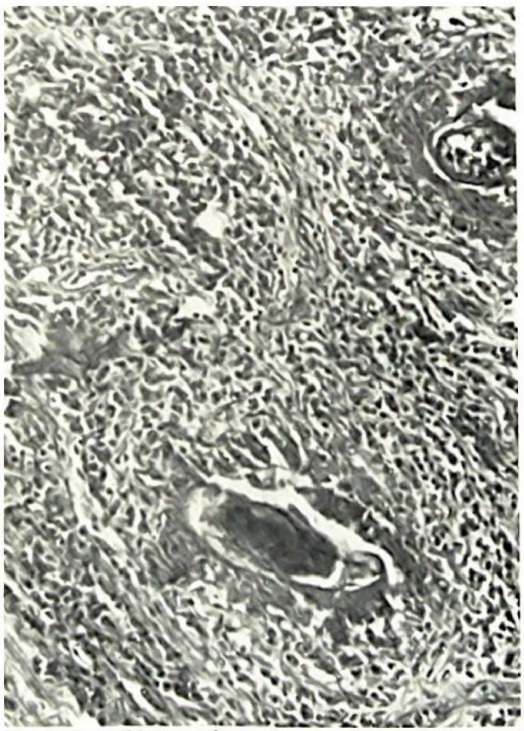

FIG. 3. Two schistosomal granulomata with eggs in the centre and surrounded by eosinophilic necrosis which in turn is surrounded by the usual inflammatory cellular infiltrate. H & E. × 175.

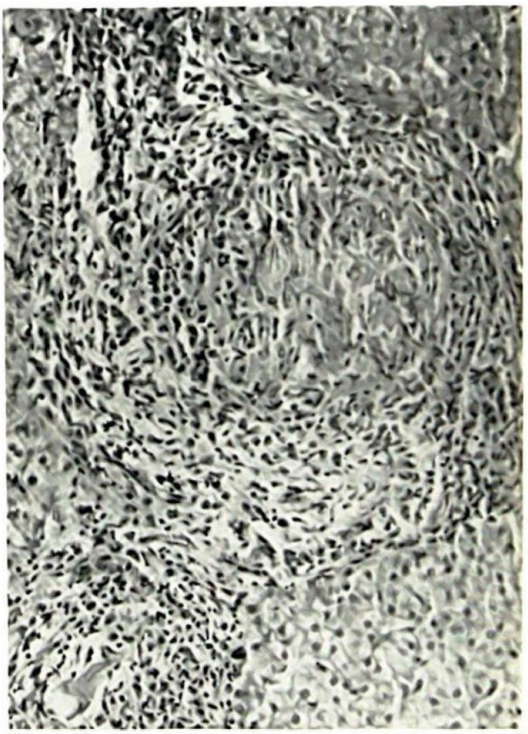

FIG. 4. Typical schistosomal granulomata with remnants of eggs in the centre, epitheloid cells and peripherally eosinophil leucocytes mixed with occasional lymphocytes. H & E. × 175.

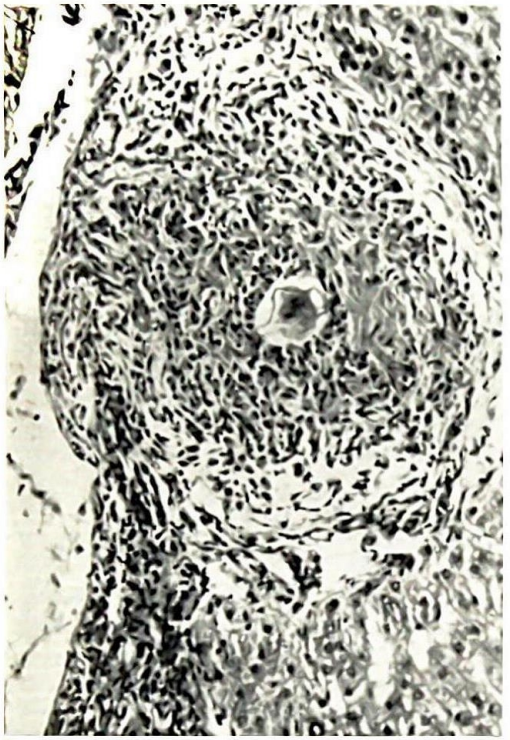

FIG. 5. Granuloma with egg in centre, cellular infiltration less intense and early fibroblastic proliferation on the periphery. H & E, × 175.

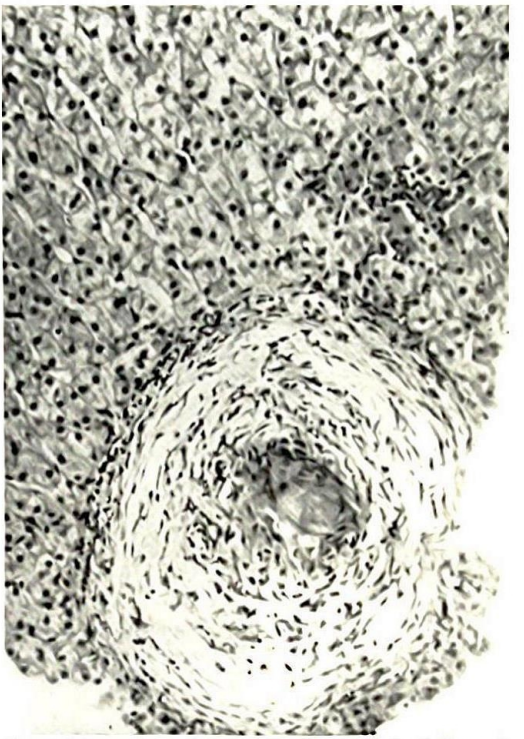

FIG. 6. More advanced stage of healing. Cellular infiltrate is negligible with fibrosis most prominent. Central giant cell reaction around egg remains is noted. H & E, × 175.

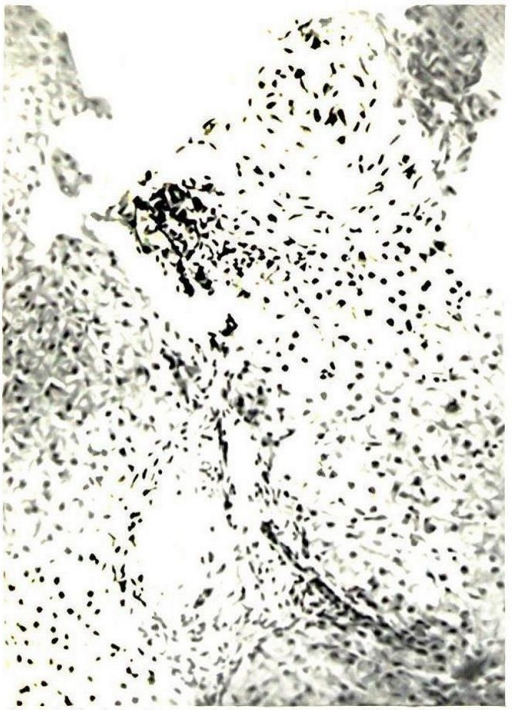

FIG. 7. Healed schistosomal granulomata. H & E, × 175.

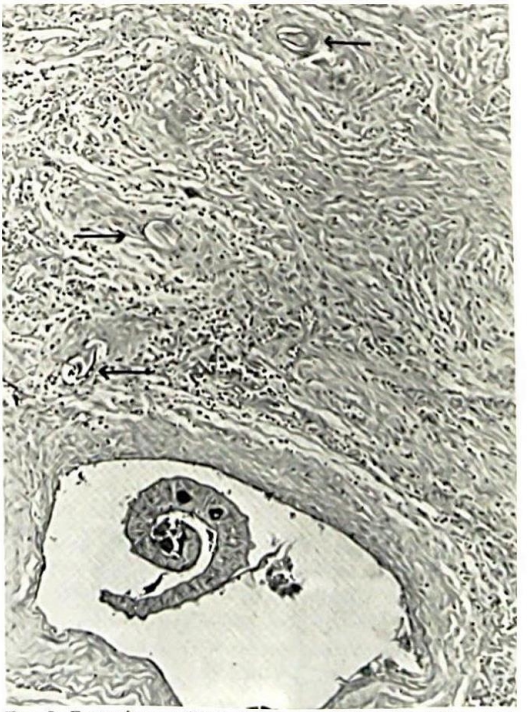

FIG. 8. Extensive established periportal fibrosis with numerous healing granulomata (remains of eggs arrowed). An adult schistosome worm is seen on a large portal vein. H & E, × 70.

FIG. 9. Gross appearance of established pipe-stem portal fibrosis produced by schistosomiasis.

Meleney *et al.* (1952) and Carter & Shaldon (1959), who noticed polymorphonuclear cellular infiltrate in the early stages, the experience of this author is that eosinophils predominate in the early lesions (Bhagwandeen, 1968).

Indeed the eosinophil infiltration may be very intense and may lead to an 'eosinophil abscess' surrounding the egg (Fig. 3). This phenomenon follows death of the miracidium and release of material from within the egg into the tissues precipitating an allergic hypersensitivity reaction. The release of antigenic material has been demonstrated around eggs (Andrade & Barka, 1962).

In my experience this intense eosinophil infiltrate is almost a constant finding in lesions produced by mature viable schistosoma eggs, irrespective of the tissue involved. However, if the eggs are calcified, immature or dead, there is almost no inflammatory reaction (Hashem, 1947).

Further development of the liver lesion

As the lesion around the egg develops there is a typical pseudo-tuberculoid granuloma (Fig. 4). In the centre is the egg or its remnants, peripheral to this is a ring of epitheloid cells and occasionally early giant cells. Surrounding the epitheloid cells are numerous eosinophils and on the periphery scanty lymphocytes. The three-dimensional reconstruction of Main (1963) is very similar. In the immediate vicinity of the granuloma the adjoining portal tract shows some widening due to cellular infiltrate. Kupffer cells show bilharzial pigment.

This histological feature is sufficiently constant in the author's experience to make a confident diagnosis of hepatic schistosomiasis, even in the absence of identifiable eggs in granulomatous lesions. However, in the author's experience serial sections invariably reveal remnants of eggs (Bhagwandeen, 1968).

The schistosomal granuloma as described is the unit of the schistosomal lesion, whichever organ or tissue is involved. It is similar to the tubercle of tuberculosis, or the Aschoff body of rheumatic fever. In the author's experience, presence of plasma cells around schistosomal granuloma is an unusual finding. This contrasts with the view of some authors (Andrade & Barka, 1962; Bogliolo, 1967; Winslow, 1967).

Healing phase of the granuloma

Hereafter the granuloma undergoes progressive healing (Fig. 5). This is first apparent by a diminution of the eosinophil infiltrate. In the centre of the granuloma there may still be remnants of the egg with giant cells attempting to remove it. Surrounding this are a few eosinophils and many more lymphocytes. Peripheral to the cells is a ring of proliferating fibroblasts (Fig. 5).

As the granuloma ages, so the cellular infiltrate becomes progressively more scanty and the fibroblastic proliferation increasingly prominent (Fig. 6).

Healed granuloma

In the last stages of healing there is no longer any evidence of the egg, there is a total absence of inflammatory cells and the only lesions apparent is the gradual collagenization of concentrically layered fibrous tissue (Fig. 7). Eventually all that remains is a small hyalinized scar. At this stage it would not be possible to determine the nature of the lesion unless granulomata in earlier stages of their natural evolution are present as well. There is, however, a variable quantity of bilharzial pigment present in the portal tracts but this cannot be differentiated from malaria pigment.

The role of schistosomal hepatic granuloma in the production of pipe-stem portal fibrosis

In an endemic area where infection is light the presence of occasional granulomata in the portal tracts would produce no major upset. The initial

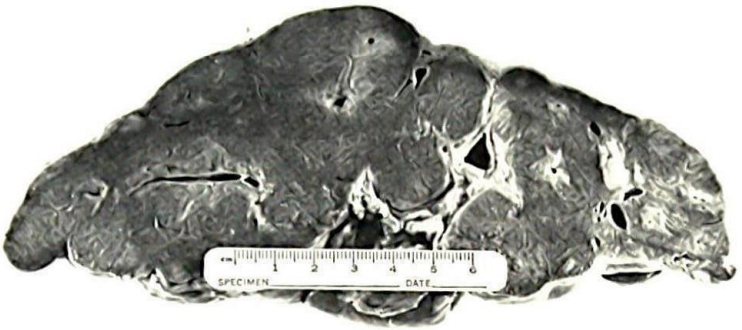

FIG. 10. Cut surface of liver to demonstrate the classical pattern of established pipe-stem portal fibrosis.

lesions are in the finer portal radicles and do not produce any major pathophysiological upset. However, when parasitism is high and egg production is abundant, then egg deposition in the liver will also be increased (Bhagwandeen, 1968). When schistosomal granulomata in the liver are multiplied a hundred-fold (Hashem, 1947; Bhagwandeen, 1968) then there is a major insult to the liver. Should this process be continued over a long period of time, then it is easy to see how confluence of these individual pseudo-tubercles (Fig. 8) could produce significant lesions in the liver even to produce severe grades of pipe-stem portal fibrosis (Figs 9, 10) (Bhagwandeen, 1968).

It is not the intention of this paper to consider in detail the pathogenesis of schistosomal pipe-stem fibrosis. There is even today no unanimity of opinion on this subject (Menezes, 1967; Bogliolo, 1967; De Paola & Winslow, 1967). All authors are agreed, however, that the lesions produced by the eggs play a significant role in hepatic schistosomiasis.

Conclusions

(1) Pipe-stem portal fibrosis is the late stage of hepatic schistosomiasis.

(2) Hepatic schistosomiasis is a result of *S. mansoni* infestation.

(3) The unit of lesion is the schistosomal pseudotubercle, a reaction around individual schistosome eggs.

(4) There is a predominantly eosinophil cellular reaction in the early stages which is later replaced by a fibroblastic reaction in the healing stage.

(5) The pseudo-tubercles are always located in portal tracts.

(6) The severity of the lesions depends on the load of parasitism.

References

ANDRADE, Z.A. & BARKA, T. (1962) Histochemical observations on experimental schistosomiasis in mouse. *Am. J. trop. Med. Hyg.* **11**, 12–16.

ANDRADE, Z.A., PARONETTO, F. & POPPER, H. (1961) Immunocytochemical studies in schistosomiasis. *Am. J. Path.* **39**, 589–597.

BHAGWANDEEN, S.B. (1964) Bilharzial cirrhosis of the Liver. *Med. Proc.* **10**, 199–206.

BHAGWANDEEN, S.B. (1968) *The clinico-pathological manifestations of schistosomiasis in the African and the Indian in Durban*, pp. 121–148. Natal University Press, Pietermaritzberg.

BHAGWANDEEN, S.B. (1973) Bilharzial pipe-stem portal fibrosis in Zambia. *J. Path.* **111**, 23–30.

BHAGWANDEEN, S.B. & BORG-GRECH, V. (1970) The incidence of bilharzia in Lusaka Schools. *Med. J. Zambia*, **4**, 199–203.

BOGLIOLO, L. (1967) The pathogenesis of *Schistosomiasis mansoni*. In: *Bilharziasis*. International Academy of Pathology. Special Monograph (Ed. by F. K. Mostofi), pp. 184–196. Springer-Verlag, Berlin.

CAMERON, G.R. & GANGULY, N.C. (1964) An experimental study of the pathogenesis and reversibility of schistosomal hepatic fibrosis. *J. Path. Bact.* **87**, 217–237.

CARTER, R.A. & SHALDON, S. (1959) The liver in schistosomiasis. *Lancet*, **ii**, 1003–1008.

DEW, H.R. (1923) Observations on the pathology of schistosomiasis (*S. haematobium* & *S. mansoni*) in the human subjects. *J. Path. Bact.* **26**, 27–39.

DE PAOLA, D. & WINSLOW, D.J. (1967) Geographic pathology of *Schistomiasis mansoni*. Studies on liver injury. In: *Bilharziasis*. International Academy of Pathology. Special Monograph (Ed. by F. K. Mostofi), pp. 212–229. Springer-Verlag, Berlin.

EL-GHOLOMY, A., NABAWY, M., GABR, M., AIDAROS, S. & OMAR, A. (1955) Hepatic schistosomiasis in children. *J. trop. Med. Hyg.* **58**, 25–33.

FAIRLEY, N.H. (1920) A comparative study of experimental

bilharziasis in monkeys contrasted with hitherto described lesions in man *J. Path. Bact.* **23**, 289–314.

GELFAND, M. (1962) The relationship between schistosomiasis and cirrhosis of the liver. *S. Afr. Practit.* pp. M1–M2.

GELFAND, M. (1964) A study of cirrhosis of the liver in (a) adult and (b) juvenile Africans with particular reference to the incidence of schistosomal infestation. *Trans. R. Soc. trop. Med. Hyg.* **58**, 339–348.

GILLMAN, T. (1957) Venous obstruction in the pathogenesis of hepatic bilharziasis. A preliminary report of comparative findings in rats, monkeys and man. *Ann. trop. Med. Parasit.* **51**, 409–415.

HASHEM, M. (1947) Etiology and pathogenesis of endemic form of hepatosplenomegaly: Egyptian splenomegaly. *J. roy. Egypt med. Ass.* **30**, 48–79.

HENDERSON, A.C. (1969) *Schistosomiasis mansoni.* Incidence at Luapula Hospital. *Med. J. Zambia*, **2**, 167–169.

HIGGINSON, J. & DE MEILLON, B. (1955) *Schistosoma haematobium* infestation and hepatic disease in man. *Arch. Path.* **60**, 341–346.

KOPPISCH, E. (1943) Manson's Schistosomiasis. *J. Am. med. Ass.* **121**, 936–942.

MAIN, D.M.G. (1963) Three dimensional models of schistosomal lesions. *J. Path. Bact.* **86**, 215–216.

MANSON-BAHR, P.E.C. (1958) The clinical features, diagnosis and host parasite relationship of schistosomiasis in East Africa. *E. Afr. Med. J.* **35**, 401–411.

MELENEY, H.E., MOORE, D.V., MUST, H. & CARNEY, B.H. (1952) The histopathology of experimental schistosomiasis hepatic lesions in mice infected with *S. mansoni*, *S. japonicum* and *S. haematobium*. *Am. J. trop. Med. Hyg.* **1**, 263–286.

MENEZES, H. (1967) *Schistosomiasis mansoni* lesions produced by dead worms. In: *Bilharziasis*. International Academy of Pathology. Special Monograph (Ed by F. K. Mostofi), pp. 175–183. Springer-Verlag, Berlin.

PRATES, M.D. (1961) Cancer and cirrhosis of the liver in the Portuguese East African with special reference to the specific age and sex rates in Lorenco Marques. *Acta Un. int. Canc.* **17**, 718–738.

WINSLOW, D.J. (1967) Histopathology of schistosomiasis. In: *Bilharziasis*. International Academy of Pathology. Special Monograph (Ed. by F. K. Mostofi), pp. 230–241. Springer-Verlag, Berlin.