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SCHISTOSOMIASIS MANSONI

PATHOLOGICAL CHANGES IN THE LIVER IN DIFFERENT STAGES OF THE DISEASE STUDIED BY MEANS OF LAPAROSCOPY AND NEEDLE BIOPSY

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SUMMARY

In 30 patients suffering from mansonian schistosomiasis, in whom no other diseases of the liver were verified, the anatomo-pathological changes in the liver were studied by means of photographic laparoscopy and needle biopsy, and were correlated with clinical, radiological, esophagoscopical, rectosigmoidoscopical and laboratorial findings. The patients were classified into four groups. Macroscopically, the liver showed in the first group a smooth surface, in the second group it had an irregular surface with furrow-like depressions, in the third group it presented a gross nodular appearance, and in the fourth group it was coated with a layer of fibrous tissue. The needle biopsy of the liver revealed in all patients a qualitatively similar histopathological picture; quantitatively the changes were more pronounced in the last two groups. The characteristic histopathological findings were: periportal fibrosis and cell infiltration, Kupffer cell reaction, black pigment deposits and granulomata with or without ova; lobular architecture was little affected and there were only mild degenerative changes of the hepatic cells. In one patient belonging to the group III, in whom the liver was examined post mortem, lesions due to the occlusion of portal branches by dead worms were also found. Clinically, the groups I and II corresponded to the intestinal form, and the groups III and IV to the hepato-splenic form of the mansonian schistosomiasis. In patients of the first two groups there was no evidence of portal hypertension and there were few or no clinical signs of hepatic involvement. In patients of the last two groups the predominant symptoms were those due to portal hypertension; all of them had esophageal varicosities and splenomegaly.

INTRODUCTION

In spite of the fact that a great deal of research work on mansonian schistosomiasis has been done in the last 50 years, the pathology of this parasitosis still presents some controversial points, especially in regard to the pathogenesis of hepatic lesions. The different points of view on this subject were critically reviewed in a recent paper by BOGLIOLO [1]. The opinions of Brazilian pathologists present at the 8th Brazilian Congress of Gastroenterology, Bahia, 1956 were summarized by SIFFERT [6].

The studies on the pathology of the mansonian schistosomiasis reported in the medical literature are based chiefly on the post mortem examinations and liver biopsies performed in cases in which the disease was already far advanced. Our investigations,

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on which we wish to report in this paper, were carried out in a different way: in a series of patients with different physical signs of the disease the anatomo-pathological changes in the liver were determined *in vivo* by means of laparoscopy and needle biopsy, performed under visual control, and were correlated with clinical, radiological, esophagoscopical, rectosigmoidoscopical and laboratorial findings.

PATIENTS STUDIED

Between September 1956 and December 1957 118 patients have been seen in our out-patient department in whom the feces examination or biopsy of the rectal mucosa revealed ova of *Schistosoma mansoni*. These patients were submitted to a screening procedure by which 88 of them were excluded from further study because of one or more of following circumstances: a) past history of a hepato-biliary affection other than schistosomiasis; b) past history of malaria, alcoholism and malnutrition; c) positive serological tests for syphilis or/and Chagas' disease. The remaining 30 patients in whom, except for intestinal helminthic infestations, there was no evidence of a concomitant disease, were the subjects of our study. All of them were born in the endemic areas of mansonian schistosomiasis situated in eastern and northeastern States of Brazil and were exposed to schistosomotic infestation from the early years of their lives till the time of their departure from those areas. With exception of one patient (case 6), they had no previous treatment for schistosomiasis. Their personal data are resumed in table I.

TABLE I

Personal Data of the Patients Studied

Case	*Sex*	*Age*	*Race* *	*Endemic area coming from (State)*	*Time since departure from endemic area*	*Concomitant intestinal parasitoses*
1	m.	23	m.	Alagoas	4 y	—
2	m.	27	w.	Alagoas	6 y.	*Ancylostoma, Strongyloides*
3	f.	24	w.	Pernambuco	6 y.	—
4	m.	14	m.	Minas Gerais	3 m.	*Ancylostoma, Strongyloides Trichuris*
5	m.	17	m.	Bahia	9 y.	*Ascaris, Trichuris*
6	m.	33	w.	Pernambuco	10 y.	—
7	m.	19	w.	Pernambuco	6 m.	—
8	m.	23	m.	Alagoas	2 y.	*Ancylostoma, Ascaris, Trichuris*
9	m.	19	m.	Alagoas	9 m.	*Ancylostoma, Ascaris, Trichuris*
10	f.	29	m.	Alagoas	17 y.	*Ancylostoma*
11	m.	39	w.	Sergipe	1 y.	—
12	f.	31	w.	Minas Gerais	3 y.	*Hymenolepis nana*
13	f.	20	m.	Alagoas	7 y.	*Trichuris*
14	f.	25	w.	Bahia	8 m.	*Ascaris*
15	f.	26	w.	Pernambuco	5 y.	—
16	f.	33	m.	Bahia	6 y.	*Trichuris*
17	f.	23	w.	Alagoas	3 y.	—
18	m.	34	m.	Bahia	10 y.	—
19	m.	55	w.	Pernambuco	9 y.	*Ancylostoma*
20	m.	32	m.	Alagoas	4 y.	*Ancylostoma, Trichuris*
21	m.	21	w.	Bahia	2 y.	*Ancylostoma, Trichuris*
22	m.	28	w.	Bahia	1 m.	*Ancylostoma*
23	m.	19	w.	Bahia	4 y.	*Ancylostoma*
24	f.	28	w.	Alagoas	2 y.	—
25	f.	30	w.	Bahia	2 y.	*Ancylostoma, Ascaris*
26	m.	28	w.	Pernambuco	1 m.	*Ancylostoma*
27	m.	44	w.	Alagoas	27 y.	*Ancylostoma, Hymenolepis nana*
28	m.	15	w.	Minas Gerais	1 m.	*Ancylostoma*
29	f.	56	w.	Bahia	2 y.	*Ancylostoma, Trichuris*
30	f.	31	w.	Bahia	1 y.	*Ancylostoma*

* w. = white, m. = mulatto.

METHODS OF STUDY

The study of our patients was carried out by means of the following examinations and tests:

1) Anamnesis and physical examination.

2) Laparoscopy, by which the macroscopic appearance of the liver and other intra-abdominal organs, such as could be visualized, was determined and recorded in color photographs *.

3) Liver biopsy performed with the Silverman needle during the laparoscopy. The biopsy needle was inserted deep into the right or left lobe at a point several centimeters distant from the anterior edge. The liver tissue specimens obtained were fixed in formalin and embeded in paraffin; 6 to 15 slices were cut and mounted in three different slides of which one was stained by hematoxylin-eosin, other by P.A.S. and the third by the method of Perdrau-van Gieson.

4) X-ray examination of the lungs, heart, eosophagus, stomach and duodenum.

5) Esophagoscopy.

6) Rectosigmoidoscopy.

7) Splenoportography (performed in 6 patients).

8) Laboratorial tests for evaluation of the liver function indicated in table II.

9) Hematological study: erythrocyte count, hemoglobin determination and leukocyte count.

10) In one patient (case 28) who died from a fatal hemorrhage three weeks after the study was completed, the post mortem examination was made in addition.

TABLE II

Laboratorial Tests Concerning the Liver Function — Methods Employed and Values Considered Normal

Test	*Method*	*Normal values*
Bromsulphalein retention	Retention determined 45 minutes after injection of 5 mg. per kg. body weight of dye	0 — 5%
Zinc sulfate turbidity	Kunkel	2 — 12 units
Thymol turbidity	Maclagan	0,8 — 5 units
Thymol flocculation	Neefe-Reinhold	0 — 1+
Cephalin-cholesterol flocculation	Hanger	0 — 2+
Iodine (Lugol) test	Salazar Mallén	0
Serum protein, total and fractions	Gornall-Bardawill-David	total: 6,0 — 8,0 gm. per 100 ml. albumin: 4,0 — 5,8 gm. per 100 ml. globulin: 1,0 — 3,0 gm. per 100 ml.
Serum bilirubin	Malloy-Evelyn, mod. Watson	total: 0,2 — 1,0 mg.% prompt reacting: 0 — 0,2 mg.%
Serum alkaline phosphatase	King-Armstrong	3,7 — 13,1 units per 100 ml.
Serum cholesterol	Sheftel	150 — 230 mg.%

* Instrument used was the Foto-Laparoskop manufactured by Deutsche Endoskopbau Gesellschaft Sass, Wolf & Co., Berlin.

RESULTS

The purpose of our study was to determine the anatomo-pathological changes that occurred in the liver and other organs and to correlate them with the laboratorial and clinical findings. The results of this study permitted to distinguish amongst our patients four groups with different pathological pictures.

Group I (Cases 1 to 9)

Macroscopic appearance of the liver and gall bladder. The liver was either normal in size or moderately enlarged (fig. 1) having a sharp or slightly rounded anterior edge. The color of the liver was red or reddish brown; the surface was smooth and brilliant. In 5 patients (cases 2, 3, 4, 6 and 8) whitish spots, up to a few milimeters in diameter, were observed on the surface (plate I, fig. A). In one patient (case 6) there were several violin-string adhesions between the anterior liver surface and the diaphragm. The gall bladder was visualized in 4 patients (cases 3, 4, 6 and 8) being in all instances filled and of normal appearance.

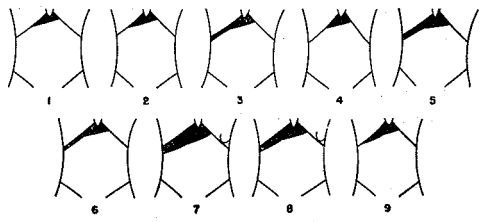

Fig. 1 — Patients of the Group I. Size of the liver and spleen.

Histopathology of the liver. Histopathological changes in the liver found in the patients of this group are shown in table III.

TABLE III

Patients of the Group I — Histopathological Findings in the Liver

	Case No.								
	1	2	3	4	5	6	7	8	9
Lobular disarray	1+	—	1+	—	—	—	—	—	—
Fibrosis — periportal	1+	1+	2+	1+	1+	1+	2+	2+	1+
Fibrosis — intralobular	1+	—	1+	—	—	—	1+	—	—
Infiltration of mononuclear cells — periportal	1+	1+	2+	3+	1+	1+	2+	1+	1+
Infiltration of mononuclear cells — intralobular	1+	1+	1+	1+	1+	—	1+	1+	1+
Kupffer cell reaction	2+	2+	1+	2+	2+	1+	2+	2+	1+
Bile duct proliferation	—	—	—	—	—	—	1+	—	—
Pigment deposits — black, granular	1+	1+	1+	2+	1+	2+	3+	1+	1+
Pigment deposits — hemosiderin	—	1+	2+	1+	—	2+	1+	1+	—
Pigment deposits — bile	—	1+	—	—	—	—	—	—	—
Granulomata — active	—	—	1+	2+	1+	—	1+	1+	1+
Granulomata — in regression	—	—	—	—	1+	—	1+	1+	—
Granulomata — containing ova of *Schistosoma mansoni*	—	—	—	1+	1+	—	2+	—	—
Liver cells — degeneration	1+	1+	2+	1+	2+	1+	1+	1+	1+
Liver cells — necrosis	—	—	—	—	1+	—	—	—	—
Liver cells — regeneration	2+	1+	1+	1+	1+	1+	1+	1+	1+

— absent
1+ slight (small number or quantity)
2+ moderate (moderate number or quantity)
3+ intense (great number or quantity)

Spleen. A slight splenomegaly was present in 2 patients (cases 7 and 8; fig. 1).

Peritoneum. The peritoneum was normal as far as it could be examined by laparoscopy.

Collateral circulation. No collateral circulation was found in the patients of this group.

Rectal mucosa. The rectal mucosa was in all patients slightly edematous showing scattered areas with granular appearance and hyperemia.

Laboratorial findings. The results of the laboratorial tests concerning the liver function are indicated in table IV.

Hematological study did not reveal any characteristic changes. The erythrocyte count and determination of hemoglobin showed values from 4 to 6 million per c.mm. for erythrocytes, and from 12 to 17 gm./100 ml. for hemoglobin. The number of leukocytes varied between 5,000 and 15,000 per c.mm.; the differential count showed a moderate to intense eosinophilia.

Clinical symptomatology. Clinical symptoms presented by the patients of this group are indicated in table VII.

Group II (Cases 10 to 18)

Macroscopic appearance of the liver and gall bladder. The liver was either normal in size or moderately enlarged (fig. 2) having a sharp or slightly rounded anterior edge. The color of the liver was brown or reddish brown; the surface was irregular, rough, showing depressions in form of shallow, straight or tortuous furrows, which varied in length between a few milimeters and several centimeters. In these depressions and nearby, the liver capsule was opaque (plate I, fig. B). The gall bladder was visualized

TABLE IV

Patients of the Group I — Laboratorial Tests Concerning the Liver Function

	Case No.								
	1	2	3	4	5	6	7	8	9
Bromsulphalein retention (45 minutes) %	3	3	1	1	0,5	1	2	2	1
Zinc sulfate turbidity	16,3	11,4	15,6	13,1	10,6	14,4	10,4	8,0	13,1
Thymol turbidity	4,0	1,4	4,3	4,3	4,6	5,3	3,9	0,5	4,3
Thymol flocculation	—	—	—	2+	2+	—	—	—	—
Cephalin-cholesterol flocculation	1+	2+	—	2+	2+	2+	2+	1+	2+
Iodine test	—	—	—	—	—	—	—	—	—
Serum protein gm./100 ml. — total	7,0	7,2	7,5	8,3	7,9	7,5	8,0	7,4	8,3
Serum protein gm./100 ml. — albumin	4,0	5,0	5,1	5,4	4,3	5,2	5,0	3,8	5,4
Serum protein gm./100 ml. — globulin	3,0	2,2	2,4	2,9	3,6	2,3	3,0	3,6	2,9
Serum protein gm./100 ml. — a./g. ratio	1,3	2,3	2,1	1,9	1,2	2,3	1,7	1,0	1,9
Serum bilirubin mg.% — total	0,4	0,6	0,2	0,6	0,5	0,5	0,2	0,7	0,6
Serum bilirubin mg.% — prompt-reacting	0,1	0	0	0,1	0	0	0,1	0	0
Serum alkaline phosphatase King-Armstrong units	6,1	3,6	4,9	3,2	2,6	2,6	3,8	5,4	4,2
Serum cholesterol (total) mg.%	177	123	118	162	114	168	139	126	172

in 6 patients (cases 12, 13, 14, 15, 16 and 17); in all instances, it was filled and of normal appearance.

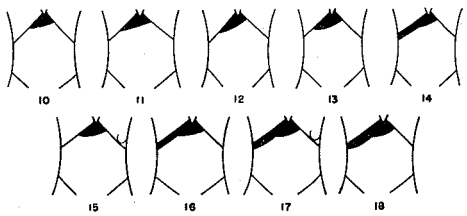

Fig. 2 — Patients of the Group II. Size of the liver and spleen.

Histopathology of the liver. Histopathological alterations in the liver found in the patients of this group are shown in table V.

Spleen. A slight splenomegaly was present in 2 patients (cases 15 and 17; fig. 2).

Peritoneum. No pathological changes were found neither on parietal nor on visceral peritoneum.

Collateral circulation. No collateral circulation was found in the patients of this group.

Rectal mucosa. The rectal mucosa showed, like in the patients of group I, a slightly edematous and granular appearance with areas of hyperemia.

Laboratorial findings. The results of the laboratorial tests concerning the liver function are indicated in table VI.

Hematological study did not reveal any characteristic changes. The values for erythro-

TABLE V

Patients of the Group II — Histopathological Findings in the Liver

	Case No.								
	10	*11*	*12*	*13*	*14*	*15*	*16*	*17*	*18*
Lobular disarray	—	1+	—	—	1+	—	1+	1+	—
Fibrosis — periportal	1+	2+	1+	1+	1+	1+	1+	1+	1+
Fibrosis — intralobular	—	1+	—	1+	—	—	1+	1+	1+
Infiltration of mononuclear cells — periportal	1+	1+	1+	1+	1+	1+	1+	1+	1+
Infiltration of mononuclear cells — intralobular	—	1+	1+	1+	1+	1+	1+	1+	2+
Kupffer cell reaction	1+	2+	2+	1+	2+	1+	2+	1+	1+
Bile duct proliferation	—	—	—	—	—	—	—	—	—
Pigment deposits — black, granular	2+	2+	1+	1+	3+	1+	1+	1+	—
Pigment deposits — hemosiderin	1+	1+	—	—	1+	1+	1+	1+	1+
Pigment deposits — bile	—	—	—	—	—	—	1+	—	—
Granulomata — active	1+	—	1+	—	2+	—	2+	—	—
Granulomata — in regression	1+	—	—	—	—	—	—	—	1+
Granulomata — containing ova of *Schistosoma mansoni*	2+	—	1+	—	1+	—	2+	—	—
Liver cells — degeneration	1+	2+	1+	1+	1+	1+	1+	1+	2+
Liver cells — necrosis	—	—	—	—	—	—	—	—	—
Liver cells — regeneration	1+	1+	1+	1+	1+	1+	2+	1+	1+

— absent
1+ slight (small number or quantity)
2+ moderate (moderate number or quantity)
3+ intense (great number or quantity)

TABLE VI

Patients of the Group II — Laboratorial Tests Concerning the Liver Function

	Case No.								
	10	*11*	*12*	*13*	*14*	*15*	*16*	*17*	*18*
Bromsulphalein retention (45 minutes) %	2	6	7	0,5	6	0,5	1,5	0,5	0,5
Zinc sulfate turbidity	13,1	14,9	14,0	11,4	13,5	16,3	26,3	12,6	13,2
Thymol turbidity	4,0	4,3	2,5	2,5	3,4	4,9	6,6	2,5	5,3
Thymol flocculation	3+	2+	3+	3+	—	3+	3+	3+	3+
Cephalin-cholesterol flocculation	3+	1+	2+	2+	1+	2+	2+	3+	3+
Iodine test	—	—	—	—	—	—	—	—	—
Serum protein gm./100 ml. — total	8,8	6,4	7,1	7,7	7,7	8,3	8,0	6,4	7,9
Serum protein gm./100 ml. — albumin	5,7	4,3	5,0	5,5	4,9	5,7	5,4	5,1	5,2
Serum protein gm./100 ml. — globulin	3,1	2,1	2,1	2,2	2,8	2,6	2,6	2,3	2,7
Serum protein gm./100 ml. — a./g. ratio	1,8	2,0	2,4	2,5	1,7	2,2	2,1	1,8	1,9
Serum bilirubin mg.% — total	0,7	0,4	0,4	0,4	0,5	0,6	0,5	0,3	0,4
Serum bilirubin mg.% — prompt-reacting	0,1	0,1	0	0,1	0,1	0,1	0	0	0
Serum alkaline phosphatase King-Armstrong units	4,7	3,1	6,4	4,0	3,2	5,2	4,8	4,6	5,3
Serum cholesterol (total) mg.%	195	206	134	168	190	184	265	142	228

cytes were between 4 and 5 million per c.mm., for hemoglobin between 13.4 and 16.9 gm./100 ml., and for leukocytes between 5,000 and 12,000 per c.mm.

Clinical symptomatology. Clinical symptoms presented by the patients of this group are indicated in table VII.

TABLE VII

Patients of the Groups I (Cases 1 to 9) and II (Cases 10 to 18) — Clinical Symptoms

	Case No.																	
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14*	*15*	*16*	*17*	*18*
Asthenia	—	+	—	—	—	—	—	+	+	+	+	+	+	+	+	+	+	—
Anorexia	—	—	—	—	—	—	—	—	—	+	+	—	—	—	—	—	—	—
Postcibal fullness	—	—	—	—	—	—	—	—	—	+	+	—	—	—	—	+	+	—
Constant dull pain in upper abdomen	+	—	—	—	+	+	+	—	—	+	+	+	—	—	—	—	—	+
Periodical attacks of dysentery	—	+	—	—	+	+	+	+	+	+	+	+	+	+	+	+	+	—
Constipation	+	+	—	+	—	+	+	—	—	+	—	—	—	—	—	+	+	—
Epistaxis	—	—	+	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Aching sensation in muscles and joints	—	+	—	—	+	+	—	—	—	—	—	—	+	—	—	—	—	—

— absent, + present

Group III (Cases 19 to 28)

Macroscopic appearance of the liver and gall bladder. The liver was enlarged (fig. 3) and deformed; the anterior edge was irregular, indented. The surface was gross nodular; between the nodules there were furrow-like depressions or flat depressed areas. The nodules had a brown or reddish brown color, while the depressions showed frequently a whitish aspect (plate I, fig. C and D). In 4 patients (cases 25, 26, 27 and 28) the liver had a typical "Kartoffelleber" appearance (fig. 10). The gall bladder was visualized in 3 patients (cases 19, 21 and 28); it was filled and of normal appearance in all instances.

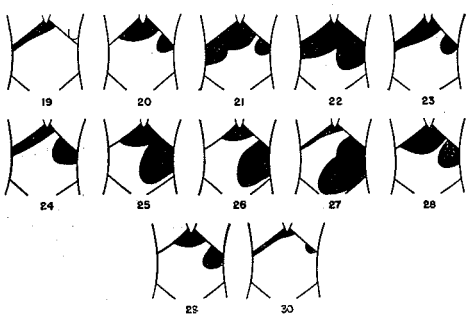

Fig. 3 — Patients of the Groups III and IV. Size of the liver and spleen.

Histopathology of the liver. See table VIII.

Spleen. All patients of this group presented splenomegaly which in some of them reached enormous proportions (fig. 3). The color of the spleen was reddish or dark brown; in some instances there existed thick fibrous patches on the surface; frequently the great omentum was adhered to the spleen.

Peritoneum. Except for changes in vascularity, referred below, and for loss of normal sheen in patients with ascites, there were no pathological findings.

Collateral circulation. Esophageal varices were present in all patients of this group. There was no collateral circulation visible on the external side of the abdominal wall; inside the abdomen, however, the laparoscopy revealed enlarged veins in nearly all instances. In 4 patients hemorrhoidal varicosities were found. For details see table IX.

Heart and lungs. In one patient of this group (case 28) the clinical and X-ray examination of the chest revealed a great enlargement of the heart, with the predominance of the right ventricle. This patient died later; at autopsy dilatation and hypertrophy of the right atrium and ventricle, and schistosomotic pulmonary arteritis were found. These findings were reported in detil in another paper [5].

Rectal mucosa. The rectal mucosa showed an edematous and granular appearance with scarce ecchymoses.

Laboratorial findings. The results of the laboratorial tests concerning the liver function are indicated in table X.

Hematological findings are shown in table XI.

Clinical symptomatology. Clinical symptoms presented by the patients of this group are shown in table XII.

Group IV (Cases 29 and 30)

Macroscopic appearance of the liver and gall bladder. In both patients of this group the liver was enlarged (fig. 3), deformed and coated with a layer of fibrous tissue. It presented the typical appearance of the "Zuckergussleber" (plate II, fig. A). The gall bladder was partly filled and also covered with a fibrous layer.

Histopathology of the liver. See table VIII.

Spleen. Splenomegaly was present in both patients (fig. 3). The spleen, like the liver, showed a thick fibrous coating.

Peritoneum. Except for loss of normal sheen, there were no pathological findings.

Collateral circulation. Both patients had esophageal varices as well as intra-abdominal collateral circulation. In one of them (case 29) hemorrhoids were found (table IX).

Rectal mucosa. The rectal mucosa showed the same appearance seen in the patients of other three groups.

Laboratorial findings. The laboratorial findings are shown in tables X and XI.

Clinical symptomatology. See table XII.

TABLE VIII

Patients of the Groups III (Cases 19 to 28) and IV (Cases 29 and 30) Histopathological Findings in the Liver

	Case No.											
	19	20	21	22	23	24	25	26	27	28	29	30
Lobular disarray	2+	—	2+	1+	1+	—	3+	2+	3+	3+	1+	1+
Fibrosis — periportal	3+	1+	2+	2+	2+	2+	3+	2+	2+	3+	1+	2+
Fibrosis — intralobular	1+	—	2+	1+	1+	1+	3+	2+	2+	2+	—	2+
Infiltration of mononuclear cells — periportal	2+	1+	1+	1+	2+	1+	2+	2+	2+	2+	1+	2+
Infiltration of mononuclear cells — intralobular	1+	1+	1+	1+	1+	1+	1+	2+	1+	1+	2+	1+
Kupffer cell reaction	2+	2+	2+	2+	2+	2+	2+	2+	3+	2+	2+	2+
Bile duct proliferation	1+	—	1+	1+	—	—	3+	—	1+	1+	—	1+
Pigment deposits — black, granular	1+	2+	1+	1+	3+	1+	2+	1+	3+	3+	2+	2+
Pigment deposits — hemosiderin	2+	—	—	—	—	—	1+	—	1+	—	—	1+
Pigment deposits — bile	2+	—	—	1+	—	1+	—	—	—	—	—	1+
Granulomata — active	—	—	1+	—	—	—	—	—	2+	—	—	2+
Granulomata — in regression	—	—	1+	—	—	—	—	—	1+	—	—	—
Granulomata — containing ova of *Schistosoma mansoni*	—	—	2+	—	—	—	—	—	1+	—	—	2+
Liver cells — degeneration	1+	1+	2+	1+	1+	1+	2+	1+	1+	1+	2+	1+
Liver cells — necrosis	—	—	—	—	—	—	—	—	—	—	—	—
Liver cells — regeneration	1+	1+	1+	3+	+1	1+	2+	1+	1+	2+	1+	1+

— absent
1+ slight (small number or quantity)
2+ moderate (moderate number or quantity)
3+ intense (great number or quantity)

TABLE IX

Patients of the Groups III (Cases 19 to 28) and IV (Cases 29 and 30) — Collateral Circulation

Case	*Esophageal varices (Esophagoscopy)*	*Hemorrhoids (Rectosigmoidoscopy)*	*Intra-abdominal collateral circulation (Laparoscopy)*	*Veins of the portal system contrasted at splenoportography*
19	small, lower third	—	networks of small vessels in upper part of abdominal wall, vein enlargements in great omentum, adhesions of great omentum to abdominal wall	
20	small, lower third near cardia	large	networks of small vessels in upper part of abdominal wall (plate II, fig. B)	
21	small, limit of middle and lower third	—	—	
22	small, lower third	—	networks of small vessels in upper part of abdominal wall, vein enlargements in great omentum	splenic, short gastric, portal
23	small, lower third	—	networks of small vessels in upper and lower part of abdominal wall	splenic, short, gastric, portal
24	small, lower third	small	a vein of large caliber running in ligamentum teres and continuing in another large vein going from umbilicus to left groin (plate II, fig. D)	splenic, portal, umbilical
25	small, lower third	large	vein elargements on anterior gastric wall and in great omentum	
26	large, middle and lower third	large	—	
27	small, lower third	—	enlarged veins in upper part of abdominal wall (plate II, fig. C)	
28	large, lower third	—	—	splenic, short gastric, inferior mesenteric, coronary, portal
29	large, lower third	small	vein enlargements on anterior gastric wall and in great omentum	splenic, short gastric, inferior mesenteric, coronary, portal
30	small, lower third	small	—	splenic, inferior mesenteric, coronary, portal

TABLE X

Patients of the Groups III (Cases 19 to 28) and IV (Cases 29 and 30) — Laboratorial Tests Concerning the Liver Function

	Case No.											
	19	*20*	*21*	*22*	*23*	*24*	*25*	*26*	*27*	*28*	*29*	*30*
Bromsulphalein retention (45 minutes) %	3	5	9,5	14	4	8	12	6	3	12	13	4,5
Zinc sulfate turbidity	19,4	14,8	17,1	27,5	25,6	17,8	16,2	11,4	10,0	20,0	23,0	26,3
Thymol turbidity	8,2	6,5	6,0	8,3	2,6	6,6	8,1	4,8	2,5	9,4	11,4	4,6
Thymol flocculation	3+	2+	3+	3+	1+	3+	3+	3+	3+	3+	3+	3+
Cephalin-cholesterol flocculation	2+	2+	3+	4+	—	3+	2+	2+	2+	3+	2+	3+
Iodine test	1+	—	2+	1+	1+	—	1+	—	—	1+	2+	2+
Serum protein gm./100 ml. — total	5,9	8,1	8,2	9,8	8,3	6,4	9,3	7,9	5,8	7,2	7,2	8,0
Serum protein gm./100 ml. — albumin	2,4	5,4	5,0	4,6	4,4	4,5	4,5	4,7	3,7	3,9	2,9	3,3
Serum protein gm./100 ml. — globulin	3,5	2,7	3,2	5,2	3,9	1,9	4,8	3,2	2,1	3,3	4,3	4,7
Serum protein gm./100 ml. — a./g. ratio	0,7	2,0	1,6	0,9	1,1	2,4	0,9	1,5	1,8	1,2	0,7	0,7
Serum bilirubin mg.% — total	0,7	0,5	0,3	2,0	0,3	0,8	0,8	0,4	0,7	0,8	0,4	1,1
Serum bilirubin mg.% — prompt-reacting	0,4	0,1	0	0,6	0	0,1	0	0,1	0,1	0,2	0,1	0
Serum alkaline phosphatase King-Armstrong units	5,0	2,9	10,1	35,5	33,1	7,5	25,6	4,9	4,6	39,3	24,3	4,8
Serum cholesterol (total) mg.%	116	152	92	136	156	115	147	118	110	155	208	103

TABLE XI

Patients of the Groups III (Cases 19 to 28) and IV (Cases 29 and 30) — Hematological Findings

	Case No.											
	19	*20*	*21*	*22*	*23*	*24*	*25*	*26*	*27*	*28*	*29*	*30*
Erythrocites millions per c.mm.	3,4	4,1	3,6	4,2	3,5	4,8	3,6	4,1	3,3	3,4	4,1	3,8
Hemoglobin gm. per ml.	11,0	11,9	8,2	12,3	8,0	15,3	9,8	13,4	10,1	10,4	12,3	10,7
Leukocytes per c.mm.	6.500	5.700	5.600	5.000	5.300	3.600	4.900	2.600	4.200	5.000	5.100	2.400
Juvenil neutrophils %	3	13	2	8	6	2	14	7	15	18	6	1
Segmented neutrophils	58	59	58	34	53	72	28	46	54	50	50	45
Eosinophils	10	11	16	22	5	7	18	5	6	9	30	3
Basophils	1	0	0	2	0	0	0	0	0	1	0	0
Lymphocytes	21	13	18	31	35	15	34	39	20	16	11	47
Monocytes	7	4	6	3	1	4	6	3	5	6	3	4

TABLE XII

Patients of the Groups III (Cases 19 to 28) and IV (Cases 29 and 30) — Clinical Symptoms

	Case No.											
	19	*20*	*21*	*22*	*23*	*24*	*25*	*26*	*27*	*28*	*29*	*30*
Asthenia	+	+	+	+	—	+	—	+	—	—	—	—
Anorexia	+	—	—	—	—	—	—	—	—	—	—	—
Postcibal fulness ..	—	—	—	—	—	+	—	—	—	—	+	+
Constant dull pain in upper abdomen	—	—	—	+	+	+	—	—	—	—	—	+
Periodical attacks of dysentery	+	—	+	+	—	+	—	+	—	—	—	—
Constipation	—	+	—	—	—	—	—	—	—	—	—	—
Epistaxis	—	—	+	+	—	+	—	—	—	—	—	—
Aching sensation in muscles and joints	—	—	—	—	—	+	—	—	—	—	—	+
Edema of lower extremities	+	+	—	—	—	+	—	—	+	—	+	+
Ascites	+	+	—	+	—	+	—	—	+	—	+	+
Hematemesis (number of occurrences)	—	1	—	—	4	—	—	—	—	1	2	—
Time since first hematemesis (months)	—	1	—	—	2	—	—	—	—	—	4	—

— absent, + present

TABLE XIII

Percentage of Positive Turbidity and Flocculation Tests in Different Groups and in Total Series

Group	Number of cases	Percentage of positive tests				
		Zinc sulfate turbidity	Thymol turbidity	Thymol flocculation	Cephalin-cholesterol flocculation	Iodine test
I	9	55,5	—	22,2	—	—
II	9	77,7	11,1	88,8	33,3	—
III	10	80,0	70,0	90,0	40,0	60,0
IV	2	100,0	50,0	100,0	50,0	100,0
Total	30	73,3	30,0	70,0	26,6	26,6

Having presented the characteristics of the four groups we will now analyse the anatomo-pathological, laboratorial and clinical findings.

Gross Pathology of the Liver

The macroscopic appearances of the liver encountered in our four groups represented evidently the different stages in the process of morphological changes occurring in the liver of patients suffering from mansonian schistosomiasis.

We can easily imagine how these changes evoluted. At an earlier stage the liver surface was smooth. Later on, depressions in form of shallow or tortuous furrows appeared which progressively became more numerous, more pronounced and confluent. Finally, the liver surface was showing a gross nodular aspect, the nodules representing the liver tissue surrounded by the depressions.

The furrow-like depressions were due to fibrotic changes in the liver. In case 28, in which the liver was examined post mortem, it was verified that fibrous bands connected these depressions with the fibrous tissue surrounding the branches of the portal vein (fig. 11). The fibrotic changes were observed also in the capsule of Glisson on the liver surface, first as small opaque spots (plate I, fig. A), later as whitish stripes and patches located in and near the depressions (plate I, fig. B and D).

In some patients belonging to the group III the liver surface was showing also smaller and bigger flat depressions. In case 28 it was verified that such depressions were due to the disappearance of the liver parenchyma and collaps of reticulum. In these areas dead worms were found occluding the branches of the portal vein (fig. 10, 11, 14, 15 and 16).

In the two cases of the group IV the liver was coated with a thick fibrous layer. Both had ascites which was very resistant to treatment. Before our examination more than 10 paracenteses were performed in each of them.

Histopathology of the Liver

In the mansonian schistosomiasis, the histopathological changes can vary greatly in their intensity in the different parts of the liver. Because of this fact, the histopathological picture encountered in the biopsy specimens is not always representative for the state of the liver as a whole. In our experience, the macroscopic appearance of the liver, as verified at laparoscopy, gives usually a better idea about the gravity of the liver condition than the needle biopsy.

The histopathological diagnosis of the liver schistosomiasis is made by demonstration of ova or worms; other histopathological elements, however, are also rather characteristic: in absence of ova or worms they may suggest this affection.

The needle biopsy of the liver revealed in all our patients a qualitatively similar histopathological picture; quantitatively, the changes were in a general way more pro-

PLATE I

Laparoscopic Photographs

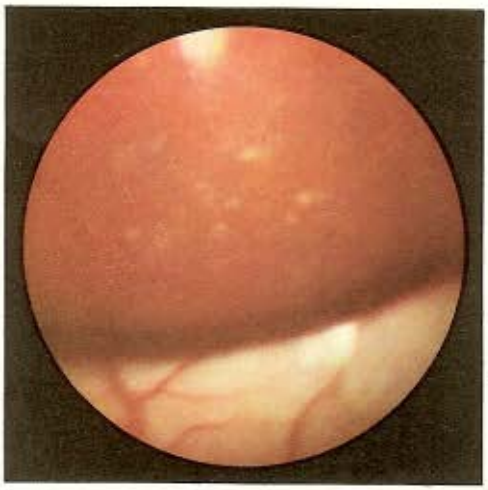

Fig. A - Case 7 (Group I). The left liver lobe showing red, smooth surface with small whitish spots. In lower part of the picture: the stomach.

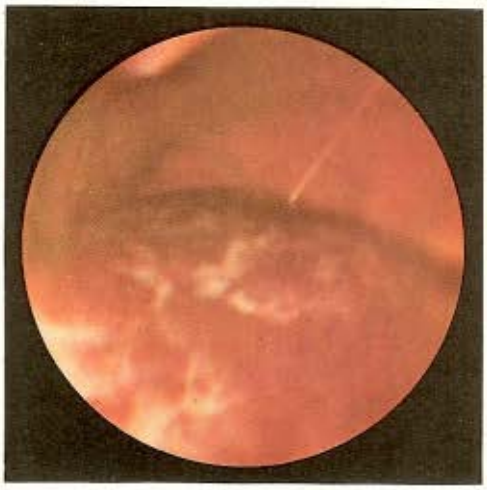

Fig. B - Case 14 (Group II). The right liver lobe presenting reddish-brown, rough surface with whitish, tortuous furrow-like depressions and a violin-string adhesion between the liver surface and the diaphragm.

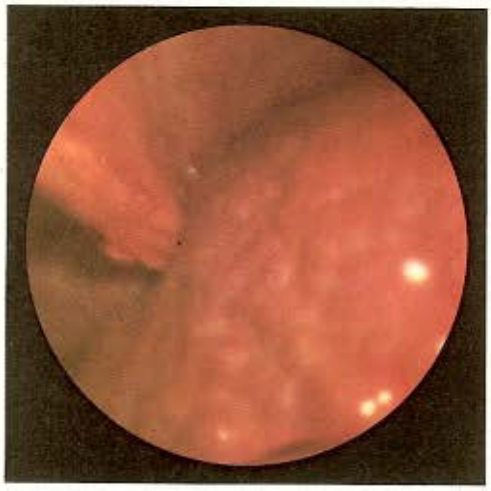

Fig. C - Case 21 (Group III). The left liver lobe with nodular surface. Upper left: round and falciform ligaments.

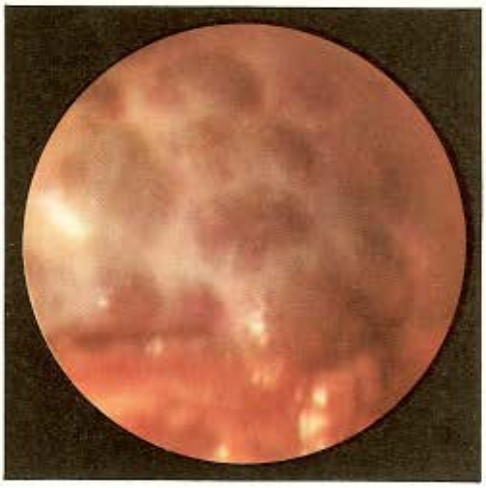

Fig. D - Case 24 (Group III). The left liver lobe showing nodular surface and fibrosis of the capsule.

PLATE II

Laparoscopic Photographs

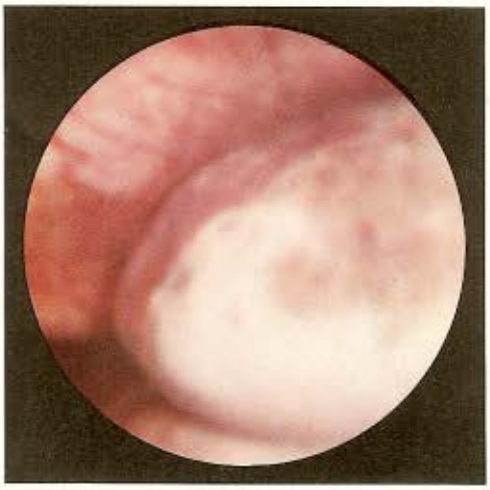

Fig. A - Case **30** (Group IV). "Zuckergussleber".

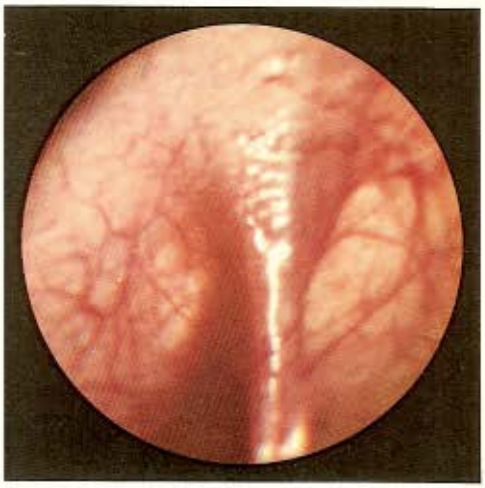

Fig. B - Case **20** (Group III). Networks of small blood vessels on the anterior abdominal wall. In the middle of the picture is the round ligament.

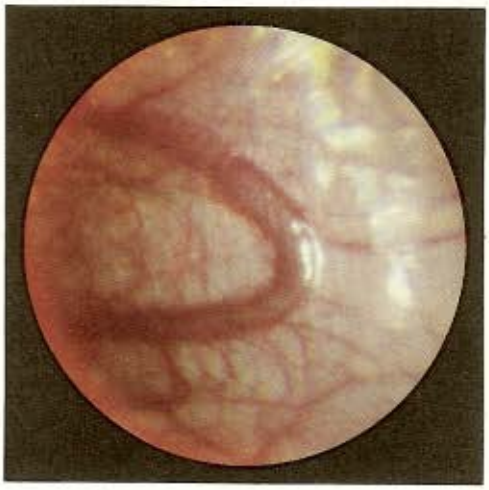

Fig. C - Case **27** (Group III). An enlarged vein on the anterior abdominal wall.

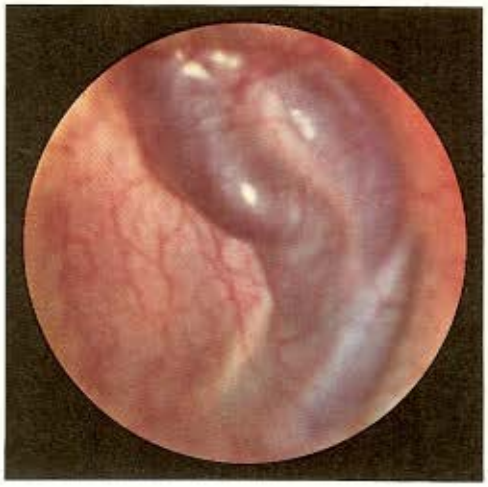

Fig. D - Case **24** (Group III). Patent umbilical (or paraumbilical) vein.

nounced in the last two groups. In tables II, IV and VII we have already indicated the histopathological changes found in the patients of the different groups. In the following, we will discuss the different elements of the histopathological picture presented by our patients.

Lobular architecture. The lobular architecture was usually maintained. In some instances small areas were found where the bands of fibrous tissue penetrated the lobules or where there was a segmentation of lobules by fibrous septs (fig. 5). In case 28, in which the liver was examined post mortem, the lobular architecture was clearly recognizable in the major part of the organ; greater changes in the architecture were observed in the areas where the liver cell plates disappeared and only the collapsed framework remained (figs. 13-16).

Fibrosis and cell infiltration. Fibrosis of the portal fields was found to a greater or lesser extent in all cases. The fibrous tissue had the tendency to expand itself from the portal fields along the peripheral limits of the lobules in form of narrow bands, getting eventually connected with the similar bands coming from the neighbouring fields (fig. 4). Not so frequently, the fibrous tissue bands penetrated into lobules, between the hepatic cell plates (fig. 5).

In the portal fields there was always an infiltrate of inflammatory cells, mainly lymphocytes and plasma cells (fig. 6). Inflammatory cells were also found in the fibrous bands outside the portal fields on the periphery or insides the lobules, as small, irregularly distributed, focal aggregates. The irregularity in distribution of the inflammatory infiltrate in the portal fields and in the fibrous bands was in our cases one of the most characteristic findings.

In case 28, in which the liver was examined post mortem, thick bands of fibrous tissue surrounded also the branches of the portal vein and the bile ducts; some of these bands continued in the direction to the surface and were connected with the depressions between the nodules (fig. 11).

Kupffer cell reaction. Proliferation of the Kupffer cells was observed in all our cases. The Kupffer cells were numerous and enlarged having big, densely stained nuclei (figs. 6 and 7).

Bile duct proliferation. The proliferation of the bile ducts was not a conspicuous finding; it was observed in a moderate degree in only a few of our patients.

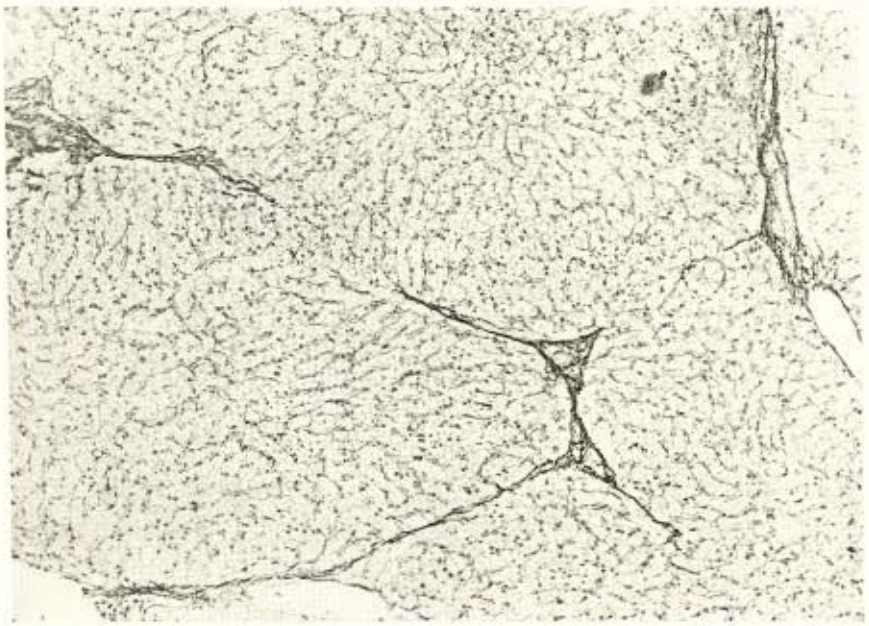

Fig. 4 — Case 8. Needle biopsy of the liver (Perdrau-van Gieson). Periportal fibrosis. Fibrous tissue expanding itself along the peripheral limits of the lobules.

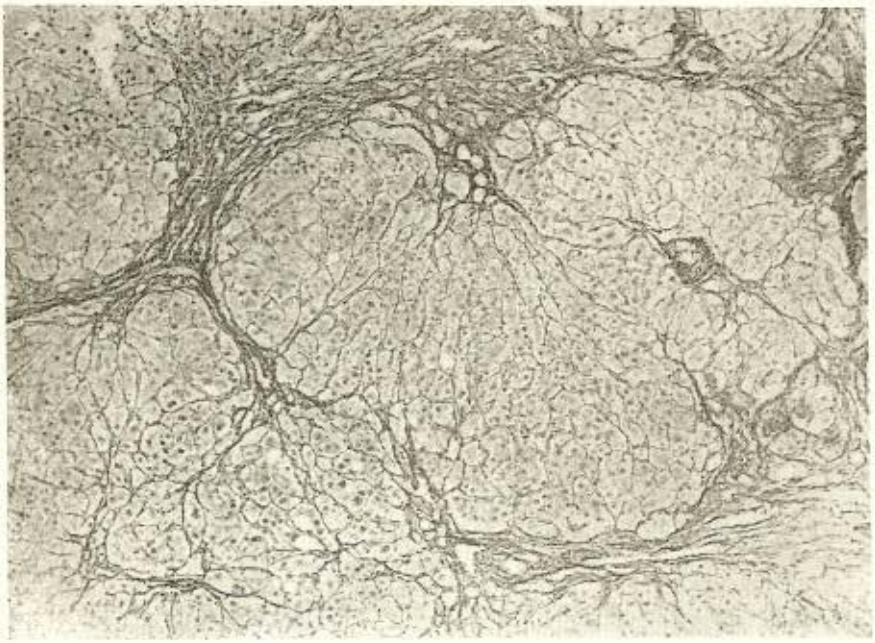

Fig. 5 — Case 25. Needle biopsy of the liver (Perdrau-van Gieson). Intense periportal fibrosis. Fibrous tissue invading the lobules. Disarray of lobular architecture.

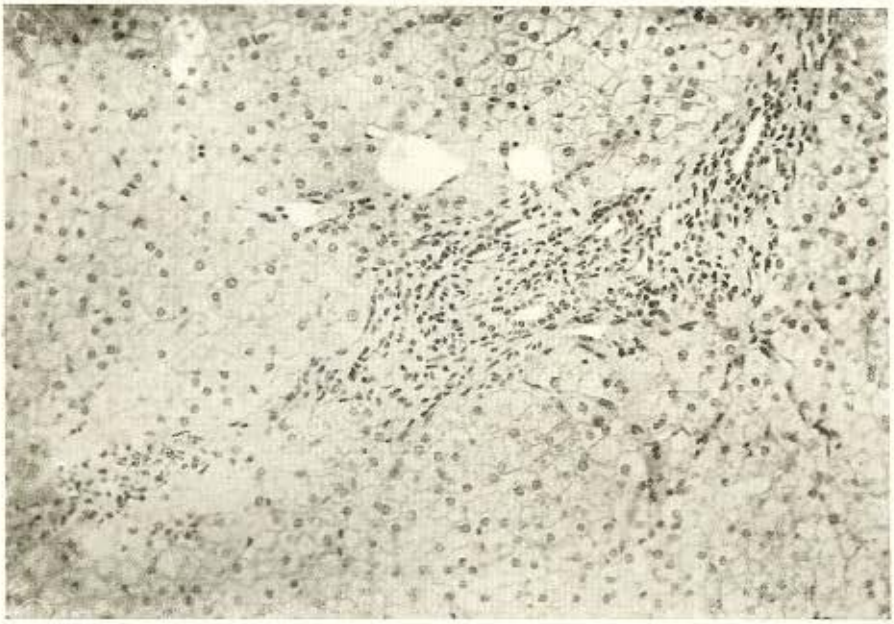

Fig. 6 — Case 26. Needle biopsy of the liver (HE). Periportal fibrosis with focal mononuclear cell infiltration. Kupffer cell proliferation.

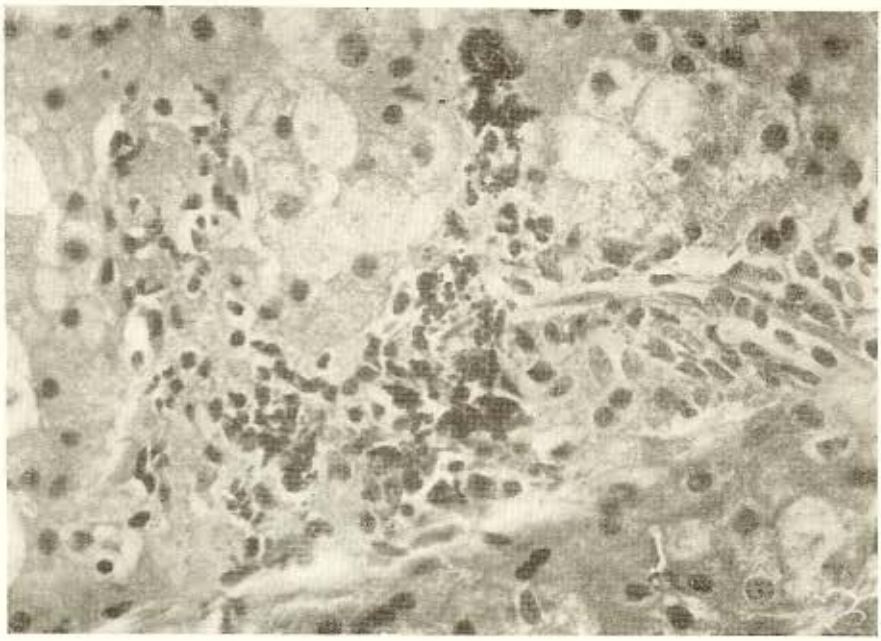

Fig. 7 — Case 14. Needle biopsy of the liver (HE). Black granular pigment in macrophages and proliferated Kupffer cells. Hepatic cells showing hydropic degeneration.

Pigment deposits. Black granular pigment was found with great regularity in the cytoplasm of the Kupffer cells as fine dust-like granules, and in the cytoplasm of phagocytic cells encountered in the portal fields and bands of fibrous tissue as larger irregular aggregates (fig. 7).

Hemosiderin was identified less frequently in the hepatic and Kupffer cells.

The bile pigment, in form of fine granules, was found in the liver cells in some instances; more rarely there were also bile plugs in the intralobular bile ductules.

Granulomata and ova of Schistosoma mansoni. The liver biopsy revealed granulomata in 14 cases. They were classified as "active" when the exsudative element was predominant (fig. 8), and as "in regression" when the reparative element was in predominance (fig. 9). In 10 cases the granulomata of either type contained ova of Schistosoma.

Adult specimens of Schistosoma mansoni and changes in the blood vessels. Only in case 28, examined post mortem, adult Schistosoma worms were found in the histopathological preparations. Near the liver surface, under the flat depressed areas, blood vessels occluded by dead adult Schistosoma worms were found (fig. 15). These vessels showed partial necrosis of their walls; they were surrounded by a cellular exsudate containing polymorphonuclear neutrophils, eosinophils, plasma cells and lymphoid cells. In the vicinity, there were arteries with focal wall necrosis and marked intimal thickening with almost complete obliteration of the lumen.

Liver cell degeneration and regeneration. The hepatic cells showed only mild degenerative changes. There was mainly hydropic degeneration; less frequently fatty vacuoles were found. The regeneration manifested itself by an increase in the number of binucleated cells, rare mitoses and the presence of some large cells with big nuclei and distinct nucleoli. The hepatic cell plates were usually orderly arranged showing the cells slight variations in their shape and volume. The sinusoids were narrowed and tortuous; the central veins had a normal appearance.

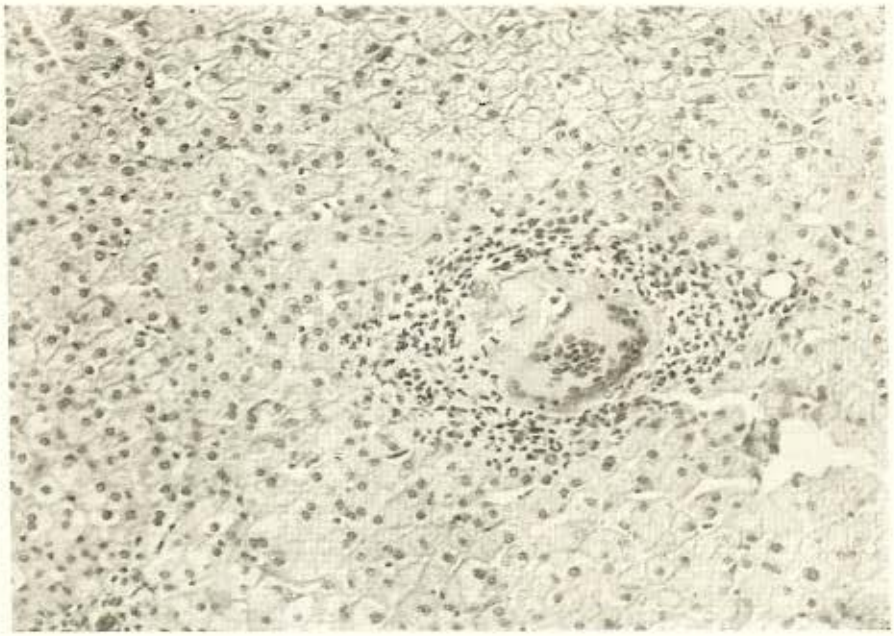

Fig. 8 — Case 4. Needle biopsy of the liver (HE). Active granuloma with fragments of ovum, giant cells and peripheral cell exsudate.

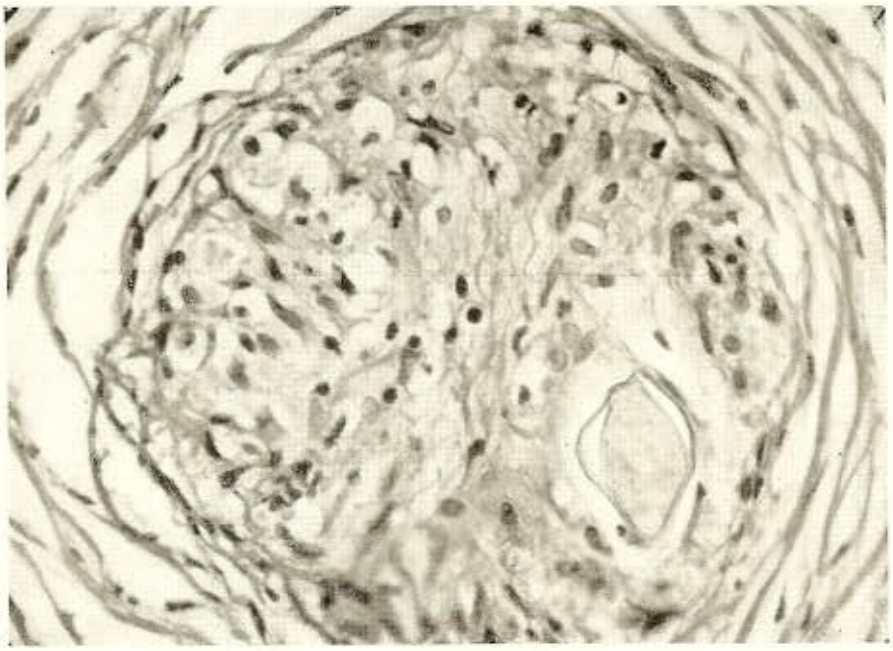

Fig. 9 — Case 10. Needle biopsy of the liver (HE). Mainly productive granuloma containing ovum.

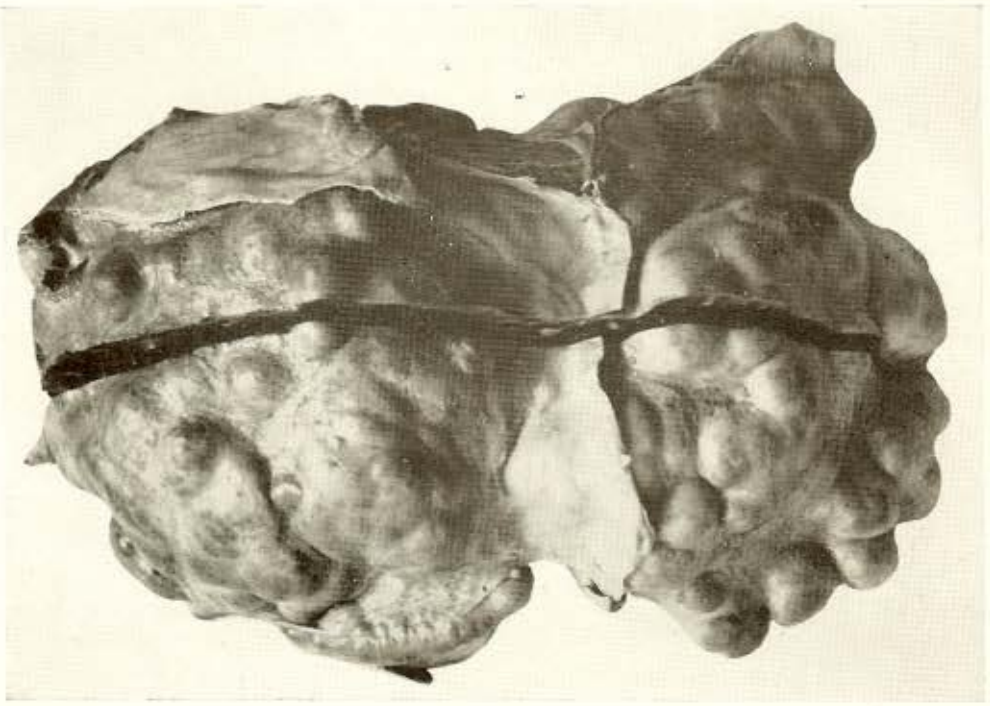

Fig. 10 — Case 28. Gross nodular appearance of the liver.

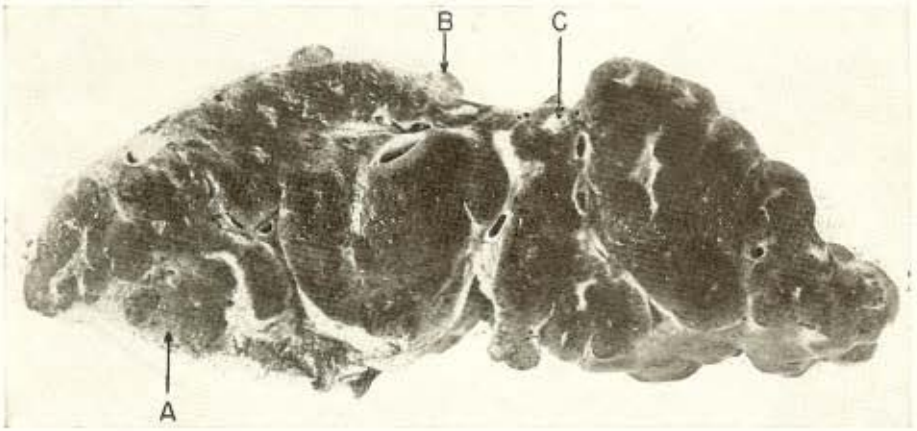

Fig. 11 — Case 28. Cut surface of the liver. Branches of the portal vein are surrounded by fibrous tissue which is connected in some places by fibrous bands with the depressions between the nodules. Under the flat depressed areas blood vessels run very close to the liver surface. The histopathology at A, B and C is shown in the following figures.

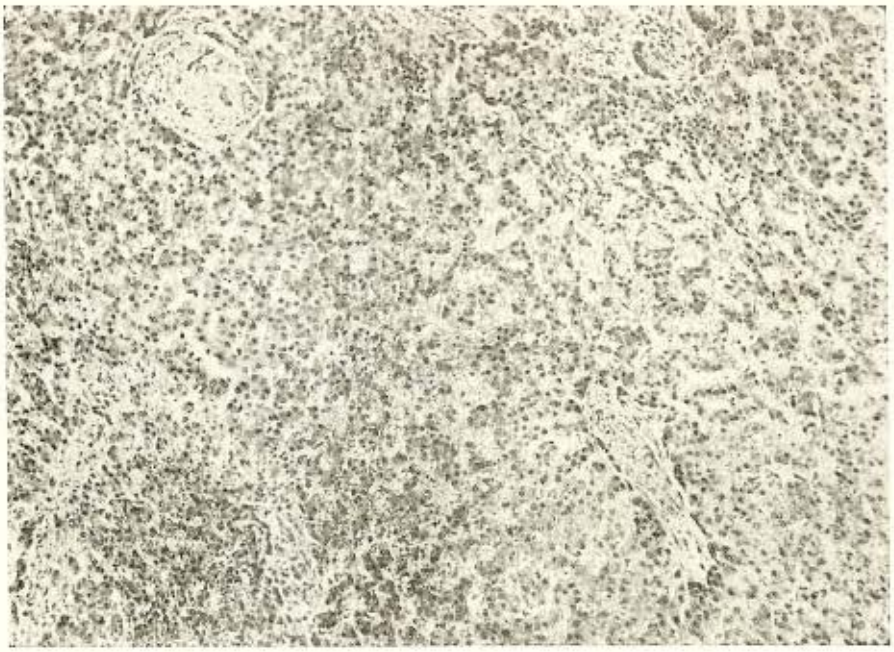

Fig. 12 — Histopathological picture at A in fig. 11 (HE). Periportal fibrosis. Atrophy of the hepatic cells and dilatation of the sinusoids.

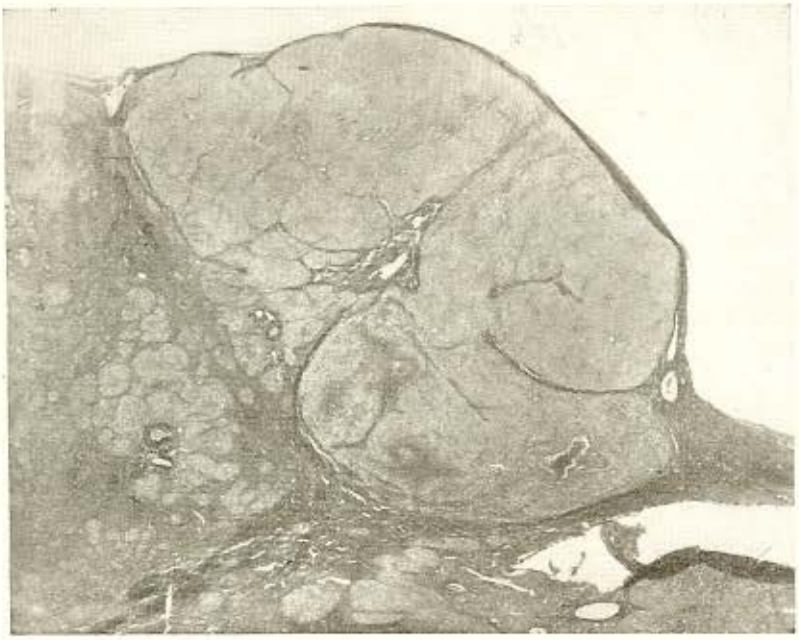

Fig. 13 — Histopathological picture at B in fig. 11 (low power augmentation, Perdrau-van Gieson). Nodule on the liver surface. Collapsed reticulum.

Fig. 14 — Histopathological picture at C in fig. 11 (low power augmentation, Perdrau-van Gieson). Intense periportal fibrosis. Collapsed reticulum. The areas at a and b are shown in the following figures.

Fig. 15 — Area a in fig. 14 (HE). Dead worm occluding a vein which shows necrosis of the wall. Inflammatory cell exudate surrounds the vein.

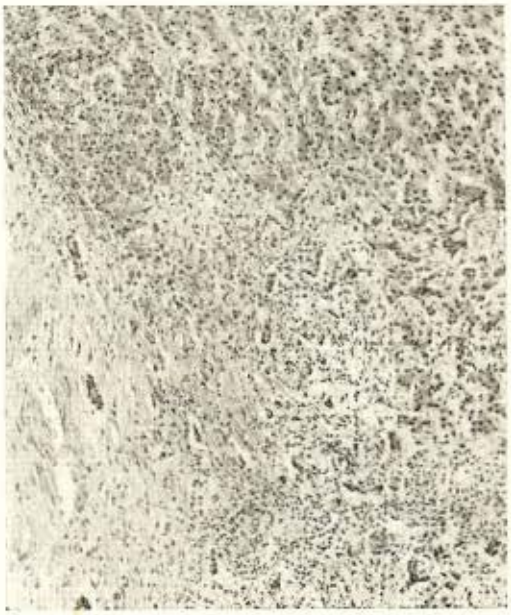

Fig. 16 — Area b in fig. 14 (HE). Atrophy of the hepatic cells and dilatation of the sinusoids. Collapse of the reticulum in area from which the liver cells disappeared.

Splenomegaly

In the groups I and II 4 patients out of 18 were found to have a slight enlargement of the spleen. In the 12 patients of the groups III and IV the splenomegaly was always present.

Collateral Circulation

While in the patients of the groups I and II no evidence of a collateral circulation was found, all patients of the groups III and IV had esophageal varices and most of them also intra-abdominal and rectal vein enlargements.

Rectal Mucosa

The recto-sigmoidoscopic findings were about the same in all groups; the rectal mucosa showed a slightly edematous and granular appearance with areas of hyperemia.

Laboratorial Tests Concerning the Liver Function

Bromsulphalein retention test was normal in 20 (two thirds) of our patients; in the group I the results were normal in all patients; in the group II a slight increase of retention was found in 3 out of 9 patients, being the maximum value 7%; in the groups III and IV a slight to moderate increase of retention was found in 7 out of 12 patients, being the maximum value 14%.

Serum protein turbidity and flocculation tests. In table XIII the percentage of different positive tests in different groups and in total series are indicated.

Serum proteins. The total protein values were over 6 gm./100 ml. in all patients except 2 belonging to the group III. The albumin fraction showed values below 4 gm./100 ml. in 1 patient (11.1%) of the group I, in none of the group II, and in 5 patients (41.6%) of the groups III and IV. The globulin fraction showed values above 3 gm./100 ml. in 2 patients (22.2%) of the group I, in 1 patient (11.1%) of the group II and in 9 patients (75%) of the groups III and IV.

Serum bilirubin. The total serum bilirubin was found to be slightly above 1 mg.% only in 1 patient of the group III and in 1 patient of the group IV. In all other cases the values were within normal limits.

Serum alkaline phosphatase. The serum alkaline phosphatase levels were normal in all patients of the groups I and II; in the groups III and IV, however, they were elevated (24.3-35.3 King Armstrong units) in 5 patients (41.6%).

Serum cholesterol. The total serum cholesterol values were within normal limits in all cases except one of the group III in which they were slightly increased.

Hematological Findings

In the groups I and II the erythrocyte count and determination of hemoglobin showed about normal values. In the patients of the groups III and IV, however, anemia of the hypochromic type, in some of them pronounced, was the rule. The leukocyte count revealed normal or slightly increased values in the patients of the groups I and II, while in those of the groups III and IV they were normal or decreased. In the differential count eosinophilia was the most characteristic feature.

Clinical Symptoms

In the patients of the groups I and II (18 cases), the prominent clinical symptoms were those concerning the intestines: 8 patients complained of periodical attacks of dysentery, 6 patients of constipation only. Other frequent complaints were asthenia (11 patients) and a constant dull pain in upper abdomen (8 patients). Less frequent complaints were: aching sensation in muscles and joints (4 patients), postcibal fullness (4 patients), anorexia (2 patients), and epistaxis (1 patient).

In the groups III and IV (12 cases) 7 patients had ascites, 6 of them also presenting edema of lower extremities. While in patients of the group III (5 cases) ascites did not reappear after paracentesis, in the patients of the group IV (2 cases) it was resistant to all treatment and remade itself promptly after paracenteses. Hematemeses occurred in 4 patients of the groups III and IV. The interesting fact is that certain phys-

ical signs appearing in the liver cirrhosis, like: jaundice, spider angiomata, palmar erythema, clubbed fingers, gynecomastia and testicular atrophy, were not found in a single instance in our series of patients.

COMMENTS AND CONCLUSIONS

Our study was carried out in carefully selected patients suffering from mansonian schistosomiasis in whom no other diseases or factors were verified which could have been the cause of hepatic injury. We have to assume that the pathological changes encountered in these patients were due only to the infestation by *Schistosoma mansoni.*

Basing ourselves on the macroscopic appearance of the liver we have classified our cases into four groups. The first two represented the earlier stages, and the last two the advanced stages of the disease. Clinically, the groups I and II corresponded to the so called intestinal form and the groups III and IV to the hepato-splenic form of the mansonian schistosomiasis.

In patients of the first two groups there was no evidence of portal hypertension. There were few or no clinical signs of hepatic involvement. The laparoscopy and the needle biopsy showed however that the liver was already affected in all instances. In four patients belonging to these groups a discrete splenomegaly was present. This finding corroborates the opinion defended already before by one of us that the splenomegaly in mansonian schistosomiasis is due not only to the portal hypertension, but also to a hyperplastic reaction of the spleen [4]. In such cases in which there is no portal hypertension the regression of splenomegaly may occur under specific treatment.

In patients belonging to the last two groups the predominant symptoms were those due to portal hypertension. Pathological changes in the liver corresponded to those described by SYMMERS [7] as *clay-pipe-stem-cirrhosis* and by HASHEM [3] as *coarse periportal fibrosis.* In case 28 the post mortem examination of the liver revealed besides the fibrotic changes also lesions due to the action of dead worms, identical to those described by COUTINHO and COELHO [2]. In different areas the portal branches were occluded by dead worms, there was necrosis of the surrounding parenchyma and collapse of the reticulum. This patient was submitted to antimonial treatment, after the study had been completed. Three weeks after having received a total of 37.5 cc. of Repodral, he died in consequence of an incontrolable hemorrhage from a ruptured esophageal varix. It is very likely that in this case some branches of the portal vein were occluded by dead worms in result of the treatment. But it is certain that the main lesions due to vascular occlusions existed already before the treatment. The flat depressions indicating the collapsed areas were observed already at laparoscopy.

The liver function, as judged by liver function tests, was impaired to some degree in all patients of the last two groups. The alterations of the liver function tests were less pronounced than usually observed in hepatic cirrhosis. In 41.6% of cases belonging to these groups the serum alkaline phosphatase levels were increased. Jaundice, spider angiomata, palmar erythema, clubbed fingers, gynecomastia and testicular atrophy were not observed in a single instance.

The needle biopsy of the liver revealed in all our patients a qualitatively similar histopathological picture; quantitatively, the changes were more pronounced in the last two groups. The characteristic histopathological findings were: periportal fibrosis and cell infiltration, lobular architecture little affected, proliferation of the Kupffer cells, black pigment deposits, mild degenerative changes of the hepatic cells, and granulomata with or without ova. It is interesting to note that the granulomata were found more frequently in patients of the first two groups.

SUMÁRIO

Os autores estudaram 30 doentes portadores de esquistosomíase mansônica nos quais não foram verificadas outras doenças ou fatôres capazes de lesar o fígado. As alterações patológicas do fígado foram evidenciadas por meio da laparoscopia fotográfica e punção-biopsia do fígado, e correlacionadas com os achados clínicos, radiológicos, esofagoscópicos, reto-sigmoidoscópicos e laboratoriais. Os doentes foram classificados em 4

grupos. Macroscòpicamente o fígado apresentava no primeiro grupo uma superfície lisa, no segundo grupo uma superfície irregular com depressões em forma de sulcos, no terceiro grupo o fígado tinha um aspecto grosseiramente nodular e no quarto a sua superfície estava recoberta por tecido fibroso que lhe conferia o aspecto de glacê de açúcar. A punção-biopsia do fígado revelou um quadro histopatológico qualitativamente semelhante em todos os casos. Quantitativamente as alterações eram mais intensas nos últimos dois grupos. Os achados histopatológicos característicos foram: fibrose periportal com infiltrado celular, proliferação das células de Kupffer, depósitos de pigmento negro e granulomas com ou sem ovos; a arquitetura lobular achava-se pouco afetada e as alterações degenerativas das células hepáticas foram discretas. Num doente do grupo III, a autópsia revelou, no fígado, também lesões decorrentes da oclusão dos ramos da veia porta por vermes mortos. Clìnicamente os grupos I e II correspondiam à forma intestinal e os grupos III e IV à forma hepatosplênica da esquistosomíase mansônica. Em doentes dos dois primeiros grupos não foram encontrados sinais da hipertensão portal e havia pouco ou nenhum sinal clínico de comprometimento hepático. Em doentes dos últimos dois grupos predominavam os sintomas da hipertensão portal, tendo se verificado em todos os pacientes a existência de varizes esofagianas e esplenomegalia.

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