Studies on Schistosomiasis Mansoni in Puerto Rico*

VI. MORBID ANATOMY OF THE DISEASE AS FOUND IN PUERTO RICANS†

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OUTLINE

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INTRODUCTION

González Martínez discovered the ova of *S. mansoni* in the feces of a native of Puerto Rico in 1904.[1] In subsequent publications[2, 3] he dealt with the pathology of the condition in the form of reviews, but these appear not to have been primarily based on Puerto Rican material.

The first contribution to our knowledge of the pathology of the disease as found on the Island did not come until 1926, when Román and Burke[4] reported an obstructing colloid adenocarcinoma of the splenic flexure of the colon of an 18-year old Puerto Rican girl with a heavy schistosomal infection. Microscopically numerous ova of *S. mansoni* were found throughout the tumor, in the adjacent gut, and in regional lymph nodes. Because of the age of the patient, the authors pointed out the possibility that the schistosomal infection might have had something to do with the development of the tumor. A complete autopsy was not allowed, so that the material examined consisted only of the neoplasm and portion of the colon, resected postmortem.

The more detailed pathologic studies began with Lambert[5], who based his observations on the same source of autopsy material that we are utilizing for the present contribution. The author emphasized the wide distribution of the disease throughout the Island, which was important at a time when epidemiologic surveys of the condition were only beginning to be made, and referred very briefly to the pathologic changes present. The latter were interpreted as due mainly to the presence of the ova rather than of the worms, and the liver was deemed the best index of infestation at autopsy.

A second report by the same author and Burke[6] was based on an additional group of 35 autopsies. At that time the author adopted the practice, which is of great value for the histologic diagnosis of light infestations, of always taking at least 2 blocks from different portions of the liver and 1 block of rectum, and of examining a sample of feces obtained at the time of autopsy for ova of *S. mansoni*. Two cases in which the disease occurred as an incidental finding of little or no clinical significance, and 2 in which it was the sole cause

of death were presented in detail. A review of some of his autopsy and experimental observations was published by Lambert[7] at about this time. The paper includes an able discussion of the relative roles played by ova, worms and toxins in the pathogenesis of the lesions, and a very brief mention of "fibroid nodules" as the final stage in the evolution of pseudotubercles.

In 1928 Pila[8] reported a case of schistosomiasis of a fallopian tube and ovary in a woman of 41 years with a history of pelvic pain during 10 years.

In 1931 the present author[9] commented very briefly on some of the pathological findings in a number of the autopsies which will now be analyzed in full, and in 1932 reported[10] a case of advanced schistosomiasis with death from hematemesis, pointing out the similarity of the clinical picture in this case to Banti's disease. Bonelli[11] had previously analyzed and presented 5 cases from this same point of view.

Gould[12] reported a case with symptoms of subacute appendicitis, in which a small abscess was found at operation near the appendix, and ova and pseudotubercles were encountered microscopically in the latter organ.

Of the few reports on the condition as found in Puerto Rican emigrants abroad, especially in the United States, the most important is that of Clark and Graef.[13] These authors described a case with advanced cirrhosis and with so marked an involvement of the pulmonary arteries secondary to schistosomiasis as to have resulted in hypertrophy of the right ventricle and heart failure.

Our contribution is a general survey of all the schistosomal material gathered in our laboratory during the past 13 years, and includes the cases on which Lambert,[5] Lambert and Burke,[6] Pila,[8] Koppisch,[9, 10] Bonelli[11] and Gould[12] based their reports.

MATERIAL STUDIED

This study is based on 147 cases of Manson's schistosomiasis encountered amongst the records of 1009 consecutive autopsies performed on native Puerto Ricans, and on 99 cases encountered amongst 18,500 specimens representing operative material and partial autopsies. Foreigners and children less than 45 days of age have not been included. The finding of ova in one organ or other was the criterion established for inclusion in the series, exception

made of a few cases to be mentioned later. Since oviposition does not begin in man until the 40th to 45th day after infection, infants below that age were excluded. The only histopathologic finding which can be safely considered diagnostic of schistosomiasis is that of ova. It is admitted that for absolute certainty one should be able to identify the lateral spine, but this is often impossible or impractical, particularly when there are only a few ova or when the infestation is so old that nothing but shell fragments remain. As far as we know and our experience carries us, in Puerto Rico there are no other parasites of which the ova might be mistaken for those of schistosomiasis in the tissues, exception made of *Fasciola hepatica*, which though present on the Island, has ova that can be usually differentiated in sections from bilharzial ones. Incidentally we may mention that no instance of the latter parasitosis has been encountered in our material.

The autopsies were performed in the great majority of cases in San Juan, where there are no bodies of water known to be infested with schistosomiasis. Positive cases therefore represent individuals who contracted the disease elsewhere on the Island and moved to San Juan for residence, or who entered a hospital in this city for treatment. The autopsy material of which these cases form a part is selective to the extent that the necropsies are performed mainly on interesting or obscure cases.

We examined the microscopic sections from all cases listed as positive in the autopsy protocols, while the sections of liver and rectum, organs which, as will be shown later, are most frequently involved, were carefully searched for evidences of the disease in all cases that had been described as negative for schistosomiasis. The latter procedure resulted in the finding of several positive cases that had been overlooked at the time of the original examination.

As previously stated, we are including as possibly schistosomal certain subjects in which ova were not found either in the feces or in sections, but which exhibited lesions that we have come to interpret as healed schistosomal pseudotubercles in which the ova have undergone complete dissolution and in which all, or nearly all, inflammatory changes have regressed. In a few such instances the cutting of additional sections has indeed resulted in the discovery of ova or shells. A more practical and surer way for the demonstration of ova in healed or doubtful cases would be maceration of the organs with caustic soda, after the method of Fairley.[14]

OBSERVATIONS ON AUTOPSIES

Age, sex and race: Table I gives the distribution of all cases according to age, sex and race. There was a total of 147 cases of schistosomiasis in 1009 autopsies, a general incidence of 14.6 per cent. Males were much more frequently affected than females, due undoubtedly to the greater frequency with which the former bathe and work in infested bodies of water. Whites were oftener the victims than would have been expected from the racial composition of the population but this is probably explained by the fact that the main endemic foci of the disease are situated in the interior, where the colored are distinctly less numerous. For both sexes and all races the decade suffering the brunt of the infection was the 3rd, followed closely by the 4th, and 72.3 per cent of all cases of known age were 21 to 50 years old.

TABLE I

Distribution of All Cases of Schistosomiasis According to Age, Sex and Race

Age	*Sex*		*Race*			*Not Specified*
	Male	*Female*	*White*	*Mulatto*	*Negro*	
Up to 10	2	0	2	0	0	0
11–20	11	8	13	5	0	1
21–30	31	12	29	12	2	0
31–40	26	4	18	6	4	2
41–50	18	3	10	8	3	0
51–60	9	2	8	2	1	0
61–70	2	0	1	0	0	1
71–80	1	1	1	0	0	1
Unknown	14	3	8	4	3	2
Total	114	33	90	37	13	7

Locality where infection was contracted: An attempt was made to determine the locality where the bilharzial infection had been contracted, but since usually the disease was not suspected prior to the autopsy, specific information on that point was not found in most of the case histories. A record of the town of birth or of residence was obtainable for 126 of the cases, but it was only rarely possible to find out how long a given individual had resided in a given place or how, actually, he had become infected.

These 126 cases had been born or had resided in the following localities. Among these towns are included those where some of the cases were known to have become infected.

Aguadilla	*Central Aguirre**	*Mayagüez**
*Aguas Buenas**	Central Mercedita	Naguabo
*Aibonito**	Cidra	*Patillas**
Arecibo	*Comerío**	*Río Grande*
Arroyo	Fajardo	*Río Piedras**
*Barranquitas**	*Guayama**	San Juan
*Bayamón**	*Gurabo*	*Santa Isabel**
Cabo Rojo	*Humacao**	Santurce
*Caguas**	*Jayuya**	Toa Alta
Carolina	*Juana Díaz*	*Trujillo Alto*
Cayey	*Lajas**	*Utuado**
Ceiba	*Las Piedras**	*Vieques**

The names in italics represent towns which are already known to have yielded cases of the disease. The asterisks indicate those which Faust et al.[15] pointed out as definitely infective or strongly suspicious. The italicized names without the asterisk are towns from which positive cases have been obtained since Faust's survey, according to Dr. Federico Hernández Morales,† Chief of the University Hospital Dispensary. The town of Aguadilla or its environs had already been deemed as possibly infested by Lambert[6] (case 12). The other towns and communities in our list have not been previously mentioned, as far as we know, in connection with schistosomiasis.

It is, of course, quite possible that the individuals for whom they are listed acquired their bilharzial infection somewhere else, and this is almost certainly true for San Juan and Santurce, but the list is given for what it may be worth. Those towns and localities are Arroyo, Cabo Rojo, Ceiba, Central Mercedita, Ciales, Cidra, Fajardo, Naguabo, San Juan, Santurce and Toa Alta.

Brief analysis of cases: The organs involved and the fundamental character of the lesions were essentially similar in all cases, with exceptions that will be brought out later, the variations being accounted for by differences in the degree of severity of the infestations and by the duration of the disease. On this basis the cases can be grouped according to whether the infections were minimal, moderate, severe, healed or doubtful.

† Personal communication.

(a) Minimal. This comprises the bulk of the material with 95 cases (64.6 per cent) presenting no clear-cut clinical manifestations of schistosomiasis, or gross pathologic changes of diagnostic import at autopsy, and with only a few ova and pseudotubercles in one organ or another. Slight fibrosis of portal spaces was present in over one-half the cases, and schistosome pigment was found in the spleen or liver of some. The feces were positive for *S. mansoni* in examinations by the simple smear method in 10 per cent of the cases. In only one of them were worms demonstrated at autopsy; in this case they were situated in the intrahepatic portal branches. These cases apparently represent instances of a single exposure to very small numbers of cercariae.

Table II shows the organs in which ova were found microscopically in the minimal, moderately advanced and severe cases, together with the percentage incidence of involvement for each organ.

(b) Moderately advanced. This group comprised 21 cases (14.2 per cent). The schistosomiasis was inapparent clinically, with the exception of 1 that had had bloody diarrhea and tenesmus during the last 5 months of life; death was from tuberculosis of the lungs and intestines, but the ulcers were limited to the small intestine, and the above symptoms may well have been due to schistosomiasis. The feces were positive for *S. mansoni* in 27 per cent of the cases by the simple smear method. At autopsy 7 cases showed slight nodularity of the surface of the liver, and in 5 instances this was confined to the inferior margin and its immediate neighborhood. In 3 there was a slight but suggestive fibrous thickening of the larger portal spaces. Microscopically the main difference from the preceding group lay in the larger number of ova and pseudotubercles found in various organs, particularly the liver and colon; in the greater proportion of cases with bilharzial pigmentation of the liver and spleen; in the more active inflammatory reaction about ova with greater infiltration by round cells and eosinophils; in the presence of definite periportal fibrosis, accompanied by the formation of pseudolobules in almost all cases and by beginning proliferation of bile ducts in about one-half of the cases, and lastly in the presence of acute colitis in 2 instances.

(c) Severe. Twelve cases (8.1 per cent) are included in this group, which is representative of schistosomiasis in the last stages and of earlier, very heavy infections. Death was directly ascribable to this disease in all but one. While this was a case of advanced schistosomal cirrhosis, death was due to a colloid adenocarcinoma of the

TABLE II

Visceral Localization of Ova in Minimal, Moderately Advanced and Severe Schistosomiasis with Percentage Incidence

Organ	Minimal		Moderately Advanced		Severe	
	Cases Examined	% Positive	Cases Examined	% Positive	Cases Examined	% Positive
Liver	94	67.7	21	85.7	12	100
Rectum	57	63.2	12	91.7	6	50.0
Colon*	42	47.6	12	83.3	12	100
Small intestine	42	9.5	13	46.1	8	75
Lungs	94	4.3	21	23.8	11	63.6
Messenteric lymph nodes	30	3.3	8	25.0	5	60.0
Stomach	26	0.0	9	0.0	4	25.0
Testis	47	0.0	14	0.0	5	20.0
Pancreas	83	8.7	20	0.0	11	18.2
Gallbladder	11	0.0	1	0.0	7	14.3
Spleen	92	0.0	21	0.0	12	8.3
Retroperitoneal tissues	1	0.0	0	0.0	2	100.0
Urinary bladder	17	5.8	4	0.0	0	0.0
Appendix	8	25.0	2	50.0	1	0.0
Kidney†	90	5.6	21	0.0	12	0.0
Suprarenal	71	1.4	16	0.0	10	0.0

* Parts other than rectum.

† No definitely identifiable ova were found in this organ, but in sections there were calcified structures which may have been schistosomal ova.

cecum. Cirrhosis of the liver was present in 10, splenomegaly in 9 and colitis in 6. Symptoms and signs suggestive of schistosomiasis were present in all, and the gross autopsy findings were well developed in every case. Periportal fibrosis of the white clay pipe-stem variety was evident in all cases with cirrhosis, and worms were demonstrable in the main portal vein once, in all tributaries of the portal vein, in hepatic veins and in the right pulmonary vein in another, and in the portal, superior mesenteric and splenic veins in a third. Simple smears of feces were positive for bilharzial ova in one-half of these cases.

(d) Healed. This group is composed of 8 cases (5.4 per cent) with no clinical manifestations or gross pathologic changes ascribable to schistosomiasis and with the feces negative for bilharzial ova, but which microscopically presented, mostly in the liver but also, though to a lesser extent, in the intestinal subserosa and lungs, rounded sharply defined fibrous nodules which we believe represent healed schistosomal pseudotubercles. These structures were likewise encountered in a certain proportion of the cases with active schistosomiasis, and a series of gradations could be traced in such cases, as will be shown later, from active pseudotubercles to healed ones. Although ova or shell fragments were usually not visible in the latter, serial sections demonstrated their presence in 3 cases in which this was tried. The group thus represents instances of minimal infections that had gone on to complete or almost complete healing. Brown pigment, presumably of schistosomal origin, since there was no indication of its being malarial, was seen in the liver and spleen in 1 case and in the liver only in another.

(e) Doubtful. In spite of our having established the finding of ova in the tissues as the criterion for inclusion of a given case in the series, this group of 11 cases (7.9 per cent) has been accepted under the above heading. They were entirely negative clinically and grossly at autopsy. Microscopically, however, slight to moderate fibrosis of portal spaces was evident in 6, at times with some lymphocytic and eosinophilic infiltration. Furthermore, nodules with the characteristic structure of pseudotubercles were encountered microscopically in the liver in 7, in the rectum in 4, and in the lungs in 2 cases. Eosinophils were found about the pseudotubercles whenever these were present. Active tuberculosis was present in the lung of only 1, and 2 others had a well-healed tuberculous focus in a bronchial gland in each. Even though ova were not encountered (serial sections were not obtained), it must be conceded that the presence of the pseudotubercles in organs like the liver, rectum and lungs, and not elsewhere, the high incidence of periportal fibrosis in the group, and the invariable presence of eosinophils about them make it highly probable that they represent schistosomal lesions.

Following this brief analysis of the cases, the findings will be discussed for the series as a whole.

Clinical features: Although a detailed analysis of the antemortem features is beyond the scope of this paper, there are a number of points which seem worth mentioning.

It is unfortunate that in the majority of cases the hospital records

had been very incompletely taken. One gathered the impression, even as regards some of the fully developed cases, that in spite of the relative prevalence of the disease on the Island, schistosomiasis was rather infrequently taken into consideration in the differential diagnosis; furthermore, that the routine use of the simple smear method of examination of the feces, or of the brine floatation method, allows many cases to go undiagnosed.

Record of examination of the feces was found for 54 cases, 12 of these or 22.2 per cent having been positive. The case histories and physical examination, on the other hand, were frankly suggestive in only 12, all of which were in the advanced stages of the disease, and in another well-advanced case were masked by the presence of a colonic adenocarcinoma. To these there may be added 5 more that gave a history of having bathed in streams known to be infested, or of having had bloody diarrhea at one time or another. This makes a total of only 17, or 11.6 per cent, in which the diagnosis could have been suspected without the fecal examination.

An analysis of these 17 cases yields the following principal symptoms with their relative frequency:

Diarrhea		15
with bloody dejecta	8	
without bloody dejecta	7	
Abdominal pain		7
In epigastrium	4	
In left hypochondrium	1	
In lower abdomen	1	
Diffuse	1	
Nausea and vomiting		5
Emaciation		5
Tenesmus		4

The more frequent physical findings ascribable to schistosomiasis, as proved at autopsy, are listed below. These were present only in the 12 severe cases:

Enlargement of spleen		8
Anemia		7
Hypochromic	5	
Hyperchromic	2	
Ascites		6
Enlargement of liver		4
Hematemesis		4
Fever		4

Atrophy of liver		2
Abdominal mass		2
Dyspnea		2
Eosinophilia		2
Leukopenia		2
Generalized edema		1

Blood studies were available for only 7 of the 12 cases, while an analysis of gastric contents was carried out in only 2. It is worth noting that eosinophilia was only encountered in 2 of the cases with recorded blood counts. One case not listed above had well-marked achlorhydria with no free acid and a total acid of 10; the gastric mucosa was atrophic and the blood picture was suggestive of a macrocytic hyperchromic anemia while the femoral bone-marrow showed hyperplasia of the type seen in hypochromic anemias. This case was one of hyperinfestation with persistent nausea and vomiting and severe colitis.

Pathological Anatomy. Of the total of 147 cases in the series, 34 (23.1 per cent) presented from extremely mild to advanced changes macroscopically. Most of the pathologic alterations, however, were only suggestive and not diagnostic. The more important may thus be listed, together with the number of times each one was observed:

Nodularity of liver surface		20
Slight	13	
Marked (frank cirrhosis)	7	
Limited to inferior margin	6	
Fibrosis of portal spaces		17
Slight	5	
Marked	12	
Splenomegaly		9
Enlargement of liver		8
Ascites		7
Subperitoneal nodules of intestine		7
Of small intestine	4	
Of colon	3	
Colitis		6
Atrophy of liver		4
Worms in portal vein or tributaries		4
Pseudotubercles in lungs		2
Hydrothorax		2
Ruptured esophageal varices		2
Thrombosis of portal vein		2
Retroperitoneal fibrosis		1

In all but the advanced cases the gross alterations were extremely mild, consisting at best of a faint nodularity of the liver surface, of slight increase of periportal fibrous tissue, or of the presence of a few small whitish nodules beneath the liver capsule as the three more suggestive findings.

In the 12 advanced cases the liver, spleen and colon were most frequently and extensively involved constituting the characteristic triad of periportal cirrhosis, splenomegaly and colitis.

Schistosomal cirrhosis of liver: The liver was cirrhotic in 10 of the 12 cases. In the cirrhotic the size was within normal limits in 2, while 4 were atrophied and 4 hypertrophied. The smallest liver (in an adult) weighed 720 gm. and the largest, 2050 gm.*

The most distinctive character of bilharzial cirrhosis in our cases was the concentration of fibrotic changes about intrahepatic portal branches (Figs. 1 and 2), with the formation of dense whitish or pinkish mantles about those veins; in one specimen the zones of fibrosis measured up to 1.2 cm. in diameter. Symmers[16] first emphasized this feature, referring to it as the "white clay pipe-stem type of cirrhosis." The affected livers presented a finely or moderately coarsely granular surface, were of increased consistency, sectioned with difficulty, and often "cried" on being cut. From the external appearance no differentiation from cirrhosis of the Laënnec type was possible, and it must be noted also that one liver was very grossly deformed, approaching a hepar lobatum in that respect. In the latter case syphilis appears not to have been present. In a few instances the surface of the organ was smooth, not at all cobbled, yet on section the larger portal spaces were markedly fibrosed. This discrepancy between the external and sectioned surfaces held in all cases, the changes on section being always more marked than the nodularity of the surface would suggest. As a whole the external nodularity was not as coarse as obtains in well-advanced instances of Laënnec's cirrhosis.

One specimen showed some cobbling along the inferior margin and to a short distance above it, while the remainder of the surface was smooth. This feature also obtained in 5 of the mild and moderately advanced cases. In a previous communication of ours[17] it was shown that in experimental schistosomiasis of the rabbit the cirrhosis always

*The normal weight of all organs in Puerto Ricans is somewhat below the standards accepted for Northern countries. The liver in normal male adults averages 1400 gm. and rarely exceeds 1500.

begins along the inferior margin of the liver and thence extends towards the dome.

In well-advanced cases the lobulations on section were sharply outlined and stood out prominently. The fibrosis rapidly diminished towards the smaller portal spaces. Minute pale yellow or whitish nodules were occasionally visible beneath the capsule and on section. The color was usually pinkish-brown, and yellowish in a few instances in which fatty change had developed. When congestion was marked the lobular pattern stood out more boldy than in pale livers. In a rare case there was a grayish cast to the cut surfaces due to the presence of abundant bilharzial pigment, and twice there was greenish spotting of portal spaces from bile pigmentation. However, generalized jaundice of the body was never observed.

Microscopically the portal spaces were much broadened by the formation of fibrous tissue which at times was quite dense and collagenous and at times loosely fibrillar and edematous. In the larger portal areas the fibrous tissue was often very richly vascularized, suggesting that granulation tissue had been present previously. The wall of the larger portal branches was thickened by edema and fibrosis (Fig. 4), and that of the smaller radicles, by edema and actual hypertrophy of the muscle coat. In the portal spaces there were more or less numerous schistosome ova that often formed the center of pseudotubercles, but that not infrequently had provoked little or no inflammatory reaction. Most of the ova were empty; others contained coagulated serum or a few leukocytes. At times, however, the embryo was present and well preserved, or else undergoing lysis. The fibrosis was diffuse in the portal spaces, and not especially concentrated about shells; it was likewise encountered in portal spaces in which no ova had been deposited. Lymphocytes, plasma cells, eosinophils and monocytes were likewise present not only about pseudotubercles or surrounding ova, but also focally in the absence of ova or shells. Occasionally, in a few cases, there would be very large dense focal accumulations of eosinophils alone. Lymphocytes and eosinophils always were the predominant cell types. Ova and pseudotubercles were also found in the lobules proper, but in lesser numbers than in the portal spaces. Often the wall of bile ducts of all calibers was thickened by fibrosis, and in two cases there was notable adenomatous enlargement of the larger ducts in many portal spaces (Fig. 5).

One advanced case (A-305), a young man of 29, was very interesting in that at the time of death no ova were found in sections of the

liver. The fibrosis was definitely periportal (Fig. 1), but the surface of the liver was quite smooth; the organ weighed 960 gm. There was splenomegaly of 690 gm. and esophageal varices with fatal hematemesis. The diagnosis had been established 10 years before death. Lateral-spined ova were found repeatedly in the feces and once in the urine. He twice underwent operation for perirectal abscess, possibly of schistosomal origin. Already 9 years before death exploratory operation had shown an atrophic liver and an enlarged spleen. Vigorous treatment with tartar emetic was instituted from the time the diagnosis was made. The last 2 years of life he spent relatively well. At the end of this period he experienced nausea and vomiting, followed 3 days later by sudden vomiting of a large amount of blood, repeated hematemesis and death the next day. No parasites were encountered at autopsy, and ova were present in the lungs only, mostly undergoing calcification. There was likewise no schistosomal pigment in the spleen or liver. This case must have had a severe infestation that was cured by vigorous treatment. In spite of this the cirrhosis and splenomegaly continued, and death ultimately came about from hematemesis. The case proves beyond doubt that even though the parasitism may be cured, the patient's fate may still have been sealed if hepatic cirrhosis had already developed by the time treatment was administered. Yet this individual lived for 9 years after frank cirrhosis had been shown to be present by exploratory laparotomy; the evolution of the cirrhotic process would most probably have been not so slow if the parasitic infection had not been cured.

There was proliferation of bile ducts to a minimal extent in 3 cases of advanced cirrhosis, and to a marked extent in 7. In mild and moderately advanced cases there was rare proliferation of bile ducts in 13 out of 114 cases, accompanying fibrotic changes of the portal spaces. The extent of proliferation seemed in all cases directly proportionate to the amount of portal fibrosis. In minimal cases, even when ova were scanty, it was frequently observed that the portal spaces were fibrosed (Fig. 6), and that there were increased numbers of lymphocytes, and at times of eosinophils, in these areas.

In a case of moderately advanced schistosomiasis a dead worm was found in a mass of necrotic eosinophils in one section of liver (Fig. 7); about the necrotic cells there was a broad zone of dense infiltration, again with eosinophils. The liver cells in the whole area of eosinophilic infiltration had been destroyed and absorbed.

Intravascular proliferations of the endothelium were only rarely

observed. Figure 8 shows a small portal branch containing an ovum, and cells growing from the intima into the lumen.

Schistosomal splenomegaly: The splenic weight in this series ranged from 75 gm. in a 6½-year old boy, to 1970 gm. in an adult (Table III). There were 2 cases without splenomegaly: a 19-year old girl and a 52-year old man; in each instance the weight of the organ was 95 gm. There was no cirrhosis in the former (except for very early microscopic changes) while the latter presented advanced atrophic cirrhosis (liver 720 gm.) with much ascites. In general splenomegaly went parallel with the degree of cirrhosis. Adhesions about the organ were found in only 2 instances. The organ was not only enlarged but also of increased consistency, and in the larger specimens had an elastic rubbery feeling. Only one case had a spleen in which the pulp was soft, and in this one the enlargement was acute rather than chronic. In those weighing over 500 gm. a very delicate diffuse fibrosis of the pulp could often be detected with the naked eye, accompanied by a pale cast, thickening of the trabeculae and inconspicuousness of the malpighian corpuscles. In the enlarged spleens the capsule was invariably thickened, this being more marked in the larger ones, and frequently was covered by flat, white dense plaques and nodules that gave it the sugar-coated appearance. Pigmentation in the form of a dark or slaty hue to the pulp was noticeable only in the spleens with a lesser degree of enlargement, and which probably represented more acute and active infections. Old infarcts were noted in only one case. In none, other than the fatal, was splenomegaly in evidence.

Microscopically, the picture in advanced schistosomiasis was consistently that of a diffuse fibrosis of the pulp (Fig. 9) with diminution of the number of cells in the Billroth cords, diminution of the number and size of the malpighian corpuscles with disappearance of germinal centers, deposition of brown, non-refractile schistosomal pigment in reticulo-endothelial elements of the pulp and follicles and in monocytes, thickening of trabeculae, in which small hemorrhages were observable, as well as occasional incrustations of calcium and iron, and thickening of the capsule by diffuse fibrosis and by formation of dense hyalinized fibrous plaques and nodules. The fibrosis of the pulp was well advanced in most cases, but in three of them it was very fine and early, although the splenic weight was 590, 940 and 1430 gm., respectively. In these the lymphoid follicles were numerous and not reduced in size, and there was fairly marked congestion of the pulp. The fibrosis showed no predilection for the

TABLE III: *Brief Analysis of Severe Cases of Schistosomiasis*

Autopsy No.	Age	Sex	Weight (gms.)		Cirrhosis	Ascites	Hematemesis	Blood Count			Ova in Stools	Remarks
			Liver	Spleen				RBC	HGB	WBC		
42	45	Male	2050	1350	Adv.	+	0	—	—	—	+	
205	36	Male	930	580	Adv.	+	0	—	—	—	+	Thrombosis of splenic and portal veins.
288	16	Male	1330	150	Adv.	+	0	—	—	—	+	Adenocarcinoma of cecum.
305	29	Male	960	650	Adv.	0	+	2.40	45%	2,400 5,100	+	Ova in urine. Fibrosis and calcification of splenic and portal veins. Ascites previously.
468	52	Male	720	95	Adv.	+	0	3.54	80%	7,260	0	
478	24	Male	1670	1970	Adv.	0	+	—	—	—	No record	Bilharzial hepar lobatum.
590	35	Male	1900	1460	Moderate	+	+	—	—	—	0	Thrombosis of portal vein. Ascites slight.
732	14	Female	870	360	Moderate	0	0	3.55	73%	3,800	+	Miliary pseudotuberculosis of lung. Eosinophilia 12%.
757	25	Male	1350	1430	Adv.	0	+	2.80	30%	8,500	0	Ascites previously.
878	18	Male	2600	940	Adv.	0	0	2.59	70%	2,250	+	Retroperitoneal fibrosis. Platelets 73,000. Eosinophilia 45%. Ascites previously.
884	19	Female	1600	95	None	0	0	2.05	48%	17,500	+	Hyperinfestation.
1037	6½	Male	1227	75	None	+	0	2.62	40%	18,930	+	Hyperinfestation. Avitaminosis. Ascites slight.

periphery of the malpighian corpuscles. When well advanced the sinuses became small and poorly defined.

Two cases, Nos. 732 and 1037, showed relatively early splenic enlargement (Table III). One of these, a 14-year old girl with a very heavy infestation and moderately advanced cirrhosis, had an enlarged spleen weighing 360 gm. This organ showed no fibrosis but was intensely congested, with enlarged lymphoid follicles, the germinal centers of which were very active and prominent; the reticuloendothelial cells were also enlarged and contained abundant bilharzial pigment. The other, a 6½-year old child with a heavy, fairly recent infestation, had no cirrhosis. The spleen was enlarged to 75 gm. and showed only congestion and schistosomal pigmentation.

A single empty egg shell was found in the pulp in a case with advanced schistosomiasis. It was almost totally enclosed in a foreign-body giant cell. This was the only case in the whole series presenting ova in this organ.

In the non-fatal cases, changes of doubtful significance were found in a very few. Thus, of 134 such cases, 5 showed a diffuse increase in the number of eosinophils throughout the pulp. Six presented a very early fibrosis of the pulp; in 5 of these the fibrosis was in the form of rare microscopic patches, while in the sixth one it was more diffuse. Presumably schistosomal pigment was found in 23 cases, usually in scant amount and finely divided form, but occasionally more abundantly, forming small dark clumps. In another case there were found 4 cross sections of a worm or worms within an intrasplenic vein. The vessel was entirely unaltered and the parasite was well preserved.

Table III gives the weights of the spleen and liver for all cases of severe schistosomiasis. No close correlation can be established between the weight of the 2 organs, but in general it seems as if advanced cirrhosis with hepatomegaly were more frequently accompanied by a greater degree of splenomegaly than atrophic cirrhosis. There is no definite evidence for the suggestion implied in this observation, that splenic size may not always be steadily progressive, or that the fibrosis may after a time bring about a diminution in the size of the spleen.

Of 9 cases with splenomegaly (Table III, Nos. 42, 205, 305, 478, 590, 732, 757, 878 and 1037), Nos. 732 and 1037 represented severe, relatively recent infections in which the splenic enlargement was for the most part early and due mainly to congestion. They undoubtedly are examples of what obtains in this organ prior to the develop-

ment of fibrosis of the pulp and true splenomegaly. In the remaining 7 there was a clinical picture closely similar to that of Banti's disease in a not inconsiderable proportion. Thus, the 3 cases of schistosomiasis with chronic splenomegaly for which information on the blood picture was obtainable (Nos. 305, 757 and 878), presented cirrhosis, splenic enlargement and anemia with leukopenia. Ascites, though not found at autopsy in any, had been present in all at some time previously, and 2 of the 3 succumbed to hematemesis. Since the fatal cases of schistosomiasis (barring those that succumb early to hyperinfestation and complications) almost invariably show cirrhosis, splenomegaly and anemia with leukopenia, it may well be said that this disease exhibits the Banti syndrome quite constantly in its terminal stages. Bonelli (*loc. cit.*) pointed out this similarity in 1932. The similarity can be quite striking when the patient is seen between attacks of diarrhea, especially, as so frequently happens in cases of long duration, if no ova are found in the stools and no eosinophilia in blood counts.

We agree with Thompson's[18] interpretation of the pathogenesis of Banti's disease, and explain the splenic alterations in advanced schistosomiasis as secondary mainly to constriction of the intrahepatic portal bed by fibrosis produced in the liver by the schistosome ova, complicated in some cases by thrombosis of the portal or splenic veins. The persistent prolonged congestive action thereby affecting the spleen eventually leads to great enlargement and diffuse fibrosis of that organ. A general response to the infection may also play a role, but the former seems the more important factor. The importance of venous stagnation in the development of splenomegaly was clearly expressed by Day[19] in 1933.

Colitis: Gross evidence of colitis was found in 6 cases, rectal papillomata without colitis in one, and perirectal fibrosis in another. When well-developed the colitis was evident as a thickening of the whole wall from cecum to rectum, with broadening of the submucosa by fibrosis and edema and with congestion of the mucosa, at times more or less diffusely, at times in areas, accompanied by some fine hemorrhagic spotting. These changes obtained in 4 cases. A finely granular or sandy appearance of the mucosa was in addition noted in 2. Ulcers were not a frequent finding, being small, scanty and at various levels in one case, and very large, ragged and limited to the rectum in another. Of the less severe cases of colitis, in one the thickening of the walls and reddening of the mucosa were restricted to the rectum, while the cecum, transverse and sigmoid colon presented small hemorrhagic nodules not over 4 mm. in diameter, some of which were pedunculated. In another case slight diffuse reddening of the mucosa was the only finding. The distal portions of the colon were usually more severely affected than the proximal.

In addition to the above 6 cases, there was one with moderate perirectal fibrosis as the only alteration. This may have been of schistosomal origin, and followed a perirectal abscess, but the microscopic studies did not settle the point. In the 8th case there were 3 congested papillomata in the rectum, the largest measuring 0.5 cm. in height, without diffuse colitis. This leaves 4 severe cases without any gross change ascribable to schistosomiasis, but for one of these no description was left of the colon.

Microscopically, ova were present in the sections of all cases examined. Most of them were situated in the mucosa (Fig. 10), where they lay in the tunica propria or within capillaries or, most rarely, within glands. In the latter case the affected gland was almost always dilated and filled with polymorphonuclear leukocytes (Fig. 11). Ova were likewise encountered in all other coats including the subserosa and the outer fatty layer of the rectum, but in rapidly diminishing numbers towards the more peripherally placed coats. Rarely, shells and pseudotubercles were encountered in solitary lymphoid nodules. Not infrequently the muscularis mucosae was interrupted by the presence of pseudotubercles or by patchy areas of fibrosis. This same coat seemed distinctly hypertrophied in a number of cases. It is interesting that a great many of the ova found in a given section often had evoked no pseudotubercle formation and very little or no inflammatory reaction about them (Fig. 10). The histologic changes were focal and diffuse in character. About ova, the mildest change consisted of infiltration with a few lymphocytes alone or accompanied by eosinophils and plasma cells. At times one or two foreign-body giant cells surrounded the ova, accompanied or not by inflammatory cells. In other cases the ovum lay in the center of a fully developed pseudotubercle. In addition to this focal reaction there often was a more diffuse one with increased prominence of reticulum cells throughout the mucosa, groups of round cells about blood vessels in the submucosal and muscular tunics (Fig. 12), and diffuse edema and fibrosis of the submucosa, extending to a lesser extent to the muscularis mucosae and even along blood vessels of the inner and outer muscle coats. Granulation tissue in different stages of organization was also found in portions of the submucosa in severe cases of colitis (Fig. 13). Eosinophils were usually present either

in the neighborhood of ova or about blood vessels, or more or less diffusely in the submucosa. In general lymphocytes were more numerous than eosinophils. In a very few instances there was a diffuse increase in eosinophils throughout the mucosa. Once, in a case of hyperinfestation, this was a most notable feature in both the mucosa and submucosa (Fig. 18). In severe cases the wall of many of the smaller veins in the submucosa was edematous, at times infiltrated with eosinophils and lymphocytes. In one case there had been multiple thrombosis of submucosal veins. There were few ova in this case and a marked diffuse eosinophilic infiltration of the submucosa. The mucosal venules and the submucosal veins were dilated and engorged with blood in many of the severe cases, even in the absence of acute colitis.

The small nodules projecting from the mucosa in various portions of the colon in one case were composed of granulation tissue that extended from the submucosa in small areas of ulceration. The rectal papillomata in another case proved, on the other hand, to be adenomatous polyps.

In one case of severe schistosomal colitis with ulceration, a microscopic adenomatous proliferation of the mucosa was encountered near the margin of one ulcer (Fig. 14). The component cells were tall columnar, cell polarity was well maintained and there were no atypical characters to most of the cells. At several points, however, groups of the epithelial cells had undergone changes consisting in loss of polarity, loss of the outline of cell bodies, swelling of the nuclei with dissolution of the chromatin, and the presence within nuclei of well-outlined, rounded or elongated, single or double inclusion bodies that took the eosin stain brightly (Fig. 15). Whether the long-acting inflammatory changes provoked by the schistosomiasis facilitated the implantation of a virus which stimulated the epithelial hyperplasia, or whether the virus entered, or developed in, the cells of the already developed adenoma, are possibilities that cannot, of course, be analyzed in the present instance.

In only one case were numerous calcified ova encountered (Fig. 16). The calcification at times had involved the chitinous shell only, and the process must have taken place quite rapidly in a number of the ova, for some details of the contained embryo were still visible.

Adult worms were found in veins of the submucosa in one case (Fig. 17) and in veins of the outer fatty layer of the rectum in another. In both instances the worms were well preserved and the

containing blood vessels seemed entirely unaffected except for some dilatation.

In none of the mild or moderately advanced cases were gross alterations of the colon in evidence. In 2 of the moderately advanced there was acute colitis microscopically, with rather numerous polymorphonuclears in the mucosa. Histologic changes were much milder than in the advanced cases, but no different in kind, except that edema of the submucosa was present in only one or two instances, while slight to moderate fibrosis was the usual finding. Of 21 moderately advanced cases, there was hypertrophy of the muscularis mucosae in 2, fibrosis of the submucosa in 3 and edema of the submucosa in 1. Table II indicates the percentage incidence of cases with ova in the rectum and other parts of the colon in the minimal, moderately advanced and severe cases.

Pulmonary alterations: There were gross alterations due to schistosomiasis in 2 cases, both of them with severe infestations. In one of these (A-305) the consistency of both upper lobes was slightly increased, and small dense nodules were palpable throughout the parenchyma. On section numerous grayish or whitish nodules occurring singly or in groups were scattered throughout both upper lobes, measured approximately 1 mm. in diameter and projected slightly above the cut surfaces. Similar nodules were scattered in small numbers over the other pulmonary lobes. No foci of active tuberculosis were encountered in the lung, and no healed or active foci in the tracheo-bronchial lymph glands. Microscopically, very numerous ova, many of them undergoing calcification, were encountered, usually in alveolar septa or in the fibrous tissue about bronchi and their accompanying blood vessels. They had provoked little or no inflammatory reaction. The nodules described grossly were composed of dense hyalinized fibrous tissue, or else presented epithelioid and giant cells in the center and a fibrous capsule at times infiltrated with lymphocytes and eosinophils, at the periphery. The giant cells were of both the Langhans and foreign-body type. Occasionally the center of the nodules was necrotic, and one nodule had undergone calcification. Some of the nodules suggested areas of reaction about necrotic worms. Ova were found in the neighborhood of nodules but not in their center. There were no tubercle bacilli in sections stained by the Ziehl-Neelsen method.

The second case (No. 732) was even more striking, being that of a 14-year old girl who had had symptoms suggestive of schistosomiasis for several years. Towards the time of her last admission to hospital

she was complaining, among other things, of coughing at night, night sweats and pain in the chest. The lungs were normal on physical examination, both the liver and spleen were enlarged, and there was anemia of 3.5 million erythrocytes and 70 per cent hemoglobin, together with a leukopenia of 3,800 whites and eosinophilia of 11 to 20 per cent. Six days after admission, following the 5th injection of fuadin, there was fever of a 100° F. and some roughening was noted of the breath sounds in the right apex. Three days later the fever continued, and although still of low grade the pulse was 120 and the respirations 30 per minute. This day slight dullness was evident over the right lung posteriorly from the middle of the scapula down, while fine râles were audible on inspiration. The cough persisted since admission and was productive of sputum which on one or two occasions was blood-tinged. Three more injections of fuadin were given at intervals of 2 days. Coughing became marked after the last injection, and there was vomiting. Twelve hours after the injection the child developed dyspnea and cyanosis, death taking place half an hour later. At autopsy small firm nodules were palpable in both lungs, particularly in the lower lobes. Beneath the pleura there were rounded, bluish or purple, non-crepitant patches averaging 0.8 cm. in diameter, and occasional small yellowish foci about 0.2 cm. across, projecting slightly from the pleura and at times surrounded by a zone of intense congestion or hemorrhage. On section the parenchyma was bright red and studded with minute glistening gray granules measuring up to 1 mm. in diameter, and distributed both singly and in clusters (Fig. 3). There also were slightly larger yellowish foci and patches of consolidation. The intervening parenchyma was not affected, save for congestion. The gray granules were evenly distributed throughout both lungs from apex to base and could not be differentiated from miliary tubercles. The hilus lymph glands were much enlarged and intensely congested; one lymph node behind the trachea, above the bifurcation, was 5 cm. in greatest dimension. Microscopically the small gray nodules proved to be schistosomal pseudotubercles (Fig. 19) in various stages of development, but for the most part surrounded by a sharply-outlined fibrous capsule and with much peripheral infiltration by eosinophils, lymphocytes and occasional plasma cells. There were frequent areas of hemorrhage into groups of air sacs, and patches of bronchopneumonia with the acini filled with fibrin and leukocytes, the latter being eosinophils in their great majority. In several fields necrotic worms were visible within veins, and the walls of these vessels were partly necrotic and

overrun by eosinophils. For a considerable distance about the necrotic worms the alveoli were intensely hemorrhagic and contained dense clumps of eosinophils, lymphocytes and large mononuclears. There were likewise prominent changes in the small branches of the pulmonary arteries, with ova directly in the walls, and with fibrosis of the intima resulting in total obliteration of the lumen at various points. These vascular features of the case were very similar to what obtained in Clark and Graef's (*loc. cit.*) and their detailed description is left for a subsequent communication. No bacteria could be found in sections stained by Gram's method. This case had a moderately advanced cirrhosis and moderate acute splenic enlargement. Ova were numerous in the colon, liver and lungs, and often formed the center of a small necrotic focus. It is possible that death came from sensitization to the products of dead worms and embryos, as the result of vigorous treatment. The worms and large numbers of ova found in the lungs must have gotten there from the inferior hemorrhoidal plexus via the inferior vena cava.

In the whole series of 147 cases, bilharzial ova were found microscopically in the lungs of 16. They were situated in either alveolar septa or in the connective tissue about bronchi and their accompanying blood vessels. At times they had evoked formation of pseudotubercles, but very frequently there was no reaction about them, or at best infiltration with only a few lymphocytes and eosinophils. No diffuse or patchy scarring of the parenchyma was ever noted, but in a few instances the ova were found in apical or subapical scars of probable tuberculous origin. In this organ the ova rarely contained embryos, exception made of the heavy infestation above described. A localized thickening of the alveolar septa in which ova were situated was occasionally observed, and was due to infiltration with lymphocytes, eosinophils and monocytes.

Ascites: An average of 2 to 3 liters of thin clear fluid was found in the peritoneal cavity of 5 cases, all of which had advanced cirrhosis. Another case had moderately advanced cirrhosis and slight ascites. Still another, making a total of 7, had a very small amount (150 cc.) of free fluid in the peritoneal cavity and no cirrhosis, but the serous effusion was almost certainly due to a nutritional deficiency. Of the 5 cases without ascites two had no cirrhosis, and in 3 the cirrhosis was well or moderately advanced. Large distended peri-umbilical veins were present in one case. In another the superficial veins on each side of the chest were prominent.

Of the 5 cases with marked ascites, one presented large adherent

thrombi in the splenic and main portal veins; a second had a large carcinoma of the cecum with widespread extension to the peritoneum, which may well have been of more importance in the production of ascites than the cirrhosis, and in a third case, with only slight ascites, one of the primary subdivisions of the portal vein was filled with a thrombus, partly adherent to the intima.

In 4 cases, serous effusion had been present before death, but the ascites disappeared spontaneously and there was none at autopsy. Altogether there were 10 cases presenting ascites at autopsy or some time previously. It was never observed in one case of hyperinfestation of short duration and in one relatively acute case with moderate cirrhosis.

Esophageal varices: Four cases gave a history of hematemesis, and in all death ultimately came from this cause. For one of these no description of the esophagus was found in the autopsy protocol; there was advanced cirrhosis, splenomegaly and marked thickening by fibrosis and calcification of the splenic, superior mesenteric and portal vein, but no ascites. In a second case no varices could be demonstrated at autopsy and ascites was not present, yet both the cirrhosis and splenomegaly were well advanced. In a third case small submucous varices were seen at the gastro-esophageal junction without, however, a demonstrable rupture; the cirrhosis was moderately advanced and there was marked splenomegaly. Ascites had been present sometime previously, but not at death. The fourth case had several markedly dilated blood vessels in the cardiac end of the esophagus, beneath the mucosa, and presented one point of rupture, plugged by a small clot. This case had undergone splenectomy for great splenomegaly one year previously; cirrhosis was advanced but there was no ascites. The microscopic changes in this last case were interesting: one of the dilated veins showed little more than slight edema of the wall, while another showed edema and moderate loose fibrous thickening of the intima, with formation at one point of a polypoid excrescence into the lumen, also composed of loose fibrous tissue and probably representing an organized thrombus. About these dilated veins in the submucosa of the esophagus, there was diffuse and focal infiltration with lymphocytes and occasional monocytes, and several ova forming the center of small pseudotubercles surrounded by lymphocytes and eosinophils. A thrombus of very recent formation filled one of the varices.

In no case, therefore, did gastro-esophageal varices occur in the absence of advanced cirrhosis.

Retroperitoneal fibrosis: There was one case representative of this modality of advanced bilharziasis. This was a young man of 18 (Table III, No. 878), with a history of attacks of bloody diarrhea since childhood. Evidences of hepatic cirrhosis appeared five years before death. A tender, firm, immovable mass in the left side of the pelvis was first palpable 2 months before death, when he came into hospital with advanced cirrhosis and severe colitis. No response to treatment. The day before death he developed symptoms of intestinal obstruction. Autopsy revealed advanced cirrhosis, splenomegaly, colitis and a firm, irregular banded thickening of the retroperitoneal tissues, particularly along, and in part about, the rectum and terminal portion of the sigmoid colon, filling the pelvic cavity and pushing the urinary bladder anteriorly. To a lesser extent the fibrosis followed the colon from the cecum downwards, retroperitoneally, and the blood vessels into the mesentery. On section the thickened tissues were dense, very pale, edematous and fibrotic. The mesenteric lymph nodes were moderately enlarged. Microscopically there were foci of lymphocytic and relatively scant eosinophilic infiltration about small blood vessels in the fibrosed, edematous retroperitoneal tissues, and rather numerous ova with and without embryos in the center of young pseudotubercles. The wall of venules at times was broadened and infiltrated with eosinophils and lymphocytes. The mechanism of obstruction must have been actual compression of the sigmoid colon and impairment of peristalsis in the portion where the sigmoid was partly surrounded by the fibrous tissue.

Changes in portal veins and tributaries: There were distinct pathologic alterations in one or more of these veins in 4 cases. No. 205, a man 36 years old with advanced cirrhosis, a liver weighing 990 gm. and splenomegaly of 590 presented large adherent thrombi in the splenic and main portal veins. No. 305, a 29-year old man with a cirrhotic liver of 960 gm. and splenomegaly of 650 gm., showed diffuse thickening of the main portal vein by fibrosis (Fig. 20). At the junction of the splenic with the portal vein the thickening became very notable and was accompanied by extensive calcification which also involved the terminal portion of the superior mesenteric vein and had caused distinct constriction of the lumina of these veins; yet there were no thrombi. Death was from hematemesis. No. 590, a 35-year old man with cirrhosis, a liver weighing 1900 gm. and a spleen of 1460, showed thrombosis of one of the primary intra-

hepatic branches of the portal, and the thrombus was partly adherent to the intima. Death was from hematemesis.

Subserosal nodules of intestines: Small dense whitish or yellowish glistening nodules projecting over the serosa of the intestines were found in 5 cases. They were sharply outlined, irregularly scattered and not over 0.15 cm. in diameter. In one case of severe schistosomiasis they were extremely numerous in both the small and large intestine, but more particularly over the sigmoid. These nodules may be mistaken for tubercles when the observer is not aware of the possibility of their being bilharzial. They can be differentiated by their density and sharpness of definition, and by the fact that they do not occur in beads along lymphatics. Microscopically they represent pseudotubercles about ova, and in our cases frequently had a well-developed fibrous capsule, often hyalinized.

Evolution of schistosomal pseudotubercles and fate of ova in tissues: The development of pseudotubercles about ova appeared to proceed along more or less the same lines in the various organs and tissues, with some exceptions. Thus, in the lungs and intestinal tract a considerable proportion of the ova encountered in a given case had evoked no formation of pseudotubercles. In the pancreas pseudotubercles were always poorly developed, while the liver usually showed the sharpest and most typical response of this character.

In our human material the mode of extrusion of ova from the venules in which they are deposited in the intestine, or to which they are carried in the liver, lung and other organs, was not very apparent. In a few instances, however, ova were seen to be covered by endothelium growing as a continuation of that lining the venule, much as was previously reported for the rabbit by us.[17] Usually ova were seen either within the lumen of venules or already in the tissues. The earliest reaction observed about them as they lay in the tissues was the accumulation of eosinophils; rarely there would be polymorphonuclears mainly or even exclusively (Fig. 21). At this early stage the embryo was still recognizable within the shell, but it soon underwent degeneration, necrosis or autolysis. This does not mean that the embryo is always absorbed very quickly, for not infrequently they were visible within ova lying in the center of well-formed pseudotubercles, and these structures undoubtedly need a few days for their development. Furthermore, in one case embryos were observed in good state of preservation within ova, the chitinous shells of which showed early calcification.

After the eosinophilic or polymorphonuclear response seemed to come the formation of one or more giant cells, usually of the foreign-body type. Generally, by this time, the embryo was no longer to be seen and its place had been taken by either coagulated serum or a few eosinophils, or even by a giant cell. Epithelioid cells next developed (Figs. 22 and 23), forming a zone that enclosed the ovum and the foreign-body giant cells. The epithelioid cells resembled those of tuberculous granulomas and need no further description. The material by us utilized was not ideal for elucidation of the difficult question of the origin of epithelioid cells. It is, however, our impression that they perhaps develop from such fixed tissue elements as fibrocytes, reticulum cells and Kupffer elements, by enlargement and multiplication. The epithelioid cells in severe infestations in which abundant bilharzial pigment is produced, may phagocytize this pigment. About the zone of epithelioid cells there was slight to marked infiltration with lymphocytes, eosinophils, monocytes and plasma cells in variable proportions, but usually in about that order of frequency and density of infiltration.

After this point in the development of the pseudotubercles, regressive changes come to the fore with concentric proliferation of fibroblasts about the zone of epithelioid cells (Fig. 24). A capsule was thus formed which at first (Fig. 25) was broad, loose and overrun by the above types of leukocytes, and which as time passed (Fig. 26) became more compact and dense. As the elements of the capsule condensed by development of collagenous fibers and by shrinkage and compression of the cell bodies of fibroblasts, the epithelioid cell zone became narrower. The foreign-body giant cells about the ovum also became smaller, whatever leukocytes were present about the ovum disappeared, and the peripheral zone of leukocytic infiltration was reduced in density, lymphocytes being the last to disappear. In this fashion the zone of epithelioid cells is replaced by fibrous tissue from the capsule until all that remains is a sharply-outlined fibrous nodule with an egg shell and one or more shrunken giant cells in the center and with a few lymphocytes about the periphery. Ultimately the egg shell undergoes fragmentation and total dissolution, while the giant cells and peripheral lymphocytes disappear completely, leaving a fibrous nodule in which only a few small nuclei of fibroblasts are to be seen. At an earlier stage the nodule is finely fibrillar (Fig. 27), but later it condenses, becomes collagenous, and hyalinizes. This is the healed schistosomal pseudotubercle (Fig. 28).

In 15 cases completely healed pseudotubercles were encountered

with others in various stages of development and regression. In 9 additional cases only healed pseudotubercles were in evidence, and in 3 of these their schistosomal origin was proven beyond a doubt by the finding of ova in their center in serial sections. Although healed pseudotubercles may be found in any organ or tissue harboring bilharzial ova, they are most numerous in the liver. In the intestinal tract they are not a frequent finding, and in the colon they are relatively more often found in the subserosa than in any other coat.

In some cases it seemed as if many of the ova never evoked formation of pseudotubercles, and it is probable that a goodly proportion of these can undergo fragmentation and dissolution through the action of leukocytes or giant cells (Fig. 29), thus explaining their ultimate complete disappearance without leaving any telltale healed nodules behind.

Inflammatory changes provoked by schistosomiasis: The cells most frequently appearing about ova were lymphocytes, eosinophils, monocytes and plasma cells, as previously mentioned, but of these the last two occur in very small numbers and rather infrequently, while the first two, particularly the lymphocytes, are the more constant and numerous. In general, the greater the number of eosinophils, the more active the infestation, but it was often puzzling to see these cells persisting in the neighborhood of old, partly dissolved egg shell fragments and of empty shells in very light cases in which oviposition, if still going on, must have been taking place at a minimum rate. This, however, may mean local sensitization of tissues to toxic products eliminated by the few remaining worms.

In 5 instances—both mild and severe—a peculiar intensely acidophilic fringe (Figs. 30 and 31) was observed immediately about some egg shells. The fringe was composed of radially disposed delicate pink radiations, or of droplets composed of an amorphous glassy material or precipitate. This was altogether comparable to what Hoeppli[20] has described for *S. japonicum* in the rabbit. In the present series we found this change only about ova in the liver, but we have likewise occasionally encountered it twice in mesenteric lymph nodes and esophageal submucosa, respectively, and in the colon in experimentally infected monkeys (*M. rhesus*). The reason for the disposition of the material in the form of a corona is not obvious, and the nature of the change is likewise not apparent. The phenomenon, however, seems connected with the embryo in some way or another, for in most cases the latter was still recognizable within such ova. One wonders whether this could not represent a specific

precipitation reaction between tissue humors and a secretion or disintegration product of the bilharzial embryos; in other words, an antigenantibody reaction of the order of what obtains in the rat about worms of *Nippostrongylus muris*.[21]

Another interesting finding was that of necrosis in the center of pseudotubercles (Fig. 32). This occurred very infrequently and always in the presence of active infections. The necrosis was of the coagulation type and was accompanied or not by infiltration with eosinophils. It was a rather prominent feature of the case, previously described, of a 14-year old girl with schistosomal miliary pseudotuberculosis of the lungs, who died in the course of vigorous treatment with fuadin. In this case the foci of necrosis about ova may have represented an allergic reaction provoked by the large numbers of worms and embryos killed within a brief period by the drug, and bring to mind the Arthus phenomenon.

The inflammatory alterations taking place in some organs, such as the lungs and pancreas, were quite strictly limited to the immediate neighborhood of ova or worms, but the same was not true of the liver and intestines. In the latter organs inflammatory changes were both focal and diffuse. This was clearly noticeable, not only in severe infestations, but also in the milder ones, particularly in the liver. In this organ, fibrosis was noted in most portal spaces in cases in which ova were extremely scanty in both the liver and colon. The fact that ova were not at all numerous in the colon and that there was no colitis precludes the possibility of an effect from products of tissue damage at the level of the gut, transported to the liver by the portal blood stream. Particulate matter reaching the portal spaces of the liver gives rise to focal and not diffuse fibrosis, as in the case of silica granules;[22] we therefore believe that in bilharziasis the possibility of a diffusible toxin in the sense of a specific toxin or of a metabolic product excreted by the adult worms should be considered in the production of the extensive fibrosis seen in this disease.

Bilharzial pigmentation: In the tissues, bilharzial pigment was seen as fine granules or small clumps of a brown non-refractile appearance, altogether indistinguishable in these respects and in its localization from malarial pigment. The Prussian blue reaction, whenever applied, was negative, indicating absence of iron. It was not possible in most cases to feel certain that the pigment was not malarial, for many of the subjects came from malarious districts.

The pigment was found in the liver, spleen and bone-marrow. Of the 12 severe cases, 11 had pigment in the liver, 8 in the spleen, and

3 in the bone-marrow. As regards the last, however, it must be mentioned that sections of femoral or vertebral bone-marrow were available from 5 cases only.

In the liver it was held within Kupffer cells in 10, in phagocytic cells of the portal spaces in 7, and in epithelioid and giant cells of pseudotubercles in 1. In the spleen it was contained within reticulum cells of the pulp (to a lesser extent in those of the malpighian corpuscles), in littoral cells of the sinuses, and in wandering phagocytes. In the bone-marrow the pigment had been engulfed by reticulum cells and by occasional free phagocytes.

Miscellaneous observations: In Table II are listed all the viscera in which ova were encountered. In no case were the alterations in the small intestine, mesenteric lymph nodes, stomach, pancreas, testis, gallbladder, kidney, suprarenal glands, appendix and urinary bladder of any real clinical significance. Pathologically the alterations in those organs were likewise not very striking. Rarely did the ova occur in large numbers in these situations and, frequently, they had provoked little or no reaction. At the most they incited pseudotubercle formation and cell infiltrations of the character previously described.

In the single case (Autopsy 468, advanced) in which they were encountered in the testis (Fig. 33), only shells were found. They occurred distributed throughout the interstitial tissues of the gland, within venules and outside them and had provoked no inflammatory reaction and no formation of pseudotubercles. At the most they had caused slight fibrous thickening in their neighborhood, and appeared not to have compromised the integrity of the seminiferous tubules.

In Autopsy 405, with minimal schistosomiasis of the colon and liver, two egg shells were encountered in the urinary bladder (Fig. 34). They were situated beneath the epithelial lining. The subepithelial layer was sparsely infiltrated with lymphocytes, but this occurred diffusely and was not especially concentrated about the egg shells.

In a moderately advanced case with early cirrhosis of the liver, microscopically, a well-preserved schistosome worm was encountered in one section within a vein in the peripelvic tissues of one kidney. In other cases (see Table II) there were peculiar small calcified structures in the stroma of the cortex. These were usually rounded or with convoluted margins. Some of them may have been ova or fragments thereof, but identification was impossible.

Two advanced cases contained numerous ova in the moderately

enlarged mesenteric lymph nodes. Most of the ova must have been recent arrivals in the nodes, for the contained embryo was often still well preserved, and there was no reaction on the part of the surrounding tissues. At the most there was feeble pseudotubercle formation with but slight peripheral infiltration with eosinophils. The enlargement of these glands, when present, was due to lymphoid hyperplasia.

Mode of death: In all but one, perhaps two, of the 12 severe cases death was due to uncomplicated schistosomiasis. The immediate cause of death seems to have been as follows:

Hematemesis	4
Cirrhosis of liver	3
Hyperinfestation	2
Cirrhosis and partial intestinal obstruction	1
Colloid adenocarcinoma of cecum	1
Obscure	1

No information could be obtained on the duration of the disease in 1 of the cases dying of cirrhosis. Symptoms of cirrhosis appeared some 6 months before death in a second case, but the duration of the schistosomal infection was unknown. In the third, enlargement of the spleen and liver was observed 10 years before death.

Of the cases of fatal hematemesis, one (Autopsy 305) was found at exploratory laparotomy 9 years before death to have an atrophic liver and splenomegaly; its history is briefly summarized under "schistosomal cirrhosis of liver." In another case there had been increasing swelling of the abdomen, progressive emaciation and attacks of hematemesis for 2 years prior to death. In a 3rd case the first symptoms were malaise, weakness and anemia 1 year before death, while hematemesis first occurred 6 months after onset of symptoms. The 4th case had bloody diarrhea, hematemesis, abdominal enlargement and splenomegaly 20 months before death. Splenectomy was performed 1 year before the fatal outcome but appears not to have modified the course of the disease.

One of the cases of hyperinfestation, a girl 19 years old, fell ill 3 months before death with severe acute colitis accompanied by bloody dejecta, fever, nausea and vomiting and rapidly developing cachexia with macrocytic anemia. Gastric analysis revealed no free acid and a total acidity of 10. At autopsy extremely numerous worms were found in all tributaries of the portal vein and in hepatic veins within the liver. There also were very numerous subserosal

nodules of the intestines, moderate atrophy of the gastric mucosa and numbers of ova in the lungs, liver, stomach, duodenum, small intestine, colon and mesenteric lymph glands. Very early cirrhosis was in evidence microscopically. The case was complicated by bilateral acute pyelonephritis. The second case of hyperinfestation was a boy 6½ years old in whom the recorded onset was 1 year before death with bloody diarrhea and vomiting, very persistent and almost continuous until death. Fever was present for a time. The condition was complicated by nutritional deficiency with a clear-cut history of inadequate diet and various ocular and dermatologic manifestations of multiple avitaminosis. At autopsy there were numerous worms in the mesenteric, splenic and portal veins and their branches, and chronic colitis with thickening of the walls and formation of small ulcers. Despite the large numbers of schistosome worms, ova were not particularly numerous in the viscera. It is difficult to decide whether the schistosomiasis or the frank dietary deficiency was the more important factor in the fatal outcome. The child died within 2 days of admission to hospital, too short a period to have tested the relative importance of the 2 conditions.

In the case dying of cancer, a boy 16 years of age, attention to the condition appears to have been called 1 year before death by a blow to the back. Two weeks after this a mass was felt in the right hypochondrium. The diagnosis of obstructing colloid adenocarcinoma of the cecum (Fig. 35) was established through exploratory laparotomy and biopsy. Ova were present in the stools in very large numbers. At autopsy the tumor was found to be primary in the cecum, and had metastasized to the liver, mesenteric and retroperitoneal lymph glands and, very extensively, to the peritoneum. There was active schistosomiasis, with worms in the mesenteric and retroperitoneal veins and advanced cirrhosis of the liver, but without frank splenomegaly. Ova were numerous in the colon and throughout the retroperitoneal tissues and neoplasm (Fig. 36).

The case of partial intestinal obstruction, a boy of 18, fell really ill 5 years before death with bloody diarrhea and tenesmus, but the history brought out that these symptoms had been present in mild form since early childhood. Enlargement of the spleen and liver and ascites became evident 4 years prior to death. Four months before demise a firm, tender mass, not movable, was felt in the left iliac fossa. The day before death he developed severe abdominal pain, with visible peristalsis and other evidences of low intestinal obstruction. Laparotomy revealed a mass filling the pelvis and extending

retroperitoneally along the left lumbar gutter and about the rectum. By compression, the mass had reduced the lumen of the sigmoid colon. Besides great retroperitoneal fibrosis (described in page 29), with formation of a mass, there was advanced cirrhosis, splenomegaly and colitis.

Case No. 732, listed as obscure, as regards the immediate cause of death, is discussed on page 24. As mentioned there, we suspect treatment with fuadin to have had something to do with the fatal ending.

OBSERVATIONS ON PARTIAL AUTOPSIES AND SURGICAL MATERIAL

A review of 18,500 consecutive entries of surgical material and of various organs or portions of organs from autopsies performed in different parts of the Island disclosed 99 cases in which undoubtedly schistosomal lesions were encountered.

The following organs were involved in the schistosomal process in various cases: colon including rectum, small intestine, liver, spleen, lung, appendix, pancreas, mesocolic lymph nodes, testis, ovary, oviduct, cervix uteri and anus. Of these, the last 5 were not represented in the autopsy material, exception made of the testis.

Ovary: One of the cases has been reported by Pila (*loc. cit.*). It presented a nodule in an ovary, composed microscopically of numerous pseudotubercles with ova about an area of granulation tissue which in turn surrounded a hemorrhagic focus. The corresponding fallopian tube was slightly dilated, the mucosa and wall were edematous, and several adult worms occupied veins in the broad ligament. A second case, 25 years old, presented an adult worm within the ovary, with much round-celled and eosinophilic infiltration, and with a few ova in the neighboring stroma.

Oviduct: In a girl of 19 the mucosa of one oviduct showed widespread necrosis and ulceration. There were pseudotubercles about ova in all coats, accompanied by edema and much infiltration with lymphocytes, plasma cells and eosinophils.

Cervix uteri: A small polypoid nodule was removed from the cervix uteri of an 8-year old child. The stroma was very edematous, richly vascularized and overrun by plasma cells. Throughout the stroma were schistosome ova, often with their embryos, and some of the ova lay in cervical glands. A very similar case was that of a 40-year old woman with numerous ova in a polypoid nodule of the cervix.

Anal polyps: There were anal polyps in 4 men of 22, 30, 42 and 50 years of age, respectively, and in a woman of 21. In four instances

they were composed of granulation tissue that was intensely inflamed and contained more or less numerous ova, some in the center of pseudotubercles, others free. Once the polyp was adenomatous.

Testis: A 32-year old male with advanced bilharziasis, a cirrhotic liver weighing 770 gm. and a spleen of 710 gm. presented numerous ova in the interstitial tissues of the testis. These tissues were edematous and sparsely infiltrated with large mononuclear cells. Some of the ova were calcified. The seminiferous tubules were unaltered.

Appendix: In 7 cases a few typical pseudotubercles were found in the appendix, affecting either the mucosa or the submucosa and, once, the subserosa. In a few instances there was rather marked diffuse eosinophilic infiltration of various coats. At no time was the appendix severely involved or acutely inflamed. In addition there were 8 cases of appendectomy for pain suggestive of appendicitis, in which no acute inflammatory alterations were found, but which presented one or a few pseudotubercles attended by much eosinophilic infiltration. Even though no ova could be identified the pseudotubercles were most probably of schistosomal origin.

DISCUSSION

Considering all our cases as a whole, the sequence of events in the disease appears to be as follows: We had, to begin with, no cases illustrating the early stages, prior to oviposition. In our group the pathologic alterations were mainly hepatic and colonic, with the spleen becoming affected secondarily, and only in the late stages of heavy infestations, while other organs were for the most part involved to a much lesser extent and produced slight if any clinical manifestations. For oviposition the worms showed a predilection for veins draining the colon, especially its aboral levels. Passage of ova into the intestinal wall, mainly in the mucosa and submucosa, gives rise to a chronic colitis with acute phases. Some of the ova laid in the venules of the gastro-intestinal tract are, however, swept back with the circulation into the liver, where they provoke irritation and fibrosis in the portal areas. This, if the infection is heavy enough, ultimately results in hepatic cirrhosis with obstruction throughout the portal bed. Such an obstruction in time is responsible for splenomegaly, ascites and esophageal varices, and for establishment of a collateral circulation which may be expressed clinically in dilatation of superficial veins of the abdomen and thorax and in the much dreaded hematemesis, which not infrequently puts an end to the patient's life. Unusual localizations of the mating or ovipositing worms

at times result in the deposition of large numbers of ova in such organs as the testis, ovary, uterus and retroperitoneal and mesenteric tissues, or facilitate their being swept into the lungs, adrenals and other organs. The pigment elaborated from the host's hemoglobin by the worms is excreted into the circulation and engulfed by reticulo-endothelial cells of the spleen, liver and bone-marrow. In heavy infections the worms tend to occupy veins draining the higher levels of the intestine, including the small gut, and even branches of the portal that drain such organs as the spleen, pancreas and stomach. Through connections between the inferior hemorrhoidal plexus and the inferior vena cava, worms may find their way to the pulmonary arteries and hepatic veins. Anemia develops as a result of various factors. Some of the more apparent of these are bleeding from the gut, particularly during the periods of dysentery, feeding on the host's blood by the worms, nutritional deficiency from the prolonged colitis and gastro-intestinal disturbance, and hematemesis. The tendency to macrocytosis, which has been pointed out by Rodríguez-Molina and Pons[23] in the late stages, and the leukopenia, are of difficult explanation, but in this respect it must be noted that macrocytic anemia has been correlated with chronic liver damage.[24, 25] One of our cases, No. 878, presented a macrocytic hyperchromic anemia with a mean corpuscular volume of 111 cu. u. The anemia with leukopenia, together with the hepatic cirrhosis and splenomegaly make for a clinical picture in the late stages which can only be distinguished from that of Banti's disease by finding an increased eosinophilic count or by discovering schistosome ova in the feces. Under treatment, or spontaneously in light infections, the tendency is probably for the number of worms to diminish, for oviposition thus to become less active, and for the lesions provoked by the ova to heal through fibrosis. It is probable, however, that once hepatic cirrhosis is well established, elimination of the parasitic infestation does not affect the ultimate unfavorable outcome of the case.

To judge from our material, which is ample enough to be considered fairly representative, schistosomiasis as found in San Juan, a non-endemic center, is not a very severe disease. It was clinically inapparent in 91.8 per cent of the cases, and directly responsible for death in only 8.2 per cent of those with schistosomiasis and in 1.2 per cent of all our autopsies. The total incidence of 14.6 per cent, however, speaks for rather a high rate of infection in the endemic centers of the Island, where bilharziasis must be important as a mortality and morbidity factor. This importance is enhanced by the fact that

the disease is more frequently observed during the 3rd and 4th decades of life.

Diarrhea, especially when the stools are bloody, and abdominal pain, stand out prominently in the clinical picture of the disease. The need for careful examination of the feces for schistosome ova in all suspicious cases is well brought out by the fact that in our series the diagnosis was made in twice as many cases, and with more certainty, by investigation of the stools than by the history of the case and clinical findings. The desirability of utilizing concentration methods in the search for ova in the feces needs hardly be emphasized. It is likewise of primordial importance, from the diagnostic point of view, to consider schistosomiasis in the differential diagnosis of all cases of Banti's disease when occurring in individuals who may have been exposed to bilharzial infection. In endemic regions this consideration must be extended to all cases with gastro-intestinal symptomatology and to all those with evidences of cirrhosis.

Our analysis of the pathological anatomy leads us to believe that, no matter how useful it may be from the bedside point of view to group cases of schistosomiasis into hepatic, intestinal, hepato-splenic and visceral forms, such classifications are basically wrong and apt to be somewhat misleading. Table II is instructive in this respect. It shows, firstly, that in a given minimal case (i. e., very mild infections), the liver, the rectum and other parts of the colon are practically the only organs apt to be found involved. In the moderately advanced, the small intestine, mesenteric lymph nodes and lungs become involved with much greater frequency than in minimal infections, in addition to the liver and colon, while the severe cases show extension to a still larger number of organs. Secondly, the chances of involvement of a given organ increase rapidly with the severity (i. e., number of ovipositing worms) and the duration of the disease. Thus, random sections of the liver, for example, contained ova in 67.7 per cent of minimal infections, in 85.7 per cent of the moderately advanced, and in all of the severe. Thirdly, for each one of the three grades of infection, the liver and colon follow each other closely in percentage incidence of involvement. From these findings it becomes evident that the disease is both hepatic and intestinal in its fundamental pathology from the beginning in all cases. It is, of course, to be expected that symptoms ascribable to the liver will not manifest themselves until a much later date than the intestinal, so that a given case probably goes for quite sometime with intestinal disturbances before any clinically demonstrable hepatic

alterations develop. By the same token, splenic damage will not become apparent until after hepatic fibrosis is well established, exception made of earlier congestive enlargements of the spleen which undoubtedly take place during the period of migration of metacercariae with its attendant febrile episode.

We have found no substantiation for the hypothesis[26] of an organ selectivity which would mark, early in the course of the disease, the viscera that would sustain the greatest damage, and that would thus impress a seal to the clinical course of a given case, determining whether the symptomatology would be primarily intestinal or hepato-splenic. We rather incline to interpret the variations in the clinical picture as a function, mainly, of duration of the infestation and numbers of ovipositing worms. In addition there probably are secondary factors at present not amenable to analysis. The curious tendency, for example, of bilharzial dysentery to occur in bouts does not reconcile itself with the fact that oviposition probably takes place as a continuous, fairly regular process. Whether the bouts of dysentery are in part at least the result of dietary indiscretions or deficiencies, or of bacterial activity, cannot be determined but must be considered, as must also the possibility that oviposition may not be, after all, a regular and continuous process.

Table II also brings out the fact that rectal involvement in oviposition is at its lowest in the most severe cases, while involvement of higher levels of the intestine increases progressively with the severity and duration of the disease. Whether the inflammatory changes obtaining in the lower levels of the colon induce the worms, after a time, to move to higher levels for oviposition, or whether there are other factors at play could not be determined from a study of our material.

The well-known fact that it is often difficult to find schistosome ova in the stools of cases of long standing has often been explained as due to fibrosis of the wall of the intestine impeding the passage of ova into the lumen. Our impression from the histologic examination of the colon is that the fibrosis is never so extreme or so extensive as to support the above contention. It seems more plausible to explain it by a reduction in the number of ovipositing worms as the infestation grows older. We were struck by the small numbers of ova in the wall of the intestine in several of the advanced cases, and by the absence of ova with embryos. We furthermore believe that ova do little or no real wandering through the tissues once they leave the vascular lumina, and that it is only those that are extruded very close to the mucosal surface that manage to get into the lumen of the intestine. These interpretations are the result of observations

on human and experimental material, and will be the subject of a subsequent communication.

SUMMARY

The pathological anatomy of Manson's schistosomiasis as found postmortem in 147 Puerto Ricans is described.

The total incidence of the disease in 1009 autopsies was 14.6 per cent. Schistosomiasis was the cause of death in 8.2 per cent of the infected and in 1.2 per cent of the 1009 autopsies.

Males were more frequently affected than females, and whites than the colored. It likewise appeared mostly in individuals in the 3rd and 4th decades of life.

The fundamental histopathologic unit of the disease is the pseudotubercle, developing about ova. The development of pseudotubercles is traced from the early stage of eosinophilic and polymorphonuclear response through that of an epithelioid cell nodule to the final healed fibrous body. There are, in addition, chronic inflammatory changes leading ultimately to fibrosis, especially in the liver and colon.

From the beginning, the disease is primarily hepatic and colonic. Pathologic changes are instigated mainly by the deposition of ova in the tissues; in the colon this leads to colitis and in the liver to cirrhosis, which is periportal in distribution. Splenomegaly develops, in part at least, secondary to portal obstruction.

The involvement of the liver and colon, and of other viscera, increases rapidly with the severity and duration of the infection.

The main anatomico-pathologic alterations due to schistosomiasis, as found in this series, are divided for purposes of description into: cirrhosis, splenomegaly, colitis, pulmonary alterations, ascites, esophageal varices, retroperitoneal fibrosis, sclerosis and thrombosis of the portal vein and tributaries, bilharzial pigmentation, subserosal nodules of intestines, evolution of the pseudotubercles, and inflammatory changes due to schistosomiasis.

The similarity of the late stages of schistosomiasis to the Banti syndrome is emphasized; likewise the need for thinking of this disease in all cases presenting that syndrome, or evidences of cirrhosis, or gastrointestinal symptoms, whenever the subject has lived in areas of endemic bilharziasis.

One case of pulmonary miliary pseudotuberculosis due to schistosomiasis is briefly described, and mention made of the possible role played in its death by treatment with fuadin. One case is briefly described of a colloid adenocarcinoma developing in the cecum of a 16-year old boy with a severe schistosomal infection.

ACKNOWLEDGMENT

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FIGURE 1. AUTOPSY 305

Advanced schistosomal cirrhosis of liver. Note concentration of fibrosis about larger portal branches ("white clay pipe-stem cirrhosis" of Symmers) and smoothness of external surface. The rounded defects in the parenchyma were produced by insufficient fixation.

GRABADO 1. AUTOPSIA 305

Cirrosis hepática avanzada. Nótese la concentración de la fibrosis en derredor de las ramas venosas portales mayores (cirrosis "en tubos de pipa de barro" de Symmers) y lo liso de la superficie externa del órgano. Los vacíos en forma redondeada, que se observan en el parenquima, son resultado de la imperfecta fijación de los tejidos.

FIGURE 2. AUTOPSY 732

Moderately advanced schistosomal cirrhosis of liver. Note the smoothness of the external surface in contrast to the periportal fibrosis.

GRABADO 2. AUTOPSIA 732

Cirrosis bilhárzica moderadamente avanzada. Nótese lo liso de la superficie externa en contraste con el grado de desarrollo de la fibrosis periportal.

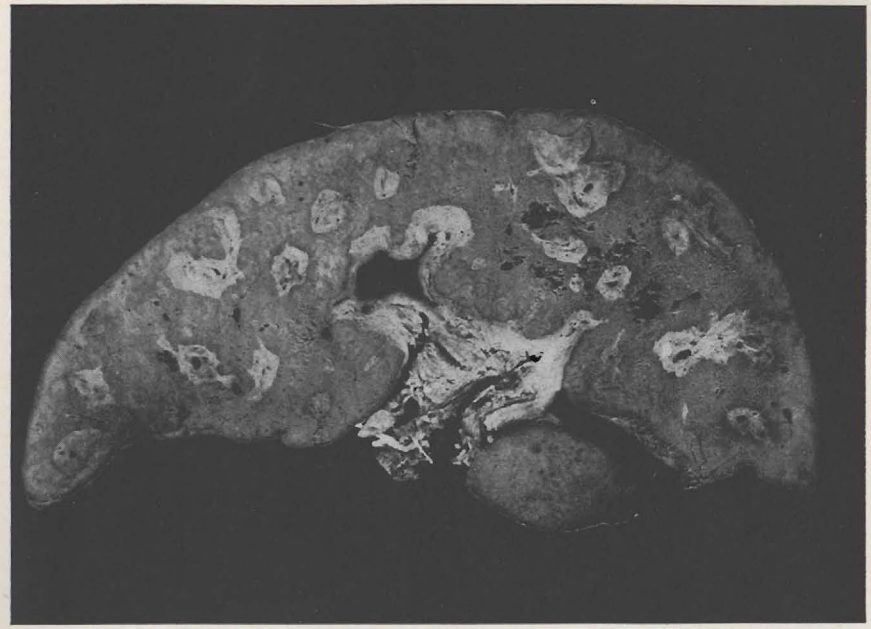

FIGURE 1

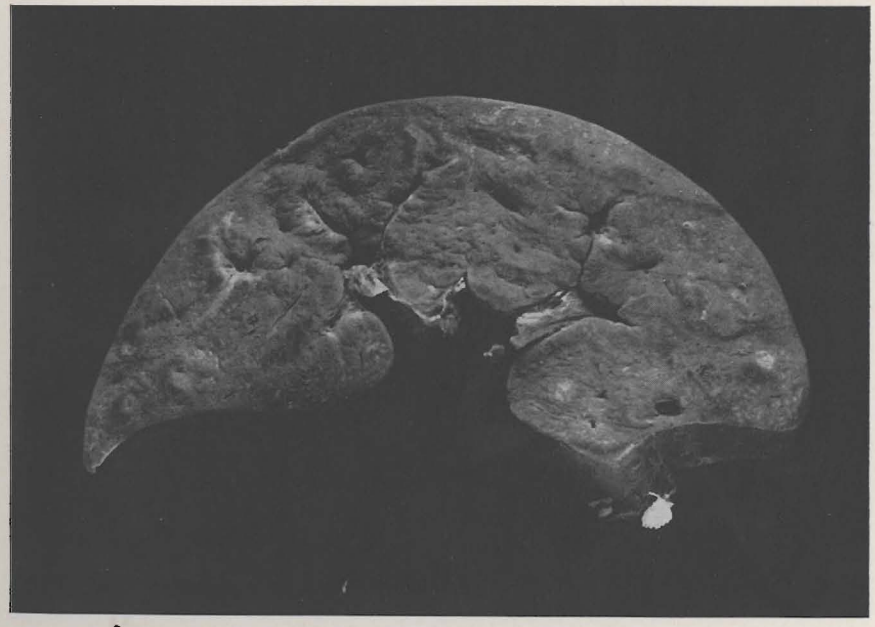

FIGURE 2

FIGURE 3. AUTOPSY 732

Miliary schistosomal pseudotubercles evenly distributed throughout the lung.

GRABADO 3. AUTOPSIA 732

Seudotubérculos miliares bilhárzicos distribuídos por todo el tejido pulmonar.

FIGURE 4. AUTOPSY 42

Portal space of liver in advanced cirrhosis, showing fibrous thickening of large portal branch, fibrosis, increased vascularization and dense lymphocytic infiltration. Black round structure near center bottom is a calcified ovum. 60X

GRABADO 4. AUTOPSIA 42

Espacio portal en una cirrosis hepática avanzada. Fibrosis de una rama venosa portal. Vascularización y densa infiltración linfocitaria. La estructura redonda y negra cerca del centro, en la porción inferior de la lámina, representa un huevecillo calcificado. 60X

FIGURE 5. AUTOPSY 42

Advanced cirrhosis with formation of dense collagenous fibrous tissue in portal space, marked proliferation of bile ducts and adenomatous hyperplasia of epithelial lining of the larger one. 60X

GRABADO 5. AUTOPSIA 42

Cirrosis avanzada con formación de tejido fibroso denso y colágeno en el espacio portal, gran proliferación de conductos biliares e hiperplasia adenomatoidea del revestimiento epitelial de uno de estos conductos. 60X

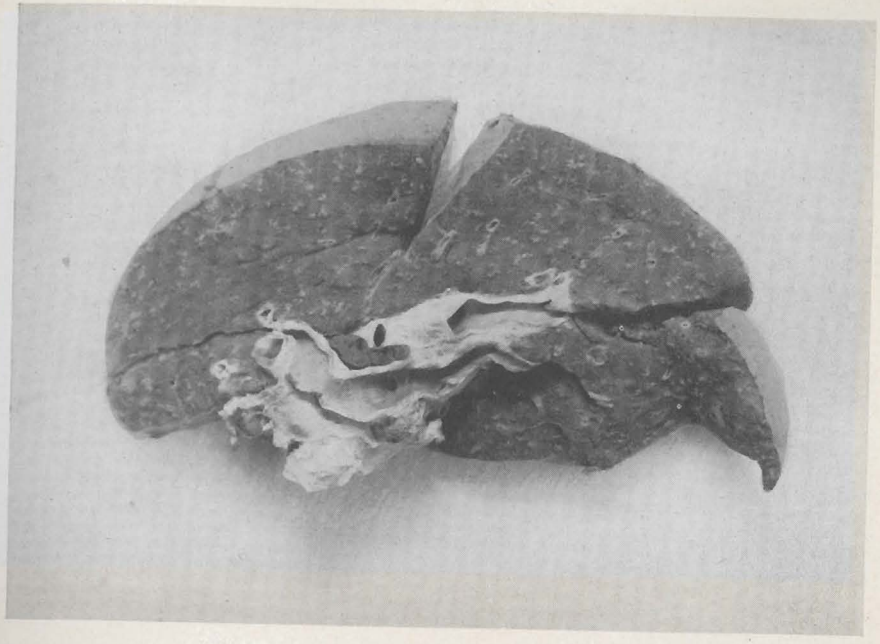

FIGURE 3

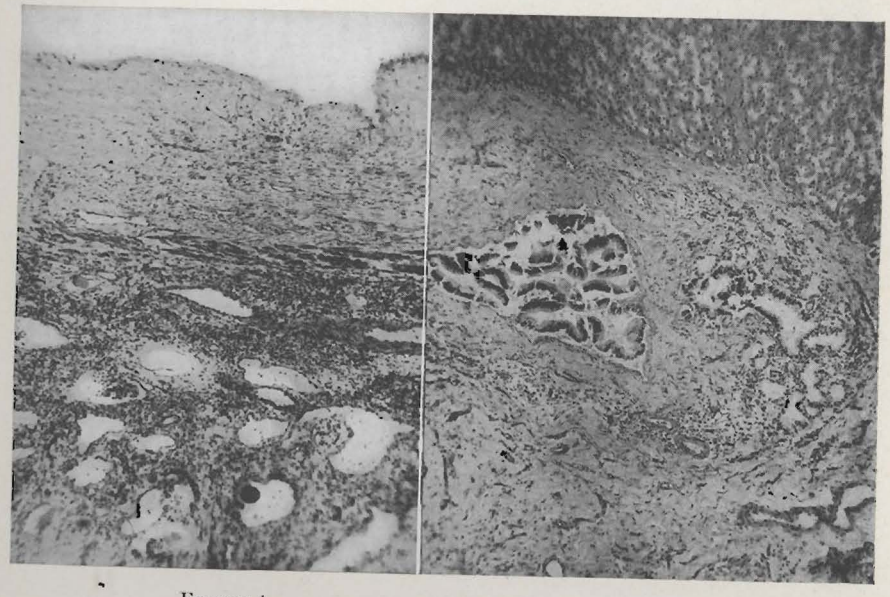

FIGURE 4

FIGURE 5

FIGURE 6. AUTOPSY 453

Liver. Early fibrosis of portal space accompanied by slight lymphocytic infiltration. Note absence of ova. 100X

GRABADO 6. AUTOPSIA 453

Hígado. Comienzo de la fibrosis en un espacio portal y leve infiltración linfocitaria. Nótese que no hay huevecillos en todo el campo. 100X

FIGURE 7. AUTOPSY 869

Liver. Cross section of dead schistosome worm in center, with formation of focus of necrosis and massive leukocytic infiltration. All cells are eosinophils. 60X

GRABADO 7. AUTOPSIA 869

Hígado. Al centro, un verme muerto, en un foco de necrosis, e infiltrado masivo por eosinófilos. 60X

FIGURE 8. AUTOPSY 149

Liver. Small portal branch with ovum in lumen which is partly filled by epithelioid cells originating in the intima or subintima. Note lymphocytic and eosinophilic infiltration of portal space. 100X

GRABADO 8. AUTOPSIA 149

Hígado. Pequeña rama portal con un huevecillo en su luz. Proliferación intravascular de células epitelioideas a partir de la íntima o subíntima. Infiltrado de linfocitos y eosinófilos en el resto del espacio portal. 100X

FIGURE 9. AUTOPSY 305

Advanced splenomegaly with marked fibrosis of pulp. 150X

GRABADO 9. AUTOPSIA 305

Fibrosis de la pulpa esplénica en un caso de gran esplenomegalia bilhárzica. 150X

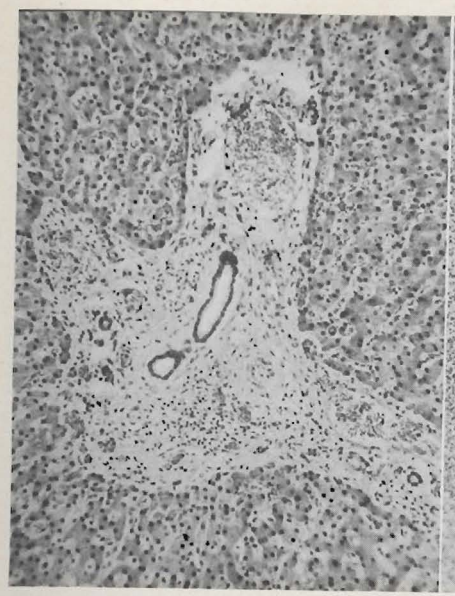

FIGURE 6

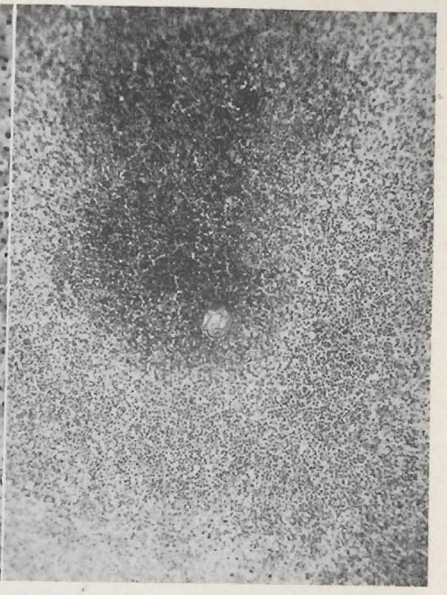

FIGURE 7

FIGURE 8

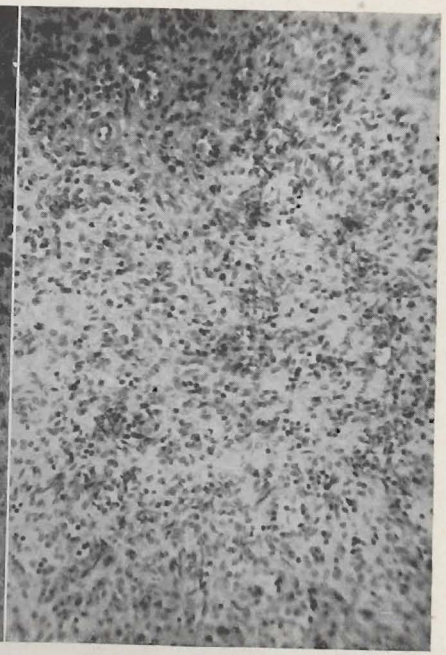

FIGURE 9

FIGURE 10. AUTOPSY 253

Marked congestion of mucosa. Numerous egg shells within blood vessels and in tissues. Note lack of tissue response about shells. 150X

GRABADO 10. AUTOPSIA 253

Colon. Gran congestión de la mucosa. Acúmulo de cubiertas ovulares dentro de los vasos y fuera de ellos. No se nota reacción inflamatoria en derredor de los huevecillos. 150X

FIGURE 11. AUTOPSY 474

Colon. Dilated gland lined by flat epithelium and containing 5 schistosome ova with their embryos and numerous polymorphonuclears and eosinophils. 150X

GRABADO 11. AUTOPSIA 474

Colon. Glándula dilatada, revestida de células achatadas y conteniendo 5 huevecillos con sus embriones y numerosos polinucleados y eosinófilos. 150X

FIGURE 12. AUTOPSY 1037

Colon. Round-celled and eosinophilic infiltration about blood vessels between inner and outer muscular coats. 100X

GRABADO 12. AUTOPSIA 1037

Colon. Infiltrado de células redondas y eosinófilos en torno de venillas entre la capa muscular interna y la externa. 100X

FIGURE 13. AUTOPSY 42

Colon. Organizing granulation tissue in submucosa in case of advanced schistosomiasis with severe colitis. 150X

GRABADO 13. AUTOPSIA 42

Colon. Tejido de granulación en proceso de organización, en la submucosa. Caso de bilharziosis avanzada con colitis intensa. 150X

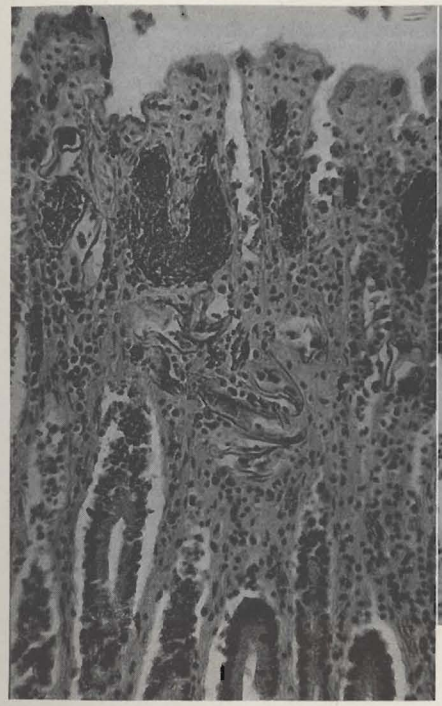

FIGURE 10

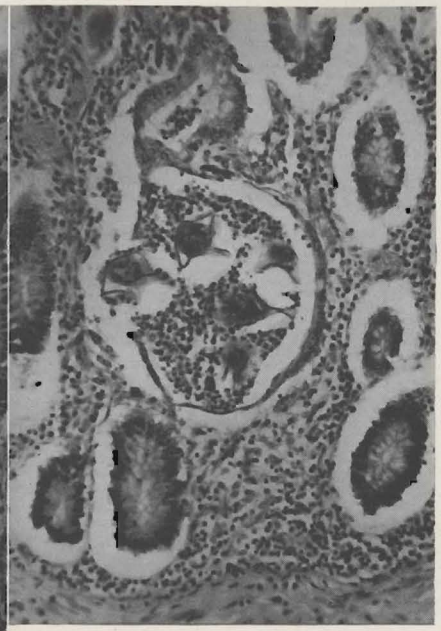

FIGURE 11

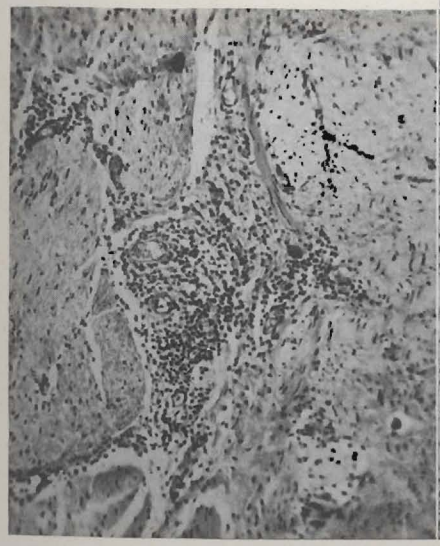

FIGURE 12

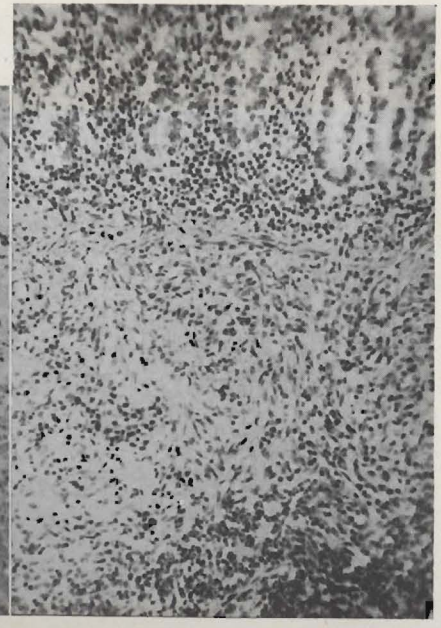

FIGURE 13

FIGURE 14. AUTOPSY 205
Colon. Advanced case with colitis. Adenomatous formation of mucosal origin. 100X

GRABADO 14. AUTOPSIA 205
Colon. Caso avanzado con colitis. Adenoma microscópico en la mucosa. 100X

FIGURE 15. AUTOPSY 205
Colon. Detail of preceding picture to show nuclear inclusion bodies within cells in adenoma 970X

GRABADO 15. AUTOPSIA 205
Colon. Detalle de la lámina anterior mostrando cuerpos de inclusión intranucleares en grupos de células del adenoma. 970X

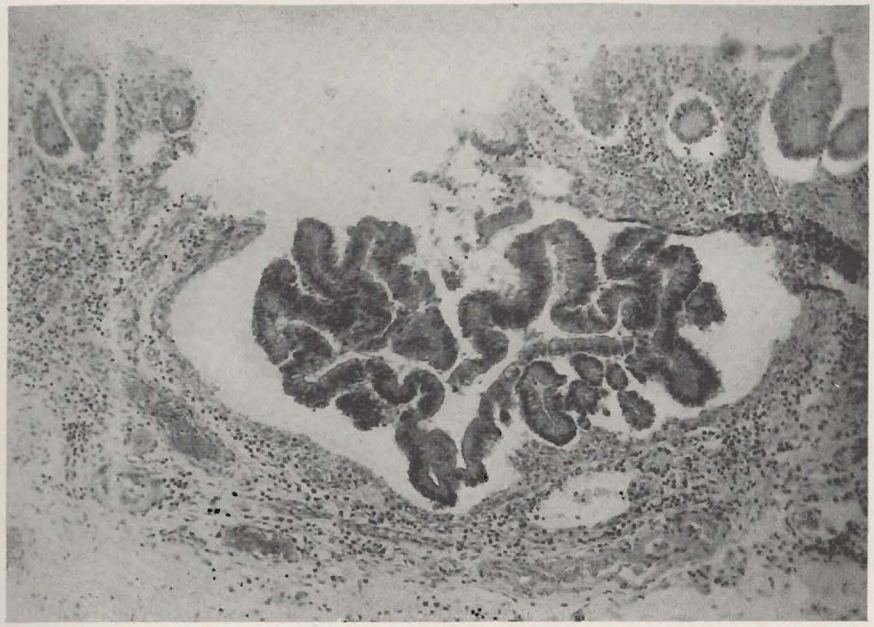

FIGURE 14

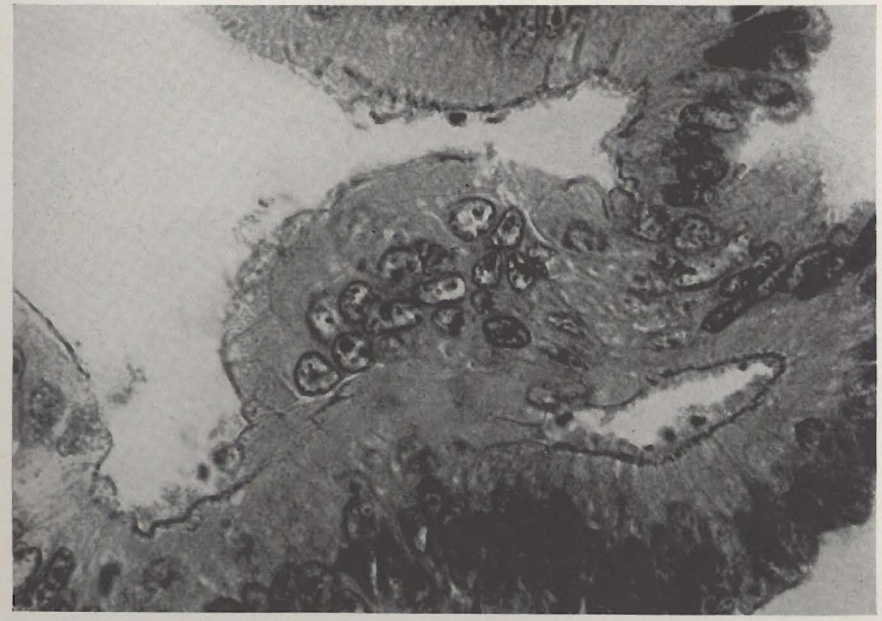

FIGURE 15

FIGURE 16. AUTOPSY 658

Rectum. Non-calcified ova with their embryos, and partly and completely calcified ones in muscularis mucosae and submucosa. 100X

GRABADO 16. AUTOPSIA 658

Recto. Huevecillos sin calcificar con sus embriones, y otros parcial y totalmente calcificados, en la muscular de la mucosa y en la submucosa. 100X

FIGURE 17. AUTOPSY 42

Rectum. Congestion and edema of submucosa. In center, dilated vein containing one or more male worms. Note schistosomal pigment in intestinal canal of uppermost worm segment. 60X

GRABADO 17. AUTOPSIA 42

Recto. Congestión y edema de la submucosa. Al centro, vena dilatada conteniendo uno o más vermes machos. En el segmento superior del verme nótase pigmento bilhárzico en su intestino. 60X

FIGURE 18. AUTOPSY 878

Colon. Intense edema of submucosa, and massive infiltration of same coat by eosinophils. Glandular epithelium has disappeared from autolysis. 120X

GRABADO 18. AUTOPSIA 878

Colon. Intenso edema de la submucosa e infiltración densa con eosinófilos. El epitelio glandular ha desaparecido por autolisis. 120X

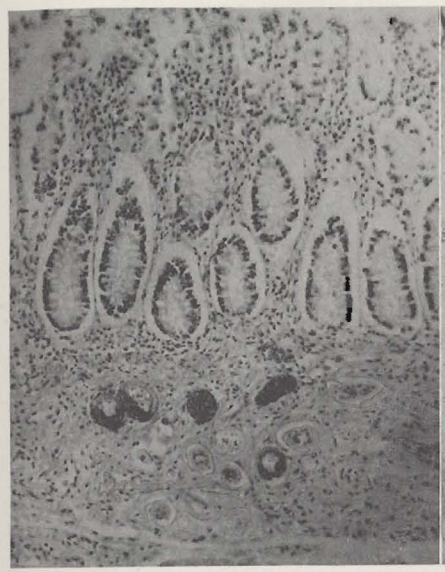

FIGURE 16

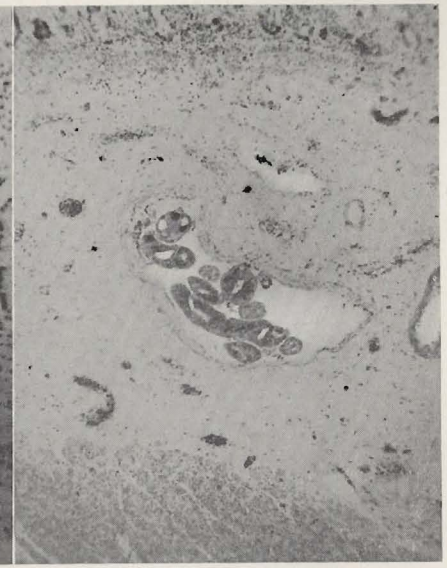

FIGURE 17

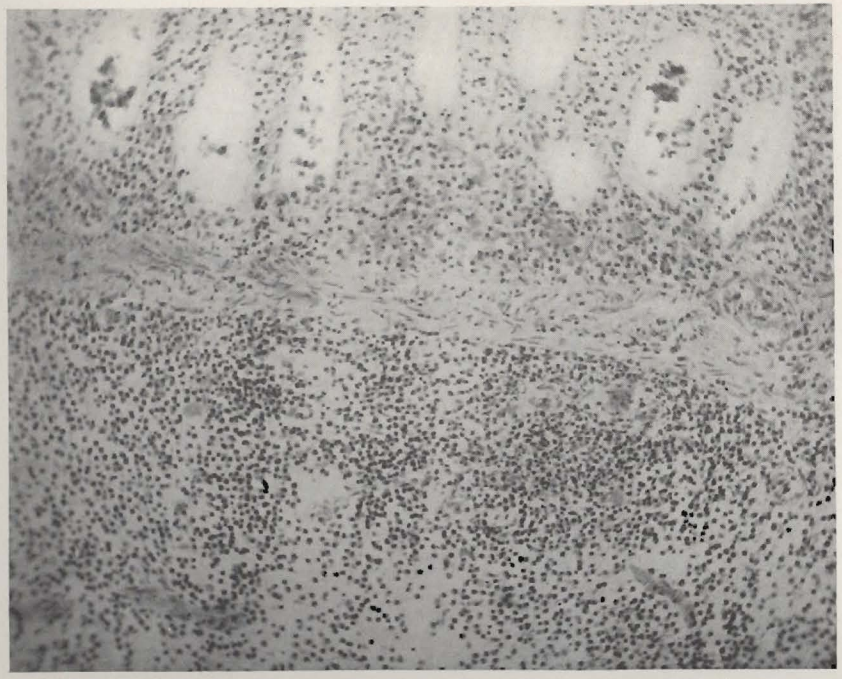

FIGURE 18

FIGURE 19. AUTOPSY 732
Schistosomal pseudotubercles in lung. 40X

GRABADO 19. AUTOPSIA 732
Seudotubérculos bilhárzicos en el pulmón. 40X

FIGURE 20. AUTOPSY 305
Main splenic vein in case of advanced schistosomal cirrhosis. Marked fibrous thickening of wall, especially of intima, with plaque formation. Muscle coat greatly attenuated. Individual aged 29 years. 60X

GRABADO 20. AUTOPSIA 305
La vena esplénica en un caso de cirrosis avanzada. Fibrosis notable de la pared, sobre todo de la intima, con formación de una placa esclerótica. La túnica muscular está muy adelgazada. Individuo de 29 años de edad. 60X

FIGURE 21. AUTOPSY 68
Liver. Very early reaction about ovum with embryo: infiltration with polymorphonuclears and a few eosinophils. 430X

GRABADO 21. AUTOPSIA 68
Hígado. Reacción inicial en torno a un huevecillo con su embrión; infiltrado de polinucleares y algunos eosinófilos. 430X

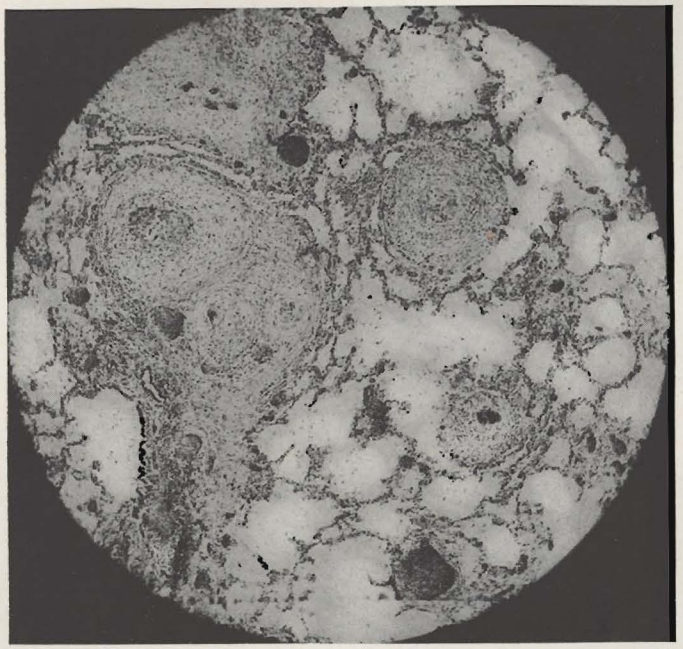

FIGURE 19

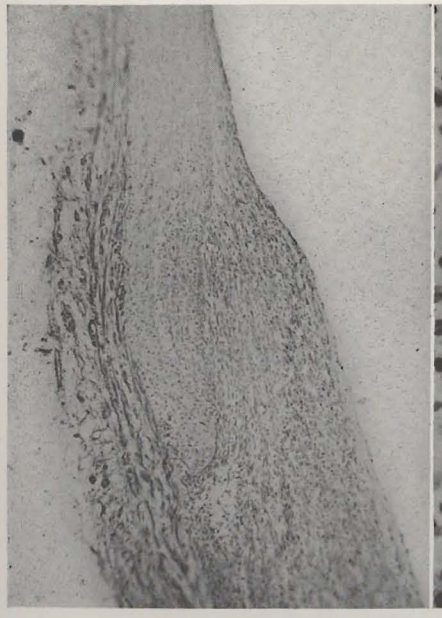

FIGURE 20

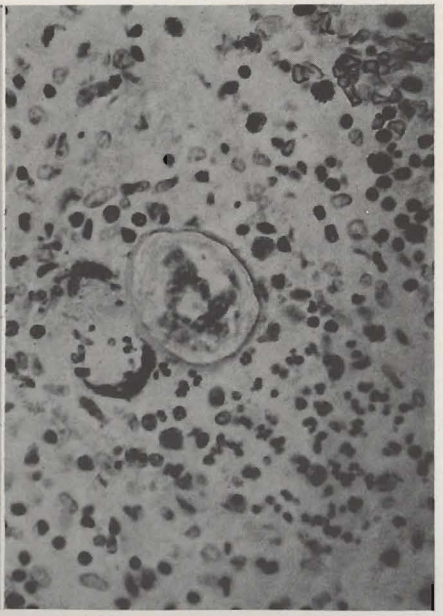

FIGURE 21

FIGURE 22. AUTOPSY 650

Liver. Ovum in center. Beginning proliferation of epithelioid cells. Peripheral infiltration with eosinophils, lymphocytes and monocytes. 240X

GRABADO 22. AUTOPSIA 650

Hígado. Al centro, el huevecillo; en su derredor se ha iniciado la proliferación epitelioidea. Hacia la periferia, eosinófilos, linfocitos y monocitos. 240X

FIGURE 23. AUTOPSY 94

Liver. Fully developed pseudotubercle with ovum in center, broad zone of pale epithelioid cells, and lymphocytes and eosinophils outermost. 100X

GRABADO 23. AUTOPSIA 94

Hígado. Seudotubérculo en máximo desarrollo con huevecillo al centro; ancha zona epitelioidea en su derredor y linfocitos y eosinófilos hacia la periferia. 100X

FIGURE 24. AUTOPSY 422

Liver. Regressing pseudotubercle: partly dissolved egg shells within giant cells, a few epithelioid cells about giant cells, concentrically disposed fibroblasts forming capsule, and lymphocytes, plasma cells, monocytes and a few eosinophils peripherally. 400X

GRABADO 24. AUTOPSIA 422

Hígado. Seudotubérculo en regresión. Dentro de las células gigantes, cubiertas ovulares en disolución. Pocas células epitelioideas por fuera de las gigantes. Láminas concéntricas de fibroblastos formando cápsula en torno al seudotubérculo, y por fuera de éstas, linfocitos, células plasmáticas, monocitos y pocos eosinófilos. 400X

FIGURE 25. AUTOPSY 453

Liver. Regressing pseudotubercle: egg shell in center partly surrounded by giant cell; epithelioid cell zone becomes narrower as capsule broadens and condenses. 100X

GRABADO 25. AUTOPSIA 453

Hígado. Seudotubérculo en regresión. A medida que la cápsula se ensancha y condensa, se achica la zona epitelioidea que circunda la cubierta ovular. 100X

FIGURE 26. AUTOPSY 282

Liver. Regressing pseudotubercle. Shell still visible in center. Epithelioid cell zone almost totally replaced by the broadening capsule. 100X

GRABADO 26. AUTOPSIA 282

Hígado. Seudotubérculo en regresión. Al centro, la cubierta ovular. La zona epitelioidea ha sido casi totalmente reemplazada por la cápsula. 100X

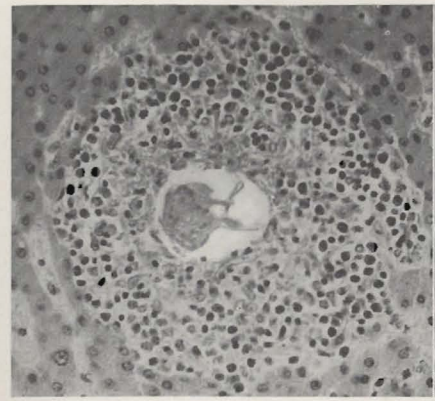

FIGURE 22

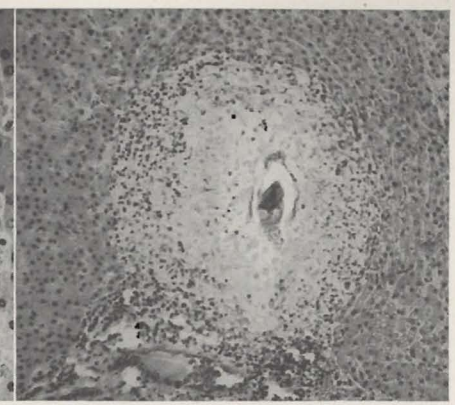

FIGURE 23

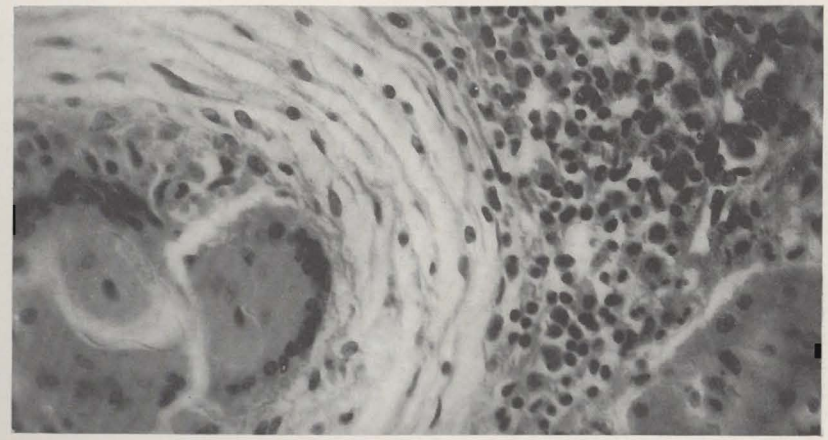

FIGURE 24

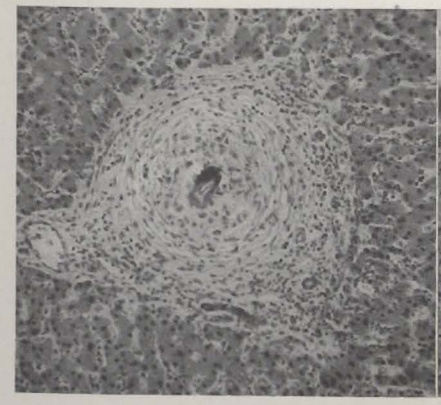

FIGURE 25

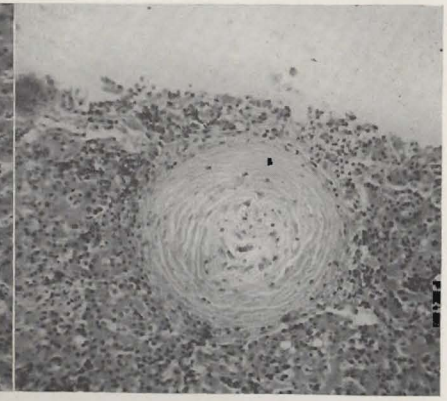

FIGURE 26

FIGURE 27. AUTOPSY 267

Liver. Healed pseudotuberlce not yet totally organized. Matrix still finely fibrillar. 100X

GRABADO 27. AUTOPSIA 267

Hígado. Seudotubérculo en proceso de organización, pero no totalmente cicatrizado. El estroma es aún fibrilar. 100X

FIGURE 28. AUTOPSY 707

Liver. Fibrous nodule marking final stage in healing of a pseudotubercle. Matrix dense and collagenous. 100X

GRABADO 28. AUTOPSIA 707

Hígado. Nódulo fibroso que marca la etapa final en la cicatrización del seudotubérculo. El estroma es denso y colágeno. 100X

FIGURE 29. AUTOPSY 389

Liver. Large giant cell containing partly dissolved shell fragments. Peripheral infiltration with lymphocytes and monocytes. Note that the reaction is taking place in a sinusoid. 240X

GRABADO 29. AUTOPSIA 389

Hígado. Célula gigante conteniendo fragmentos de cubierta ovular en disolución. Hacia la periferia, infiltrado de linfocitos y monocitos. Nótese que la reacción está teniendo lugar en un sinusoide. 240X

FIGURE 30. AUTOPSY 121

Mesenteric lymph gland. Egg shell surrounded by eosinophilic fringe. Embryo appears to have disappeared through postmortem autolysis. 100X

GRABADO 30. AUTOPSIA 121

Ganglio linfático mesentérico. Cubierta ovular rodeada de precipitado eosinófilo. El embrión parece haber desaparecido por efecto de la autolisis postmortem. 100X

FIGURE 31. AUTOPSY 68

Liver. Ovum with degenerating embryo and eosinophilic fringe. 400X

GRABADO 31. AUTOPSIA 68

Hígado. Huevecillo con embrión degenerado y franja eosinófila periovular. 400X

FIGURE 32. AUTOPSY 732

Liver. Zone of necrosis about ovum with embryo. Note dense fibrosis and cell infiltration of portal space. 100X

GRABADO 32. AUTOPSIA 732

Hígado. Zona de necrosis en torno a un huevecillo con su embrión. Nótese la fibrosis densa y el infiltrado leucocitario del espacio portal. 100X

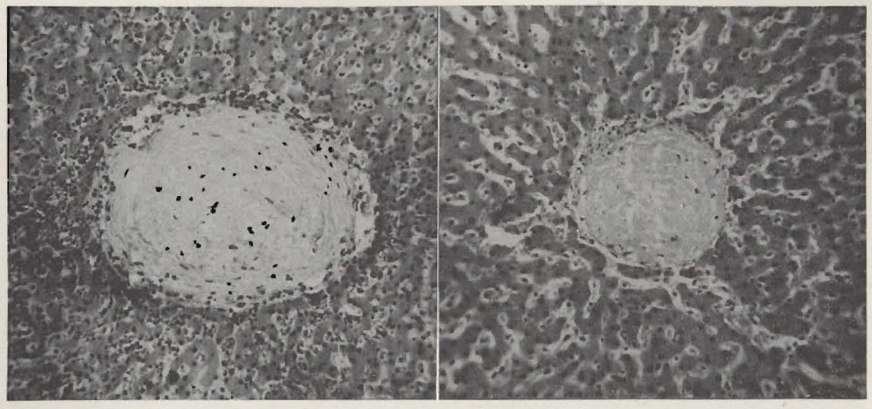

FIGURE 27

FIGURE 28

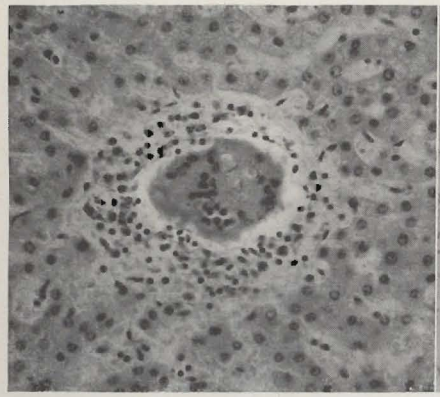

FIGURE 29

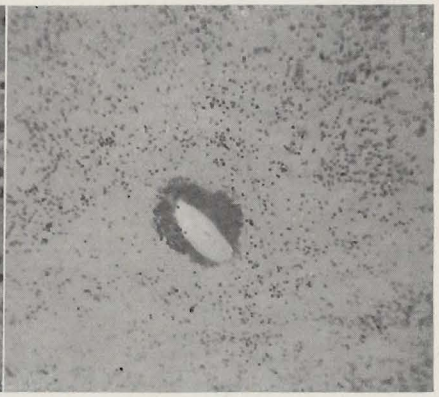

FIGURE 30

FIGURE 31

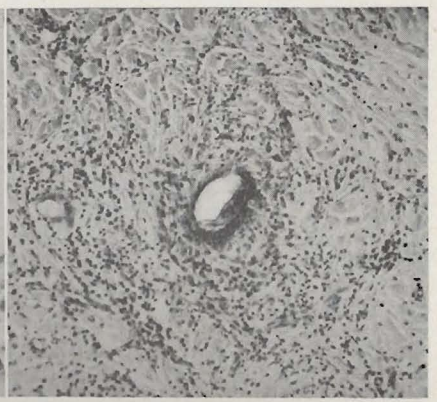

FIGURE 32

FIGURE 33. AUTOPSY 468

Testis. Numerous empty shells, some calcified, in slightly thickened interstitial tissues. 100X

GRABADO 33. AUTOPSIA 468

Testículo. Numerosas cubiertas ovulares, algunas calcificadas, en los tejidos intersticiales ligeramente fibrosados. 100X

FIGURE 34. AUTOPSY 405

Urinary bladder. Two empty egg shells in subepithelial layer. 150X

GRABADO 34. AUTOPSIA 405

Vejiga urinaria. Dos cubiertas ovulares en el tejido subepitelial. 150X

FIGURE 35. AUTOPSY 288

Colloid adenocarcinoma of cecum in 16-year old boy with heavy schistosomal infection. 100X

GRABADO 35. AUTOPSIA 288

Adenocarcinoma coloide del ciego en un niño de 16 años con intensa bilharziosis. 100X

FIGURE 36. AUTOPSY 288

Retroperitoneal tissues. Fibrosis, feeble pseudotubercle formation about 2 ova, and dense lymphocytic infiltration in colloid adenocarcinoma of cecum. 100X

GRABADO 36. AUTOPSIA 288

Tejido retroperitoneal. Fibrosis, seudotubérculos rudimentarios en torno a dos huevecillos e infiltración linfocitaria densa en el mismo adenocarcinoma coloide. 100X

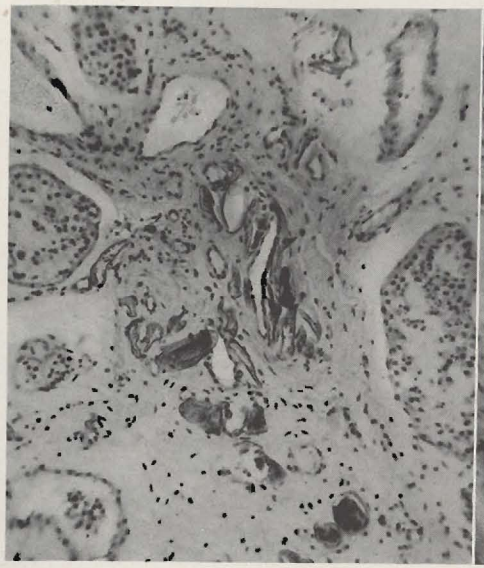

FIGURE 33

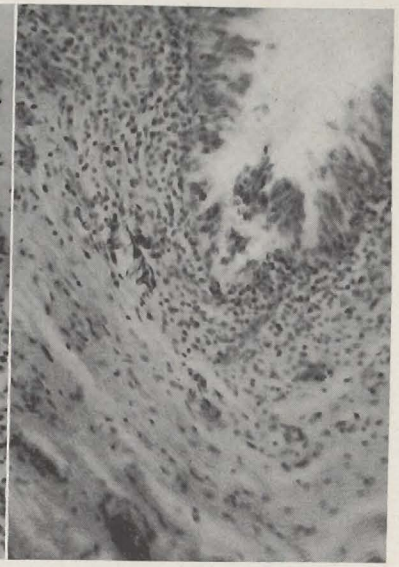

FIGURE 34

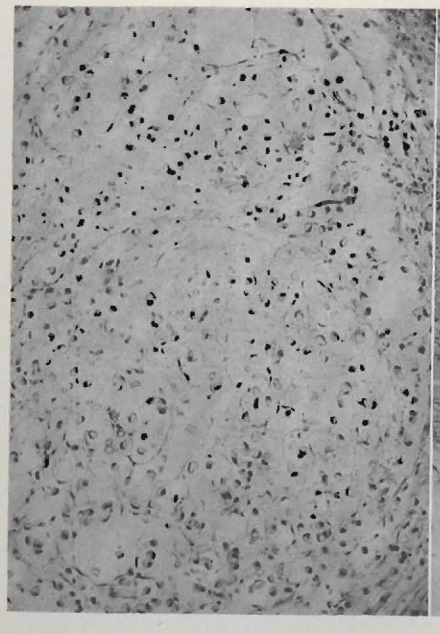

FIGURE 35

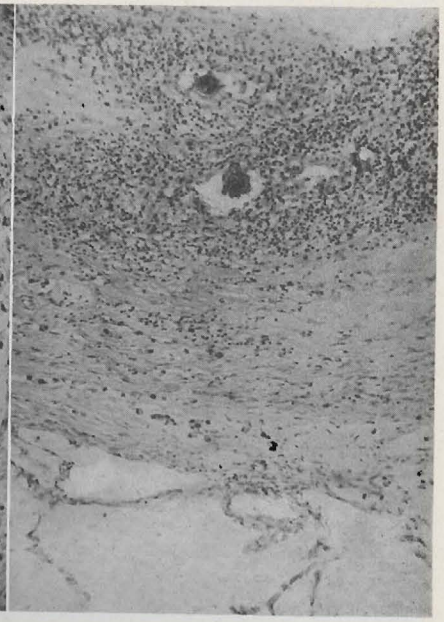

FIGURE 36