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FACTORS AFFECTING THE OUTCOME OF TREATMENT OF PULMONARY TUBERCULOSIS IN SUB-OPTIMAL CONDITIONS:

An 18-month Follow-up of 224 Patients

By

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Cirrhosis and Bilharzial Fibrosis of the Liver in Rhodesia

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Bilharziasis is a very common disease in Southern Africa. In Rhodesia infections with both *S. haematobium* and *S. mansoni* are common (Blair, 1965; Clarke, 1966). Amongst the organs in which bilharzial ova are frequently deposited is the liver. Two types of lesion may result. The first, and by far the commonest, is produced when the ova reach the small portal radicles. The ovum dies and a small granuloma, called a pseudotubercle, is formed (Fig. 1). This heals to leave a tiny fibrous nodule (Fig. 2). The extent of damage to liver cells is minimal, so general health is unimpaired. The second type, originally described by Symmers (1904) and called by him clay pipe-stem cirrhosis, is a gross fibrous thickening of main portal areas (Fig. 3). However, as there is no true cirrhosis as defined by Sherlock (1963), the term bilharzial fibrosis of liver is used in preference to clay pipe-stem cirrhosis. Bilharzial fibrosis produces portal hypertension and is therefore a serious complication. The impression is that bilharzial fibrosis is rather uncommon in Rhodesia, but its incidence has not yet been assessed.

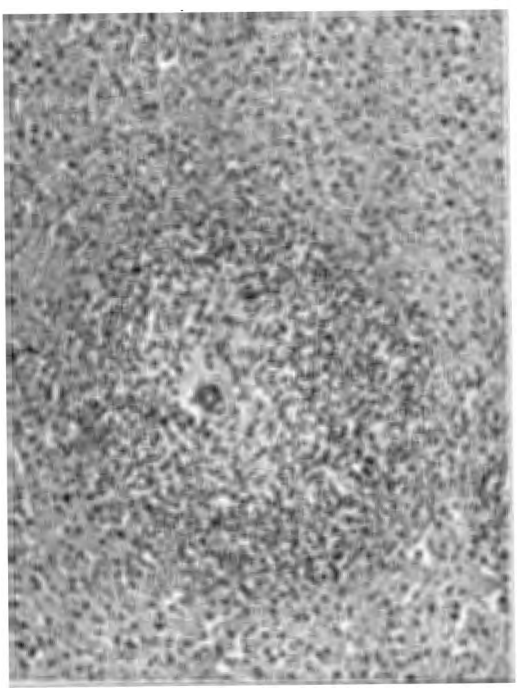

Fig. 1—This shows the typical strictly localised granulomatous reaction that occurs round a dead bilharzial ovum in the liver. H. & E. (x 125.)

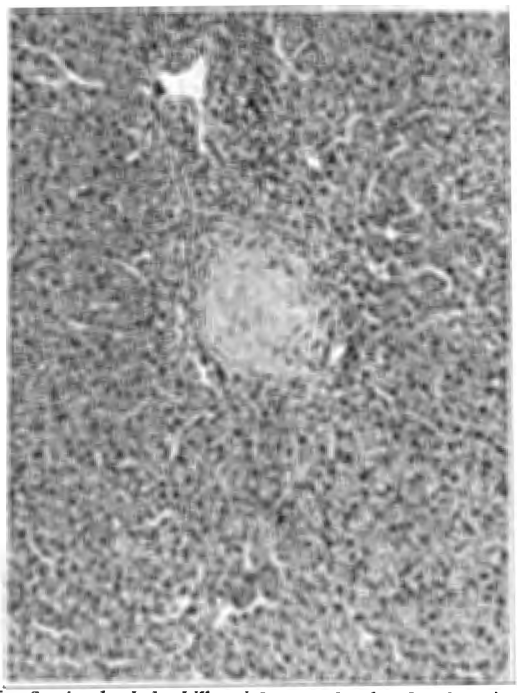

Fig. 2—A healed bilharzial pseudotubercle in liver adjacent to a small portal radicle. H. & E. (x 125.)

The following paper presents the results of a small survey searching for the presence of bilharzial pseudotubercles and bilharzial fibrosis in livers of Rhodesian Africans using autopsy material. The incidence of cirrhosis and the relationship of bilharziasis to cirrhosis is also examined.

Fig. 3—Bilharzial fibrosis of liver. A section of the liver showing gross fibrous thickening of the main portal areas.

MATERIAL AND METHODS

Tissues were derived from 1,000 unselected autopsies on African subjects of all ages. Blocks of tissue were taken from the right lobe of the liver. Each block measured approximately 5 x 10 x 20 mm. Three sections 4μ in thickness were cut from every block, stained with H & E and examined microscopically for the presence of bilharzial tubercles and ova.

In 50 cases, where ova were seen, sections were also stained by the Z.N. method to estimate the incidence of *S. mansoni*. Ova of *S. mansoni* are acid-fast, while those of *S. haematobium* are not (Edington and Gilles, 1969), and this was the criterion used to differentiate the ova of the two species.

RESULTS

Table I shows the incidence of bilharzial pseudotubercles in the liver of each decade. Table II divides the first decade into those subjects under five years and those between five and ten and shows the frequency of the pseudotubercles in the two groups.

It becomes immediately apparent that bilharzial pseudotubercles are rarely found in livers of children under five years. The youngest in this series with tubercles was aged three years. The highest incidence was between five and 20 years. This high level was maintained in males in the third decade, but fell after that. The incidence in females fell after the age of 20 years. Except in subjects under 20 and over 60, fewer females were affected than males.

Table III compares the frequency of cirrhosis and bilharzial fibrosis. In both males and females cirrhosis was more common over the age of 50 than under 50. The incidence of cirrhosis was appreciably higher in males (10.1 per cent.) than females (5.2 per cent.). Bilharzial fibrosis was not common in any age group, but was not found in the very young and the very old. It appeared to occur with equal frequency in both sexes.

In 50 livers with recognisable ova, *S. mansoni* were seen in 24, *S. haematobium* in 13 and both in 13. In the 11 cases of bilharzial fibrosis adult worms were found in two. In one the worms were viable, while in the other they were necrotic. In

Table I

INCIDENCE OF BILHARZIAL PSEUDOTUBERCLES IN LIVER

(1,000 Cases)

Age Decade	MALES			FEMALES		
	Number in Group	No. with Tubercles	Per cent. Affected	Number in Group	No. with Tubercles	Per cent. Affected
1st	101	11	10.9	92	7	7.6
2nd	40	12	30.0	38	11	28.9
3rd	73	22	30.1	67	13	19.4
4th	109	24	22.0	51	6	11.8
5th	110	26	23.7	53	9	17.0
6th	105	21	20.0	40	4	10.0
7th +	76	8	10.5	45	6	13.3
Total	614	124	20.2	386	56	14.5

Table II

INCIDENCE OF BILHARZIAL PSEUDOTUBERCLES IN LIVER

(193 Children in First Decade)

Age	Number in Group	No. with Tubercles	Per cent. Affected
Under 5 years	148	3	2.0
5-10 years	45	14	31.1

the fibrosed portal areas of all 11 cases ova of *S. mansoni* were found, and in eight ova of *S. haematobium* were also present. The fibrous tissue reaction around both types of ova appeared to be approximately the same.

Bilharzial pigment was a common finding in livers with pseudotubercles and with portal fibrosis. The pigment was found in Kupffer cells and portal areas. It did not appear to be responsible for any fibrous tissue reaction.

Table III

INCIDENCE OF CIRRHOSIS AND BILHARZIAL FIBROSIS

(1,000 Cases)

Age Decade	MALES				
	Number in Group	Cirrhosis		Bilharzial Fibrosis	
		No.	Per cent.	No.	Per cent.
1st	101	—	—	—	—
2nd	40	3	7.5	1	2.5
3rd	73	4	5.5	2	2.8
4th	109	7	6.4	1	0.9
5th	110	15	13.6	3	2.7
6th	105	21	20.0	—	—
7th	76	12	15.8	—	—
Total	614	62	10.1	7	1.1

Age Decade	FEMALES				
	Number in Group	Cirrhosis		Bilharzial Fibrosis	
		No.	Per cent.	No.	Per cent.
1st	92	1	1.1	—	—
2nd	38	1	2.6	1	2.6
3rd	67	1	1.5	—	—
4th	51	3	5.9	—	—
5th	53	4	7.5	1	1.9
6th	40	5	12.5	2	5.0
7th	45	5	11.1	—	—
Total	386	20	5.2	4	1.0

DISCUSSION

If one uses the criteria laid down by Himsworth (1954) for the diagnosis of post-necrotic scarring, it is this type of cirrhosis that virtually always occurs in Rhodesian Africans. In many cases there were features suggestive of portal cirrhosis, e.g., the pseudolobules were rather small and comparatively uniform in size. However, in all cases a few normal portal areas and central veins in normal relationship to one another were seen. Alcoholic hyaline (Mallory, 1911) was never demonstrated and fatty change, even of a slight degree, was very uncommon. These findings agree with Edington and Gilles (1969), who state that "the most usual type of cirrhosis seen in the tropics is post-necrotic".

Cirrhosis was twice as common in African males as females. This might be due to some intrinsic factor, because when this type of cirrhosis was produced experimentally in rats, males were more susceptible than females (Himsworth, 1954; Zaki and Hoffbauer, 1966; Patek *et al.*, 1969). It could also be related to environment or diet. Male Africans, for example, consume much larger quantities of traditional beer than females (Buchanan, 1967). As the method of production of this beer is rather crude (Strachan, 1929) many toxic substances are probably elaborated during the process and these may be related to liver damage. Toxic substances in the food may also be important, e.g., Senecio alkaloids present in ragwort have been shown to produce cirrhosis in experimental animals (Schoental and Megee, 1957; Nolan, Scheig and Klatskin, 1966), but as male and female African diet is approximately the same, this would not account for the difference in incidence between the sexes. The absence of cystine in the diet has been shown to produce a post-necrotic type of cirrhosis in rats (Himsworth, 1954). Cystine is found in protein foods and the average African diet is poor in protein, so this may be an important factor. It has been suggested elsewhere in the world that infectious hepatitis may be an important aetiological factor in the production of post-necrotic cirrhosis (Higginson and Keeley, 1960; Sherlock, 1963). As infectious hepatitis is common in Rhodesia it may be, at least in part, responsible for cirrhosis in Africans. Though siderosis is common in this population there is little concrete evidence that haemosiderin plays any part in the genesis of cirrhosis (Buchanan, 1969). Cirrhosis would not appear to be related to the deposition of bilharzial ova, as ova were not seen in the scar tissue of any of the 82 cases of cirrhosis examined. Forbes and Gel-

fand (1962) also found no bilharzial lesions in 30 cases of cirrhosis of liver.

Eighteen per cent. of the livers examined contained pseudotubercles. This is a lower incidence than reported by Gelfand (1967). That author found that the average incidence of bilharziasis in his series of 400 autopsies was approximately 75 per cent., and 50 per cent. subjects with bilharziasis had ova in the liver. The discrepancy is probably due to the fact that Gelfand used a digestion technique which resulted in the examination of a larger piece of tissue than seen in the present series. Thus the incidence of 18 per cent. found here does not reflect the true incidence, which is much higher.

It has been noted elsewhere (Mohamed, 1936) that in most cases of bilharzial fibrosis the numbers of ova seen in the liver are small in comparison to the extensive fibrosis. This has given rise to the suggestion that the fibrous tissue reaction is not due to ova but to male worm infestation of the liver alone (Girges, 1931; Girges, 1932) or to toxic products of the worm (Dew, 1923; Gillman, 1957). A further theory was that the fibrosis was the result of an abnormal immune response (Edington and Gilles, 1969). If this were so the abnormal immune response must be to the worm and not to ova, because excessive fibrous tissue reaction is never seen round single ova in pseudotubercles. Another important point is that though in some cases of bilharzial fibrosis ova are scanty, there are others in which ova are present in the portal areas in quite sufficient numbers to account for the degree of fibrosis seen.

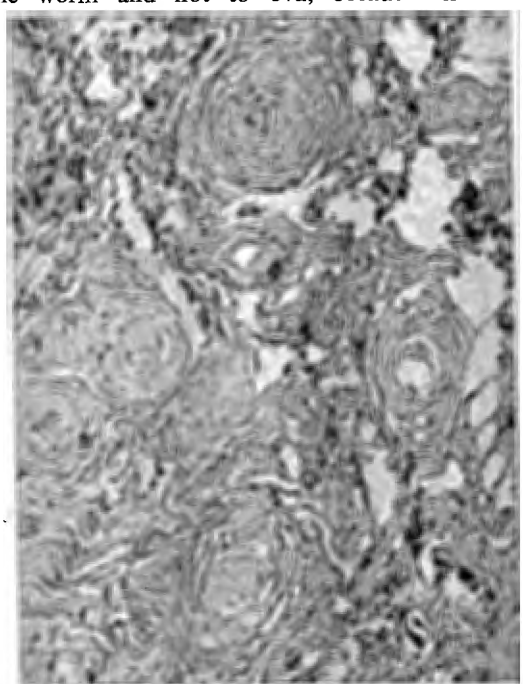

Fig. 4—This is a section taken from the normal layer of the colon in a case of severe intestinal bilharziasis. The ova are absorbed, but the remaining fibrous tissue has still a whorled appearance. H. & E. (x 125.)

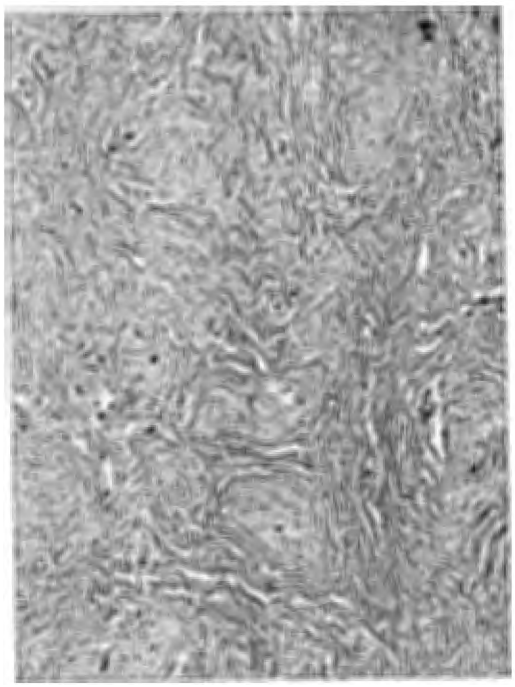

Fig. 5—A section taken from another site in the colon of the same patient. Here the whorled pattern of the fibrous tissue can just be recognised. H. & E. (x 125.)

Experimental evidence that bilharzial ova were responsible for clay pipe-stem fibrosis was provided by Warren (1966). He infected mice with relatively small numbers of carcariae of *Schistosoma mansoni*. The development of the liver lesions was followed over a period of 52 weeks and it was observed that a clay pipe-stem fibrosis developed. Ova were gradually absorbed and it appeared that the fibrotic bands of the greatly thickened portal areas originated from residual collagen around the granulomas.

The findings in the present investigation seem to indicate that ova were responsible for the fibrosis. In all, 11 cases of bilharzial fibrosis ova were found in the grossly fibrosed portal radicles, albeit in some the ova were very scanty. There is no reason to believe that because ova were scanty or absent in the fibrosed portal areas that there never were ova at this site. Experience gained from examination of human histological material from organs other than liver indicates that ova

are frequently completely absorbed. Directly after absorption there remain small nodules of relatively acellular collagenous tissue, still with a whorled pattern (Fig. 4). In older lesions the whorled pattern disappears and bands of collagen without special arrangement are left (Figs. 5 and 6). It is believed by the writer that it is at this last stage that many cases of bilharzial fibrosis are seen at autopsy, giving rise to the impression that ova are not responsible for the fibrosis.

In only two of the livers in the present series were adult worms found. In one case the worm was viable and had evoked no inflammatory response (Fig. 7). In the other there was a granulo-

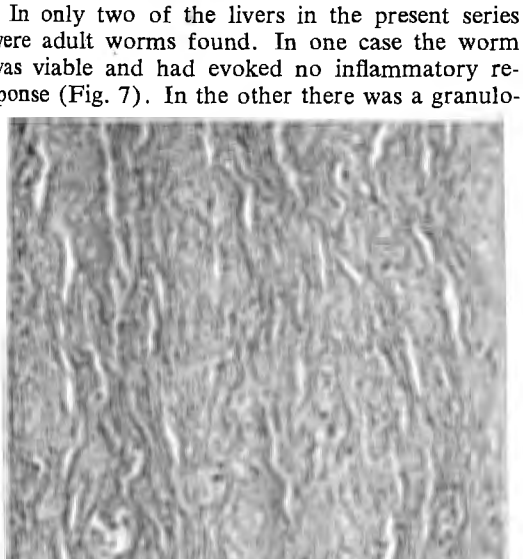

Fig. 6—At a third site in the same tissue the whorled pattern has completely disappeared. One ovum is seen. This is a common appearance in the enlarged portal areas of portal fibrosis. H. & E. (x 125.)

matous response with obvious fibroblastic proliferation round a dead schistosome (Fig. 8). Following the complete disintegration of the dead worm, there would undoubtedly be some residual fibrous tissue. As a result of this observation it is felt that though adult schistosomes may partly contribute to the fibrosis in liver, in these cases the most important cause is the deposition of the ova.

In the thickened portal areas of three cases of bilharzial fibrosis only *S. mansoni* ova were found, while in the remaining eight cases ova of both *S. mansoni* and *S. haematobium* were seen. As the ova of *S. haematobium* appeared to have

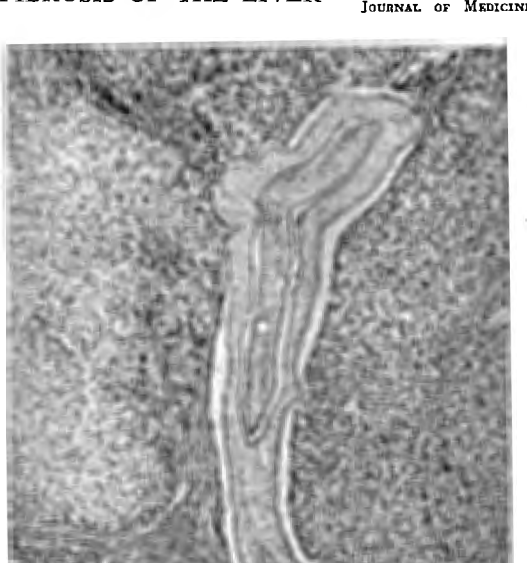

Fig. 7—A viable schistosome in a small portal vein at the edge of a grossly thickened portal area. H. & E. (x 44.)

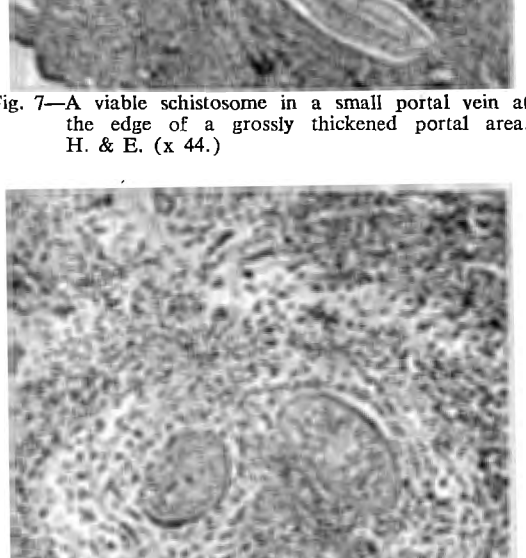

Fig. 8—A dead schistosome in a fibrosed portal area showing fibroblastic reaction and a cellular infiltrate composed largely of eosinophils and lymphocytes. H. & E. (x 125.)

evoked as much fibrous tissue response as that of *S. mansoni*, it would appear possible that bilharzial fibrosis could be produced by *S. haematobium* alone. Erfan (1947) implies that *S. haematobium* alone can produce bilharzial fibrosis, but details no cases and cites no references in support of this. Also, though a significant relationship between hepatomegally and *S. mansoni* infection has been shown in Rhodesian African children, there was no relationship between *S. haematobium* and hepatomegally (Whittle, *et al.*, 1969).

SUMMARY

Examination of sections of liver from 1,000 African autopsies showed cirrhosis to be present in 8.2 per cent. and bilharzial fibrosis in 1.1 per cent. Cirrhosis is always post-necrotic in type and is about twice as common in males than females. Bilharzial fibrosis shows no sex bias.

Despite the fact that ova are frequently not plentiful in bilharzial fibrosis, it is thought that they rather than adult schistosomes are responsible for the fibrosis. Experimental evidence of others and personal observations on human tissues are detailed in support of this thesis.

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