THE PUERTO RICO JOURNAL OF PUBLIC HEALTH AND TROPICAL MEDICINE

VOL. 13 SEPTEMBER, 1937 NO. 1

STUDIES ON SCHISTOSOMIASIS MANSONI IN PUERTO RICO

IV. THE PATHOLOGICAL ANATOMY OF EXPERIMENTAL SCHISTOSOMIASIS MANSONI IN THE RABBIT AND ALBINO RAT *

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A perusal of the available literature on experimental schistosomiasis (mansoni) shows the existence of gaps in our knowledge of tissue reactions, notably of the changes in various viscera during the period of migration of the young parasites prior to their localization in the mesenteric and portal veins.

It is therefore our aim to present a detailed chronological record of tissue changes resulting from a single experimental inoculation with *S. mansoni,* and extending from the moment of infestation to the sixth month in the rabbit and the ninth month in the rat. We shall at the same time attempt to correlate the pathologic changes with the route followed by the parasite in its wanderings through the host and with its development within the latter. Our work will be an extension of Faust, Jones and Hoffman's [1] recently published investigations on the mammalian phase of the schistosome parasite.

In the course of his classical observations conducted in Egypt from 1915 to 1918 Leiper [2] found a number of mammals to be highly susceptible to schistosomiasis and was able to infest experimentally white rats, Egyptian desert rats, black mice, guinea-pigs, and mangaby, sooty and Indian monkeys, but failed with one calf and one lamb. On the other hand, fowls (geese, ducks, chickens, crows, wagtails) proved refractory. Infestation was accomplished through the skin of the hollow of the groins, through the mucous membrane of the upper alimentary tract and, in at least one instance, by injection of cercariae into the subcutaneous

* Received for publication May 26, 1937.

tissues. The mode of invasion was demonstrated in a young mouse killed after immersion for half an hour in water swarming with cercariae, penetration of the larvae being found to take place "through the unbroken skin and not through the pores or hair-follicles". The first animals to become infested—white rats and black mice—"died from occlusion of the portal system before the Bilharzia worms had reached sexual maturity". These animals were hyper-infested, apparently because of repeated inoculations. Rats surviving until the third month after exposure showed the liver to be "enlarged and deeply pigmented with black amorphous granules. The surface was speckled with minute white spots" that contained accumulations of lateral-spined eggs.

In 1919 Iturbe [3] infested white rats, house rats and guinea-pigs and observed that cercariae penetrated the skin through hair follicles, and produced a leukocytic infiltration of the skin that was visible for several days as a minute vesicle.

In 1919 Lutz [4] studied the pathologic alterations in white rats, guinea-pigs, rabbits and a small pig, all inoculated by the cutaneous route. Anatomical changes were said to begin three weeks after exposure with congestion of the mesenteric veins, while round-celled infiltration of the interstitial tissues of the liver was considered to mark the onset of cirrhosis. The author noted the similarity between the cellular reaction about ova in the intestinal mucosa and that of a tubercle.

In 1920 Manson-Bahr and Fairley [5] reported the development of skin rashes in monkeys the day after cutaneous inoculation, but failed to find young parasites in sections of the lungs of one animal sacrificed three days after exposure. This same year Fairley [6] made a thorough study of experimentally produced lesions in monkeys that died within thirty-five days and from six to fourteen weeks after inoculation, which was by way of the upper alimentary tract, through the skin and by subcutaneous injection of cercariae. In animals dying within thirty-five days, *i. e.*, before beginning of deposition of ova in the tissues, the changes were mainly those of an acute toxemia with congestion and cloudy swelling of parenchymatous organs. From the sixth to the fourteenth week the alterations were for the most part "dependent on the deposition of ova in the tissues as well as upon the action

of the circulating toxin'', and the schistosome pseudotubercle was described as the typical lesion. Anatomic changes were most marked in the liver, where beginning with round-celled infiltration they culminated in cirrhosis; in the spleen, where congestion led to enormous dilatation of the sinuses and atrophy of the pulp; and in the small and large intestine, in which subserous whitish nodules and varying grades of inflammation of the mucosa and submucosa were the main features. Pseudotubercles occurred in the lungs in 10 per cent of the animals, and there were, in some instances, patches of bronchopneumonia surrounding dead worms; the cellular exudate in these patches was largely eosinophilic.

Lambert and Burke[7] observed in heavily parasitized animals (including rabbits and monkeys), dying three to eight weeks after exposure, that phlebitis or arteritis was found only about dead worms. In a separate communication Lambert[8] summarized his findings in twelve rats, three rabbits, one guinea-pig and two monkeys. Congestion only was observed in the skin, but the lapse of time between exposure and removal of the skin was not stated. Monkeys dying within one month of exposure presented parenchymatous changes in the myocardium and kidneys, and in two instances a peculiar acute inflammatory reaction was in evidence in the liver, kidney and intestine. There is a possibility that this was due to secondary bacterial infection, although blood cultures were negative. Early death in heavily parasitized animals was thought to depend on mechanical blocking of vessels and toxemia from products of disintegration of dead worms.

Brumpt[9] noted the occurrence of ova of *S. mansoni* in the urinary bladder of one mouse, out of seventy-two in which this organ was examined histologically. Fairley (*l. c.*) had previously observed this in one monkey.

In 1931 Brumpt and Chevallier[10] presented a detailed study of the spleen and liver in experimental schistosomiasis of mice. Splenomegaly was found in some animals. The histologic alterations of the spleen were deemed to have a double origin and nature: (1) changes secondary to the presence of ova, with proliferation of reticulum cells and formation of pseudotubercles, and (2) those representing a toxic effect upon the organ, with proliferation of reticulum

cells, increase in phagocytes, hemosiderosis, and the presence of plasma cells and polymorphonuclear leukocytes as the main features. In the liver, fibrosis occurred only about ova and not diffusely as in true cirrhosis, and the histiocytic reaction about eggs was tentatively ascribed to proliferation of Kupffer cells. The authors concluded that the spleen and liver reacted independently of each other to toxins of the worms or to the presence of the parasites or their ova.

EXPERIMENTAL

I. The Rabbit

Material and Methods: Twenty-five adult rabbits were utilized. Their weight at the time of inoculation varied from 1,470 gm. the lightest, to 2,650 gm. the heaviest.

Snails of the species *Australorbis glabratus* were infested in the laboratory with miracidia of *Schistosoma mansoni* obtained from the feces of human cases of the disease. Four or five weeks later, when cercariae began to be discharged in numbers, numerous snails would be placed in a beaker containing 800 c.c. of tap water, so as to assure the presence of both male and female producing cercariae. This was done at eight in the morning, the beaker with snails being then exposed to direct sunlight until one or two in the afternoon. At this time the rabbit to be infested was put in a cylindrical jar of the kind used for storage of pathological specimens, with a capacity of 6 liters and containing 1,600 c.c. of tap water. The water with cercariae was then carefully poured into the jar, making a total volume of liquid of 2,400 c.c.; this was sufficient to keep the inferior extremities and lower abdomen of the animal submerged. The animal was allowed to remain there for one hour, after which it was removed from the jar and allowed to dry. Each rabbit was exposed only once, so as to avoid massive infestation. The hair of the abdomen of all animals was closely clipped or shaven one or two days prior to inoculation.

Four of the rabbits were infested by dropping a concentrated suspension of cercariae on the skin of the lower abdomen and hollow of the groins, keeping these areas moist with the liquid for one hour.

A longitudinal strip of skin measuring approximately 2.5 × 1 cm. was removed under ether anesthesia from the lower abdomen of 14 animals, at intervals of one hour, counting from the beginning of exposure. These were all sectioned serially and every fifth section mounted and stained.

The experimental animals were sacrificed by ether or chloroform anesthesia at intervals of 2, 4, 13, 25, 37, 49 and 61 hours, and 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 30, 40, 50, 60, 75, 87, 101, 120, 150 and 183 days after exposure to cercariae.

A complete autopsy was performed immediately after death, including the brain and marrow of long bones in most instances. The lungs were removed *en masse* with the neck organs and heart, and fixed by injection of Zenker fluid through the trachea, avoiding over-distension. The spleen was weighed and measured. The liver was weighed and cut into slices not more than 3 mm.

thick, prior to immersion in the fixative. The stomach and intestines down to the rectum were separated from their mesenteric and ligamentary attachments; portions 2 to 4 cm. long of different levels of the intestine were tied off and injected with Zenker's fluid before placing in the fixative, and the remainder was then opened for inspection of the mucosal surface.

The tissues were fixed in Zenker's fluid, embedded in paraffin, cut at 5 microns and stained with hematoxylin and eosin. For some of the animals, sections of lung, spleen, liver, intestine, lymph nodes, skin and bone-marrow were also stained by divers methods such as hematoxylin-eosin-azure, Weigert's elastica-saffranin, Masson's trichrome, Foot-Bielschowsky's, Gram's and Giemsa's. Serial sections were cut of blocks of heart, lung, spleen, liver, kidney, stomach, intestine, lymph nodes and brain of some rabbits.

Great restlessness ensued almost immediately after confinement of the animal in the infesting jar, and continued for 4 to 5 hours after removal therefrom. This was accompanied by other evidences of irritation of the exposed parts, such as rubbing of the front legs against the face.

The weight remained stationary or diminished in a few rabbits that at autopsy proved to have been heavily infested, but all others gained more or less as normally. Excepting two animals that became obviously emaciated, the behavior and appearance was not remarkable throughout the experimental period.

A pinkish, punctate and macular rash was noted in the skin of the abdomen of a few rabbits on the day following exposure, and persisted for 2 and 3 days, respectively, in two animals in which its duration was closely followed. This was accompanied in a few instances by occasional, very minute, pale yellow or gray granules that projected slightly, measured a fraction of a millimeter in diameter and were not unlike the miliary sudaminal lesions of man.

At autopsy, petechial hemorrhages were never observed in the subcutaneous tissues, musculature (including diaphragm), epicardium and parietal peritoneum and pleura, neither did any occur in the kidneys. Ascites was likewise not encountered.

Skin:

In addition to the strips of skin removed under anesthesia at intervals of one hour after exposure, skin was also obtained at autopsy from animals sacrificed 25, 37, 49 and 61 hours, and 3, 4, 5, 8 and 10 days after inoculation.

The cercariae penetrated across the epidermis in the areas between hair shafts. None could be demonstrated in

the act of entering down hair shafts or gland ducts through the pores, but in several instances the parasite had bored obliquely into the corium through the opening of hair follicles (Fig. 1); at times they were encountered definitely within follicles some distance below the plane of the epidermis (Fig. 2). Unless it were supposed that the parasites may wander into these structures from the corium, which does not seem very probable, it must be concluded that they occasionally enter along hair shafts. A very small space or tunnel is at times left in the epidermis in the wake of the penetrating parasite (Fig. 3). About this space, the epidermal cells are compressed and have shrunken, pyknotic nuclei. The most, however, that could usually be discovered in the epidermis opposite cercariae that had just passed through it was a slight disarrangement of the cells with at times swelling of their nuclei. Two and three cercariae were encountered a few times in small clefts between the stratum corneum and the rete mucosum and, in some animals, dense groups of eosinophils and pseudoeosinophils had congregated in these spaces, that apparently represented the minute vesicles previously described as forming part of the skin rash. Passage through the epidermis was only infrequently in a direction perpendicular to the skin surface; the parasite usually wanders for a little distance more or less horizontally along the stratum mucosum before penetrating the corium (Fig 3).

In the derma they were usually found in two situations: (1) immediately beneath the epidermis and (2) next to hair follicles (Fig. 5). In both these situations they usually occurred in well defined spaces limited by flat cells resembling endothelium, and probably representing lymphatics of the papillary plexus. After two hours a few parasites began to appear in the deeper portions of the papillary layer and in the more superficial levels of the reticular zone, where they appeared in lymphatics (Fig. 4) or else made spaces for themselves by separation of areolar and collagenous fibers; they were not encountered deeper than this level.

The number of cercariae in situations other than immediately beneath the epidermis and about follicles was always very limited throughout the period of fourteen hours covered by our biopsies. Although more than 3,500 sections of skin

were examined, no parasites were observed in the act of entering blood vessels, and only twice were they seen within capillaries that probably represented blood channels.

A few well preserved parasites were still present in the epidermis and corium 37 hours after inoculation of the animal. Relatively few cercariae appear to be lost on their way through the skin, since it was rather unusual to find any in process of degeneration. In a few instances necrotic cercariae were the center of dense infiltration by pseudoeosinophils. (Fig. 6).

The study of inflammatory reactions to the invader was more or less vitiated in some animals by shaving of the skin prior to inoculation. This procedure, which seems to have been rather strenuously carried out, resulted in the production of multiple abrasions, with necrosis of the superficial layers of the epidermis and infiltration of the affected portions by leukocytes. In control animals, similarly shaven 37 to 49 hours before removal of abdominal skin, the papillary layer of the derma was edematous and diffusely though not densely infiltrated with lymphocytes, monocytes, rare plasma cells and eosinophils and in places by groups of pseudoeosinophils. It was therefore necessary to base our observations on animals whose hair had been clipped and not shaven, and on others which though previously shaven presented no abrasions nor areas of epidermal necrosis.

The skin of the rabbits responded to the parasitic invasion with congestion, edema and leukocytic infiltration. These alterations were limited to the papillary layer of the derma and to the more superficial portions of the reticular zone. Edema, which was rather slight but diffuse, was first evident one hour after beginning of exposure, but by the 10th hour occurred in some areas only; it could still be noted 49 hours after infestation. The cellular infiltration was already in evidence one hour after exposure and consisted mainly of pseudoeosinophils and monocytes until the tenth hour, after which the former began to disappear, while monocytes and lymphocytes as well as a few eosinophils persisted in places. Occasionally, pseudoeosinophils and a few eosinophils would be grouped about penetrating parasites, but in general the infiltration was diffuse until the 10th hour, when it reached its height and then began to recede in some portions though

still lingering in others. Congestion was never marked, but in some animals numerous pseudoeosinophils and occasional eosinophils would fill the capillaries and be grouped about them. Areas of hemorrhage were at no time seen, and there never was actual destruction of tissues in the derma and, therefore, no scarring. Sections in which the number of parasites was scanty showed very little inflammatory reaction. Small groups of lymphoid cells and monocytes were still found 4 days after inoculation, but parasites did not occur after 37 hours.

Axillary, inguinal and popliteal lymph glands:

A single petechial hemorrhage was observed in a popliteal gland 25 hours after infestation, and a slightly larger area of hemorrhage at the 49th hour, while by the 3rd day both popliteal nodes were diffusely congested and hemorrhagic in their central portions. On the 5th day the axillary and popliteal nodes were distinctly enlarged and presented multiple petechial hemorrhages beneath the capsule and throughout their substance. On the 6th day there were a few fading petechiae, and by the 7th day all peripheral nodes were grossly unaltered, save for enlargement, which gradually diminished until the 15th day, by which time they had regained their normal size.

Young parasites were first found 25 hours after inoculation in all nodes, and persisted until the 4th day. They occurred in peripheral and medullary sinuses (Figs. 7 & 8), as well as in the lymphoid tissues (Fig. 9) at all distances from the marginal sinus. Not more than 7 parasites were ever seen in a single section, this being on the 3rd day and presumably marking the height of invasion of peripheral nodes. The parasites seemed to excite no focal cell reaction, all changes to be described, excepting the hemorrhages, being diffuse. Only one degenerating schistosomule was encountered, which may mean that the great majority of these parasites are able to leave the nodes.

Microscopic alterations were evident first in the popliteal nodes of the 13-hour rabbit, with recent small hemorrhages into the sinuses and lymph cords, with increase in the number of eosinophils throughout the gland and of macrophages in the sinuses, and with diffuse infiltration of the lymphoid tissues, particularly the sinuses, by large numbers of pseudoeosinophils—truly an acute lymphadenitis (Fig. 10). This change was seen only in the popliteal and inguinal lymph glands from the 13th to the 49th hour, inclusive. By the 4th day, most of the extravasated erythrocytes had been phago-

cytosed by macrophages, and on the 5th day after inoculation all evidence of recent hemorrhage had disappeared. The reticulum cells of the lymphoid tissues responded with slight enlargement, first distinctly visible in the 37-hour rabbit, but this, as well as the increase in macrophages and monocytes within the sinuses, and of eosinophils in the tissues, was last evident in the 15-day animal.

Heart:

The heart remained grossly normal in all animals. A single transverse section including the wall of both ventricles was taken through the middle for microscopic study. One or two minute foci of infiltration with large mononuclear cells and of beginning proliferation of fibroblasts were encountered in the 37-, 61-, 72-hour and 8-day rabbits; a few eosinophils were also present in the lesion of the last-mentioned animal. We cannot feel certain that this change was due to the schistosomal infestation, since no parasites were found in the myocardium in relation to the lesions or elsewhere. In the cavity of the right ventricle, a single schistosomule was present 7 and 10 days after inoculation. In the 75- and 101-day rabbits the right ventricle contained fully mature male and female living worms, but the endocardium appeared unaltered. It was these two animals that contained (see description of lungs) numerous living and dead worms in dilated blood vessels within the lungs. The worms must have reached the right ventricle from the hemorrhoidal vein plexus via the postcaval vein, or from the liver; a third possibility is that they may have wandered against the blood current from the lungs by way of the pulmonary arteries.

Lungs:

Petechial hemorrhages comprised the first evidence of the invasion of these organs by the young parasites. In the following description, the number of petechiae refers to those visible through the pleura. A single minute hemorrhage first appeared in the 25-hour rabbit in one lung. None were visible 37 and 49 hours after infestation, but by the 3rd day two or three could be observed in each lung. On the 5th day they were very numerous and bright red, measured from a fraction of a millimeter to 1.5 mm. and were at times surrounded by a delicate brownish halo; they were perhap

most numerous in the mesial and diaphragmatic surfaces, and least so in the apices. These hemorrhages were found in greatest number in the 6-day rabbit. By the 10th day a definite diminution in their numbers was noted, especially of the larger ones measuring from 1 to 1.5 mm. in diameter, which had now assumed a brownish color in contradistinction to their previous bright red hue. By the 15th day not more than seven brown petechiae were observed in each lung, and they had all disappeared by the 20th. Ten days later, however, well past the period of migration of the parasites from the skin and nodes, they again began to appear. Thus the 30-day animal presented one in one lung; the 40-day rabbit presented two; the 50-day rabbit, about 10 in each lung; the 75-day rabbit, approximately 15 in each lung, and all other animals always showed from a few to 10 or 15 petechiae or larger foci of hemorrhage that measured up to 4 or 5 mm. in main diameter.

Beginning at 37 hours, pinkish or brownish patches that at times assumed a maximum diameter of 0.5 cm. appeared in the lungs of most of the animals, immediately beneath the pleura and in their substance. These patches showed a distinct predilection for the lower lobes, though at times occurring in the upper ones. In some of them, and in the center of occasional small hemorrhages, minute grey or pale yellow, glistening granules like tubercles would often be observed after the 75th day.

Additional interesting alterations were evident in the animals killed 75, 101 and 120 days after inoculation. These consisted of the development in the pulmonary parenchyma of one or two more or less spherical or quadrangular nodules, firm to palpation and measuring up to 0.5 cm. across, and of more numerous dark bluish elevated areas 0.3 to 0.4 cm. in diameter, usually situated along the margins of all lobes, and always surrounded by a rim of congestion. The large firm nodules were usually found in the lower lobe, near the anterior margin and in close proximity to the diaphragmatic border; the overlying pleura was roughened by the presence of fibrous adhesions. On section, these larger nodules exhibited one or more cyst-like cavities varying from 1 or 2 mm. in diameter to 5 mm. These cavities were smooth-walled, sharply outlined, contained numerous adult schistosome

worms and blood, and represented aneurysmal dilatations of the pulmonary arteries. They were surrounded by pale grey or yellowish zones of consolidation, discretely mottled with small areas of hemorrhage. The smaller purple nodules at the margins of some of the above-mentioned animals proved on section to be small infarcts, and there were within them dilated vessels that contained quite numerous adult schistosome worms, somewhat shorter, however, than those in the mesenteric veins of the same animals. A similar dilatation, though to a lesser degree, had also taken place here and there in all portions of the lung from anterior margin to hilus. In these three rabbits, small foci of consolidation were to be seen in the cut surface of the lungs at various points; usually they were pale grey or yellowish but at times would be tinged with brown, presumably the result of previous hemorrhage.

Microscopically, schistosomules were not encountered until the 3rd day, by which time 5 to 6 would be found in each transverse section of the organ, but evidence of their presence there could be observed as early as the 37th hour in the form of rare, very minute foci of thickening of the alveolar walls due to localized infiltration by eosinophils, lymphocytes and monocytes in various proportions, and in part also to proliferation of endothelial cells of the alveolar capillaries at the affected points (Fig. 11).

From the 3rd day, when young parasites were first found in sections, the tissue alterations consisted of localized areas of broadening of the alveolar walls and of minute foci of hemorrhage into the alveoli. Although the parasites always caused great distension of the alveolar capillaries through which they traveled, they were as often as not surrounded by normal tissues (Fig. 12). That they were not always found in the foci of cell reaction may mean that they had already passed on or else that the lesion was sectioned near one of its margins; the former is more probably true since the diameter of the lesions was remarkably constant. The distribution of parasites and lesions was quite even throughout all portions of the lungs. One section included a schistosomule in a capillary immediately beneath the pleura, which was slightly thickened, and the parasite was surrounded by the characteristic cell reaction (Fig. 13). Only rarely did

the parasites project into alveoli, and never were they found lying wholly in the air sacs. In the few instances in which they projected into the alveoli, neither exudation of leukocytes nor hemorrhage were noted. Small groups of phagocytes, however, had occasionally collected within alveoli, at times in the neighborhood of the foci of broadening of the wall of air sacs.

In some lungs, after the 5th day, there also were small star-shaped areas of localized congestion of the alveolar capillaries, either without cell reaction of any kind, or with infiltration of the alveolar septa by round cells and eosinophils, and with the capillary distension gradually lessening away from a central point (Fig. 14). After the 6th day, small syncytial masses apparently derived from phagocytes developed in rare alveoli, but no parasites could be found in relation to them. That these syncytia form as a result of the parasitic invasion seems most probable, as the surrounding alveolar walls usually exhibited the foci of congestion and cell infiltration that appear to be characteristic evidence of the presence, or recent passage, of schistosomules. The number of parasites and lesions seemed highest in the 5- and 6-day rabbits, after which both diminished. Dense groups of eosinophils occurred about some of the smaller blood vessels beginning on the 8th day. From the 15th to the 30th day the above described alterations of the alveolar septa were rarely found, and when present the infiltrating elements were mostly small round cells.

At 30 days there was distinct edema about some of the smaller arteries, accompanied by infiltration with numerous eosinophils and lesser numbers of histiocytes and plasma cells. Prominent foci of septal thickening due to the accumulation of eosinophils and round cells again began to appear, and the adjacent alveoli would at times contain cells with pale cytoplasm and vesicular nuclei; these cells occurred isolated and in the form of syncytia. Two young worms with black pigment in their intestines lay within small arteries and had excited no cell reaction whatsoever in their neighborhood.

In the 40-day rabbit the septal thickenings contained still more eosinophils than previously, and the adjoining air sacs would at times be occupied by a mosaic of sharply outlined epithelioid cells that had engulfed dark brown schistosomal

pigment. The pulmonary parenchyma was diffusely congested; there was a little edema of the air sacs, and fairly numerous isolated phagocytic cells were present within many of the latter.

Stunted, poorly developed worms were again found in the 50-day rabbit. One of the parasites had strayed into the lumen of air sacs, where it was undergoing disintegration and had attracted large numbers of eosinophils and epithelioid cells (Fig. 15). A pulmonary blood vessel, apparently a vein, showed obstruction of most of its lumen by a solid mass of epithelioid cells that had grown from the intima (Fig. 16). About this blood vessel and in neighboring alveolar septa were numerous eosinophils and lymphocytes.

Ova were first encountered on the 75th day. They occurred in the alveolar walls and in the neighborhood or within the lumen of small blood vessels. The contained embryo probably dies very soon after deposition of the ovum, for it was very rare to find more than the empty egg shell. In most instances, very little reaction was noted on the part of the tissues, there being a few eosinophils (Fig. 17), or a foreign-body giant cell and eosinophils; no fully developed pseudotubercles had formed.

The large firm nodules described grossly first appeared in the 75-day animal. These nodules presented greatly dilated blood vessels in their central portions, and these were packed with male and female worms, not infrequently in copula. The worms were pale-staining and obviously dead, but not disintegrated. The walls of the blood vessels were greatly attenuated (Fig. 18) and over extensive portions had been replaced by zones of epithelioid cells or else by the fibrous tissue that had developed in the surrouding pulmonary parenchyma. Special stains demonstrated the fragmentation and disappearance of elastic fibers from these portions of the circumference of the vessels (Fig. 19). Thrombi had occasionally formed where the arterial wall was deficient. The remainder of the nodule was composed of the surrounding pulmonary tissues, which had been replaced in places by young, somewhat edematous fibrous connective overrun by eosinophils, and in other areas showed the alveoli to be packed with pseudoeosinophils and eosinophils (Fig. 18).

Widespread necrosis of the alveolar walls and exudate had taken place over extensive portions, probably from interruption of the blood supply, so that the nodules were at the same time inflammatory and of the character of infarcts. Where necrosis of the wall of blood vessels was most advanced, the adjacent worms were undergoing bland disintegration and calcium was beginning to be deposited in the wall and in the parasites. In the neighborhood of the larger blood vessels were numerous rounded or odd-shaped calcified structures, apparently ova. The pleura over the nodules was slightly thickened and in some portions covered by a delicate layer of fibrin. In some areas the necrosis and cell infiltration had not extended to the surface of the organ, from which it was separated by a zone of dilated air sacs lined by cubical epithelium (Fig. 18). This change was also noted in the lining of alveoli along the periphery of the nodules, and the bronchioles at times showed squamous metaplasia. The mediastinal tissues adjacent to one of the nodules were massively infiltrated by eosinophils. In the more fibrotic portions of the nodules the infiltrating cells were eosinophils, large mononuclears and round cells.

In the remainder of the lung, away from the above-described areas, many of the larger arterial branches were dilated and contained living worms. At times there was attenuation of the muscle coat and fragmentation of the elastic membranes, while in other areas hypertrophy had occurred (Fig. 20). The intima of the larger arteries and the adventitia and peribronchial tissues were rather densely overrun by eosinophils. The most arresting alteration, however, was the partial or complete obliteration of the lumen of medium-sized and small arteries and veins by masses of epithelioid and large foreign-body giant cells, that were growing inwards from the intima in polypoid fashion (Fig. 21). In this manner the dead worms were isolated from the blood current. Where the worms were alive and well preserved, only eosinophilic infiltration, with or without formation of polyps in the intima (Fig. 22), was usually observed; in some instances the endarteritis was eccentric (Fig. 23). Localized areas of broadening of alveolar walls were often in evidence, and this was mainly due to eosinophilic infiltration (Fig. 24). These cells also formed occasional groups within alveoli.

The 87-day animal showed nothing more than congestion and slight edema, even though schistosomal changes of the liver were marked.

At 101 and 120 days the changes were fundamentally as in the 75-day animal, but more widespread. In some areas necrotic worms lying in air sacs or alveolar capillaries formed the center of small patches of bronchopneumonia in which the infiltrating cells were mostly eosinophils (Fig. 25). Extensive portions of the lung showed slight broadening of alveolar septa and groups of eosinophils in the air sacs. There were no wide zones of necrosis, but hemorrhagic infarction was seen in places at the margin of the organ. The dilated blood vessels were surrounded by atelectatic parenchyma. In arteries containing dead worms, epithelioid cells had at times replaced the blood vessel wall (Fig. 26) and at other times were filling the lumen.

At 150 days the lungs presented very few alterations and no worms or ova.

At 183 days only a few worms were found within arteries. All parasites were dead and had provoked an intense eosinophilic infiltration of intima and adventitia and moderately marked polypoid endarteritis.

Liver:

In animals killed during the first 10 days after inoculation the liver varied in weight from 45.8 to 83.0 gm., with an average of 61.3 gm. In those sacrificed after the 15th day, when organic alterations were first clearly evident, the weight ranged from 53.8 to 175.5 gm.—an average weight of 75.9 gm. The heaviest liver (175.5 gm.) was found in a rabbit killed on the 120th day after inoculation, and presented the most advanced changes.

Slight lesions of hepatic coccidiosis were encountered in 12 of the rabbits and were visible grossly as rare, soft, pale yellow nodules, not more than 5 mm. in diameter. Gross evidence of involvement with the schistosomal infestation was first seen on the 10th day as congestion of the organ. This was distinct by the 20th day, when dilatation of the intrahepatic portal branches began to be noted. Lobulation of the surface made its appearance at 30 days as an increased prominence of the lobular pattern of the inferior margin of the lobes, especially of the central subdivisions. Minute grey nodules (pseudotubercles), projecting slightly from the capsule, and short, whitish or yellowish streaks (worms)

made their appearance at the 40th day. After this the nodulation of the surface became more marked, the depressions assumed a grey tint, the color in general became dark bluish or purple, and the unevenness of the surface extended towards the dome from the inferior margin, where it was always most advanced. A large portion of the organ, however, remained smooth. The most marked changes were found at 120 days (Fig. 27). The larger nodulations on the liver of this animal assumed a convoluted or serpiginous outline, and on section were found to consist of enormously dilated veins, often measuring 0.8 cm. across, which collapsed when emptied of their large content of blood and schistosome worms. In the lower 2 cm. of this liver the hepatic parenchyma had disappeared almost totally, the cut surface resembling a cavernous hemagioma.

Up to and including the 8-day animal, no microscopic changes were found that could not be explained by the light coccidiosis with which the liver of all rabbits of this period, save those of the 61st and 72nd hour, was tainted. An exception may be made of congestion, which appeared on the 10th day and from then on became one of the most notable features of hepatic schistosomiasis; as early as this day the interlobular veins were quite distinctly widened and engorged with blood.

On the 10th day, up to 12 parasites were found per section, and these were situated in interlobular veins mostly, in sinusoids to a lesser extent, and in efferent veins only occasionally (Figs. 28, 29 and 30). This indicates that young parasites are able to pass from the portal to the hepatic veins through the sinusoids, in this manner being transported to the lungs a second time. All but a few of the parasites contained blackish pigment in their intestinal canals. Evidence of injury to the tissues could be seen in rare places as a slight accumulation of lymphoid cells and rare eosinophils within the sinusoids and of larger ones with ill-defined cell bodies and vesicular nuclei, apparently derived from Kupffer cells. Some of the Kupffer cells in these areas contained a few granules of blackish pigment. In one portal space, the intima of a small interlobular vein that contained a living young parasite had become unevenly and slightly broadened by infiltration beneath it of lymphocytes, histiocytes and rare plasma cells and eosinophils.

By the 20th day the cellular infiltration about the interlobular veins had become dense, larger numbers of eosinophils and histiocytes being in evidence. Occasionally the infiltration of the intima resulted in narrowing of the lumen of the smaller veins (Fig. 31). The neighboring sinusoids at times contained small groups of lymphocytes, proliferating Kupffer cells and a few large, finely vacuolated macrophages. A rare Kupffer cell near a portal space had already engulfed very fine dark brown granules. Although most of the parasites were quite well developed, a distinctly immature one was discovered in a sinusoid. Even at this early date a vein appeared partly occluded by the formation in its intima of a very early pseudotubercle containing oxyphilic necrotic material in the center and histiocytes, lymphocytes and eosinophils about the periphery; the necrotic material apparently represented the remnants of a parasite.

Thirty days after infestation, which was very heavy in this animal, the most notable alteration consisted in the further development of endophlebitis (Fig. 32) affecting most of the interlobular veins, which at this time, it must be noted, harbored only living worms not yet fully mature. The endophlebitis was characterized by infiltration of the intima with histiocytes, numerous eosinophils and lesser numbers of lymphocytes forming polypoid projections into the lumen, which was thus almost totally obliterated in places. Most of the portal spaces were broadened because of proliferation of histiocytes or infiltration by eosinophils and round cells. The wall of the larger interlobular veins, when affected by the endophlebitis, showed edema of the muscle coat and infiltration between the muscle fibers of round cells and eosinophils. In rare places the worm within the lumen had died, and was surrounded by necrotic eosinophils that had gathered in the adjacent parts of the polypoid intimal projections. Granulation tissue infiltrated by eosinophils had developed in a few of the portal spaces. The changes in the sinusoids had progressed, but were usually limited to those parts that bordered on portal spaces. Brownish-black pigment was found in abundance in the swollen Kupffer cells of the outer third of the liver lobules, in histiocytes in the intimal polyps and in the intestinal tract of worms. Congestion of the sinusoids in the peripheral portion of the lobules was beginning to be marked.

At 40 days the dilatation of the interlobular veins was more advanced and the intimal polyps had taken a different character; they were more compact, fairly abundant collagen fibers had developed in many of them; the intimal infiltration was denser and consisted mainly of plasma cells and eosinophils. In some veins the uneven intimal thickening appeared due not to fibroblastic and histiocytic proliferation, but to edema of the subintima and more or less dense infiltration by plasma cells, eosinophils and lymphocytes. Pigmentation of Kupffer cells was more advanced, and the amount of pigment diminished towards the center of the lobules. The changes now began to localize very definitely near the inferior margin, where the venous dilatation, endophlebitis and cell infiltration of the portal spaces were most advanced as compared with the upper portions of the liver, and where these changes affected practically all the portal spaces. The alterations in the sinusoids were seen at their best in these portions, with areas of congestion, with enlargement and proliferation of Kupffer cels which at times formed syncytial and rudimentary giant cell systems, and with accumulation of lymphocytes and eosinophils. These changes diminished towards the efferent vein, but it was once or twice noted that the subintima of these veins was slightly overrun by round cells and eosinophils, in much the same fashion as the interlobular veins, though to a far lesser degree. A single empty egg shell was found in a greatly narrowed interlobular vein, and was partly surrounded by a syncytium containing much blackish pigment. Very slight fibrosis had taken place in some portal spaces, and there was much edema about the portal veins, as well as marked dilatation of periportal lymphatics.

Not until the 50th day did ova make their appearance in numbers, being found immediately outside the smaller interlobular veins, occasionally within the lumen of these vessels and more rarely in sinusoids near the portal spaces. In the tissues they were surrounded by the cells infiltrating the portal spaces, or more frequently by giant cells which were always laden with dark pigment. Rarely they were enclosed in a well-formed pseudotubercle (Fig. 33) with epithelioid cells about the ovum or shell and a few layers of fibroblasts about the periphery, as well as eosinophils and round cells. In the veins, dead worms were not infrequently

seen, usually surrounded by dense clumps of fragmented eosinophils. Where the worms were still alive, the intima responded with polypoid formations as before, or with cell infiltration, but where dead, a broad zone had formed about the circumference of the vessel, made up of large epithelioid cells, often concentrically arranged and growing from the intima. In these instances the lumen of the vessel was totally obliterated, save for the small space occupied by the remnants of the worm (Fig. 34). Near the inferior margin of the organ the veins were markedly dilated and contained large numbers of male and female worms. The polypoid endophlebitis (Fig. 35) was marked, and the polyps often consisted of pseudotubercles in which egg shells and very large giant cells, at times black with pigment, would occasionally be found. About the veins the cell infiltration was slight, and fibrosis almost totally absent, edema being the more notable change. Thrombi were attached to the vegetations. Only a thin septum of loose fibrous tissue remained between some of the dilated veins at the inferior margin. The muscle fibers of the dilated veins atrophied and ultimately were replaced by a narrow layer of fibrous tissue. Living worms were often found in copula, and there were numerous groups of dead worms.

At 75 days, the upper portion of the liver appeared relatively unaffected. The outline of the lobules in these portions was rendered slightly prominent by a negligible increase in the fibrous tissue of the portal spaces; an occasional interlobular vein was surrounded by a mantle of round cells and eosinophils, and there was no endophlebitis. The more outstanding change was in the deposition of pigment, which occurred in large masses in phagocytes in portal spaces and veins, and in Kupffer cells. The amount of pigment in the latter was greatest immediately about the portal spaces, being more and more scanty as the efferent vein was approached, and practically absent in the inner third of the lobule. It was the distribution of the pigment (Fig. 36) that rendered the outline of the lobules prominent, rather than the fibrosis of the periportal areas. Egg shells were numerous and situated as before; some had disintegrated, leading to the formation of small rounded or oval fragments that were surrounded by pigment-laden giant cells. It was most exceptional to find ova still containing embryos. At the

inferior margin endophlebitis was practically absent, except in small veins. Great dilatation of veins was again observed, with coalescence of adjacent ones, so that spurs would only remain to tell of the preëxisting partitions. Intimal polyps, when present, had undergone dense fibrosis, save in the smaller veins, in which pseudotubercles were again occasionally seen in the polyps. About the dilated veins was a broad dense zone of fibrosis that, near the very margin of the organ, was extending diffusely between the cords of hepatic cells, thereby causing their atrophy; in the fibrous tissue there was fairly profuse proliferation of bile ducts. It was seen in some areas that the dilated veins merged with expanded sinusoids about them, and it seems that further progression of this process results in formation of a large lake of blood that reaches to, and includes, the efferent vein in certain lobules.

By the 87th day the marginal portions of the liver consisted of enormous pools of blood containing schistosome worms and surrounded by broad zones of fibrosis that had almost totally replaced the intervening hepatic cells. In an interlobular venule was an egg shell still within the basement membrane, but already partly covered by endothelium that was growing over it (Fig. 37).

At 101 days the veins in the superior portions of the organ were rather markedly dilated and surrounded by abundant fibrous tissue that outlined the portal spaces sharply, and even in places extended into the parenchyma subdividing it into pseudolobules. There were numerous isolated and confluent areas of necrosis of the liver cells throughout the middle third of the lobules, at times extending to include the outer third. In these portions the liver cells were pink-staining and hyaline, while the Kupffer cells remained unaffected. Endophlebitis was almost totally absent, save near the inferior margin, and only rare eosinophils and round cells would be found about the veins. Towards the inferior 1 cm. the venous dilatation and fibrosis became extreme.

At 120 days dilatation of veins had further advanced, and there was marked edema and infiltration of portal spaces with eosinophils. The polypoid endophlebitis was much less marked. About ova and worms within blood vessels, broad zones of epithelioid cells had replaced the intima. There

were proliferating bile ducts about the dilated veins. At 150 days the alterations were mainly as a month before, except that the intimal polyps were large, at times occluding small veins, and often were densely infiltrated by plasma cells. In an interlobular venule was a group of egg shells which, although still lying within the lumen, had been covered by endothelial cells continuous with those of the inner lining of the venule (Fig. 38).

Spleen:

The weight ranged from 0.2 to 3.7 gm. The heaviest and largest were invariably found in the later stages of infestation. Thus, up to the 20th day, the average weight was 0.76 gm. and the length and width ranged from 3.1 × 0.8 cm. to 4.8 × 1.8 cm., while from the 20th to the 183rd day, the weight averaged 2.24 gm. and the length and width varied from 4.0 × 0.9 cm. to 6.5 × 1.7 cm. The largest spleen (3.7 gm. and 6.5 × 1.7 cm.) was removed from the 40-day rabbit, and the smallest of the group of more than 30 days' infestation, from the 183-day animal. It seems, in general, that the weight and size of the organ increased with the duration of the disease and depended on the intensity of infestation.

The gross examination revealed but little. After the 30th day the increase in size was noted in some of the animals, and there was a bluish cast to the surface, while on section the tissues had a slaty hue after the 40th day due to accumulation of pigment. The surface was always smooth and free of adhesions.

The microscopic observations were based on a single longitudinal section of the whole organ, for each animal. Schistosomules, adult worms, ova and pseudotubercles were never encountered. A slight increase in the number of pseudoeosinophils in the pulp took place the 2nd day after inoculation. This was seen in all animals but one until the 10th day, and was at its maximum at the 4th and 5th. Many of these leukocytes had shrunken pyknotic nuclei, while others were fragmented; phagocytosis of fragments of chromatin was occasionally observed. There was at the same time some increased activity of the germinal centers of the malpighian corpuscles, and from the 8th day the reticulum cells of the pulp were more prominent than usual. The increase in pseudoeosinophils was no more in evidence after the 10th day, but the other alterations did not regress, although they were at a minimum in some of the animals.

By the 30th day the malpighian corpuscles were larger than normal and consisted mainly of large and medium-sized lymphocytes, and the hyperplasia of the reticulum cells of

pulp and follicles was distinctly evident. In the follicles were numerous mitotic figures. Pigment first appeared in very small amounts at this time in the form of delicate dark brown non-refractive granules, situated within occasional reticulum cells of the pulp, within phagocytes in the sinuses and, to a much lesser extent, in the reticulum cells at the periphery of the follicles. By the 40th day the sinuses were engorged with blood and moderately dilated, and eosinophils appeared in fairly large numbers throughout the pulp. After the 40th day, the only definite additional change was the increasing accumulation of pigment, which would form dense blackish clumps in the pulp and follicles; in the latter it was usually deposited in reticulum cells at the periphery, but occasionally was found towards the center. The congestion and dilatation of the sinuses did not progress, so that the pulp remained quite abundant and more cellular than normal. This increased cellularity was mainly due to hyperplasia of reticulum and lining cells and to a lesser extent to increased numbers of eosinophils and lymphocytes. Fibrosis was never observed.

Gastro-intestinal tract:

Gross changes in the stomach and intestines were extremely meager throughout the period of observation. Petechial hemorrhages occurred only twice: in the cardia of the stomach of the 10- and 101-day animals, respectively. Congestion of the blood vessels in the subserosa of the small intestine first made its appearance on the 20th day. This gradually increased and later became noticeable in the colon and larger branches of the superior and inferior mesenteric veins from the 30th day on, but was never extreme. Worms were found by inspection from the 30th day in the portal vein and larger branches of the superior and inferior mesenteric veins, being always most numerous in the portal and in the branches of the superior mesenteric draining the small intestine; in a few animals none were found in the inferior mesenteric vein. In most rabbits a few were seen in veins over the greater curvature of the stomach, and in the splenic. Subserous nodules, hemorrhage or other evidences of the disease were never observed externally in any part of the alimentary tract. There were occasional hemorrhages in the mucosa of the small intestine, but no areas of ulceration. Microscopically, young parasites were not included in any of the sections in the earlier stages.

Stomach:

A large section was always taken of the cardia, body and pyloric end and, in addition, of any suspicious areas. Paired or single adult worms were occasionally encountered, in animals sacrificed during the later stages, in subserous veins

at the pyloric end and body. Ova occurred from the 87th day in all portions of the mucosa, but in relatively scant numbers. Usually they excited no reaction on the part of the surrounding tissues, save for slight hemorrhage (visible grossly in the 101-day rabbit) in a few instances. In the 120-day animal, in which no ova were found, a small vein in the muscular coat near the submucosa presented a small polypoid projection from the intima due to accumulation of lymphocytes and plasma cells beneath the endothelium; about this part of the vein there were a few eosinophils. At 150 days occasional small groups of eosinophils and lymphocytes were observed in the submucosa.

Small and large intestine:

Microscopically, an adult male worm was found in a subserous vein of the ascending colon 40 days after inoculation, and there was marked congestion of mucosal and submucosal blood vessels. By the 50th day, numerous ova occurred at all levels of the small intestine, including the duodenum, and in the appendix. They were usually situated within capillaries in the basal portions of the mucosa and in the submucosa, isolated or in groups. The tissues about them were overrun by eosinophils. A few ova occurred in the tissues, were partly enveloped by giant cells of the foreign-body type and lay in the center of pseudotubercles composed of epithelioid cells (Fig. 40). At this time, there was diffuse eosinophilic infiltration of the basal portions of the mucosa, and worms occurred in the submucosa (Fig. 39) and subserosa. At 101 days the ova were extremely numerous, and giant cells often occurred about them, alone or in the center of pseudotubercles. Some of the villi were congested and even hemorrhagic. In the ileum and appendix the central portions of the lymphoid follicles were very active and rich in reticular cells, macrophages and young lymphocytes. At 120 days the same changes obtained. Numerous ova and egg shells were found within dilated capillaries of the mucosa and submucosa, about which was a massive infiltration with lymphocytes, plasma cells and eosinophils. Rarely ova occurred in the muscle coat and most rarely in the subserosa. At 150 days ova were even more numerous, and a pseudotubercle in the mucosa had undergone necrosis in its central portions. Ulceration of the mucosa was never observed. In

the colon and rectum, adult worms would occasionally be sectioned in the subserosa, but ova, pseudotubercles and groups of eosinophils were very scanty, and always slightly more numerous in the ascending colon.

The appearance and behavior of ova within capillary venules of the mucosa and submucosa was studied in detail. Their contained embryo apparently undergoes disintegration very quickly after extrusion from the worm, for usually only the empty shell is found in sections. These structures come to rest against the endothelial lining of the capillary, after which the endothelial cells soon extend to cover the ova completely. In this fashion the shell or ovum comes to lie between the endothelial lining and basement membrane of the capillary. In one instance (Fig. 41) the endothelium was extending over the ovum, and the spine of the latter was pressing against the basement membrane of the capillary, but had not yet pierced it. Even before rupture of the basement membrane, foreign-body giant cells and a few eosinophils and round cells may gather about the ovum between the basement membrane and endothelial lining of the capillary. In other instances (Fig. 42), groups of ova are covered by endothelium as they lie against the inner wall of the capillary. This was already noted in sections of the liver, and seems to represent the first step in the extrusion of ova into the tissues.

Mesenteric lymph glands:

Gross appearances were insignificant, save for the notable increase in size after the 60th day in some of the animals.

The presence of hemosiderin in reticulum cells and macrophages about the hilus was noted from the 37th hour, but was probably unrelated to the schistosome infestation, at least previous to the 30th day. At 20 days the sinuses were filled with macrophages, many of which contained hemosiderin. There were, in addition, rather numerous eosinophils in the lymphoid tissues and sinuses by the 30th day, at which time two worms were found coupled in a vein near the hilus. By the 101st day, there was enlargement of reticulum cells throughout the lymph cords and germinal center of the follicles, and filling of the sinuses with macrophages; a few ova, some with embryos, appeared in the lymphoid tissues. The ova were surrounded by syncytia in which, as well as in

reticulum cells and macrophages, were occasional fine granules of black pigment. Eosinophils were not numerous. At 120 days the pigment was forming dense blackish clumps within reticulum cells and macrophages, the medullary sinuses were filled with eosinophils, and there was phagocytosis of erythrocytes in the sinuses of the hilus. At 150 days a large focus of conglomerate pseudotubercles was found, without peripheral fibrosis and without eosinophilic infiltration.

Kidneys:

Gross alterations, particularly petechial hemorrhages, were never noted.

Microscopically, cloudy swelling did not occur. At 10 days, four or five foci of lymphoid infiltration, early proliferation of fibroblasts and slight invasion by eosinophils were found in the intertubular stroma of the cortex, but parasites were not in evidence in these areas. A glomerulus presented a large syncytial mass. Other glomeruli showed greatly congested capillary loops, and one of these contained a well preserved young parasite which had not given rise to hemorrhage or cell infiltration.

At 120 days some of the convoluted tubules presented minute hyaline droplets in the cytoplasm of their epithelial cells. This evidence of degeneration might be of significance, since the animal was very heavily infested.

Bone-marrow:

A detailed study of this tissue was not attempted, and only the salient features will be recorded. A distinct increase in the number of pseudoeosinophils became evident 61 hours after infestation, was at its height on the 5th day and had receded by the 9th or 10th. This period coincides with the time of maximum invasion of the lungs by young parasites, and corresponds quite closely with the time of duration of the acute splenic tumor. No alterations were then noted until the 40th day, by which time fairly marked hyperplasia, particularly of the granulocytic series, and more especially of the eosinophils, was noted, and though not at all striking in some animals, persisted throughout the remainder of the experimental period.

Pigment did not appear in the marrow until the 75th day, and at this time was very scanty, finely divided and hardly noticeable. It became more abundant with each subsequent

period, but never formed the large black masses seen in the spleen and liver.

Pancreas:

There were no gross alterations.

A young parasite was found in the lumen of a large vein next to the pancreas, probably the splenic or one of the gastrics. This parasite was probably on its way to the liver after having migrated through the spleen or stomach. A sparse infiltration with eosinophils and monocytes in an interlobular space was noted at the 40th day; in an adjacent vein were three pairs of adult worms. No additional change was noted until the 120th day. At this time there were moderately numerous though small accumulations of eosinophils in the interlobular septa, usually in the immediate vicinity of small veins. The wall of one of these venules was swollen, pale-staining and hyaline. Two or three egg shells surrounded by a syncytium and a few eosinophils were found next to a venule and, at another point, one egg shell occurred inside the venule, while a second one had just left it. Pseudotubercles were not in evidence.

Thymus:

The only change seen in this organ which might be due to the schistosomal infestation consisted of small hemorrhages in the 13-, 49-, 72-, and 120 hour animals. They were, however, not accompanied by eosinophilic infiltration, and no parasites could be demonstrated in relation to them. In the 3-day rabbit, they were very numerous, but it must be observed that similar small hemorrhages were found in some of the controls.

Gallbladder, suprarenal gland, submaxillary gland, urinary bladder, internal genitals, esophagus:

Remained normal throughout the period of observation, both grossly and microscopically.

Summary of pathologic findings in the rabbit:

It becomes evident, after study of the above data, that the definitive localization of worms in the portal vein and its branches, the full maturation of the parasites, and the deposition of ova in various organs bring about a decided change in the character and localization of the pathologic manifestations in this disease. It is convenient, for this

reason, to subdivide the consideration of tissue changes into two stages.

We include in the first stage all alterations prior to full maturation of worms and deposition of ova and, therefore, incidental to (*a*) invasion of the host by the cercariae, (*b*) passage of the young wandering parasites through the blood vessels of various organs, (*c*) localization of parasites in the intrahepatic branches of the portal vein, and (*d*) beginning deposition in various organs of the pigment extruded from the intestinal tract of the parasites. Since ova were first found outside worms on the 40th day, this stage embraces in our series the first 30 days after inoculation. A more precise determination of the onset of oviposition was not attempted, but the above seems close enough, since at 40 days only one ovum was found and this was situated intravascularly.

The second stage is characterized principally by changes incidental to (*a*) definitive localization of worms in mesenteric and intrahepatic portal veins, (*b*) occasional passage of worms to the lungs, (*c*) deposition of ova in various organs and (*d*) increasing accumulation of pigment in the tissues.

First stage: In the rabbit, cercariae penetrate obliquely through the skin between hair follicles and only rarely down the latter. The corium is reached well within one hour and the parasites soon find their way into the lumen of lymph and blood capillaries, particularly the former. The corium responds to the presence of cercariae with edema, lasting not more than 49 hours, and leukocytic infiltration, which for about 10 hours is predominantly pseudoeosinophilic and after this is mainly round-celled and may persist for 4 days. These histologic alterations are diffuse and not centered about the parasites, except when the latter undergo necrosis.

In the peripheral lymph nodes parasites are found in both the sinuses and lymphoid tissues, provoking hemorrhages in these situations and a diffuse acute lymphadenitis, which lasts from the 13th to the 49th hour after inoculation. The extravasated erythrocytes are removed by phagocytosis. There are also varying degrees of eosinophilic infiltration and lymphoid hyperplasia lasting approximately 15 days.

In the lungs, petechial hemorrhages result from the occlusion of capillaries by the parasites, and first appear within

25 hours after inoculation, reach their maximum number on the 6th day, and have disappeared by the 20th. Localized patches of congestion of alveolar capillaries and foci of broadening of alveolar walls, with histiocytic proliferation and sparse round-celled and eosinophilic infiltration, mark the passage of the schistosomules through the capillaries. These changes may be accompanied or not by extravasation of erythrocytes into air sacs. The parasites may occasionally pass into air sacs, provoking hemorrhage, exudation of large mononuclear cells, and formation of rudimentary foreign-body giant cells, but without the development of pneumonia. Some of the parasites are thus lost in the lungs.

In the liver, young parasites begin to appear in sections on the 10th day after inoculation and may be found within interlobular veins, sinusoids and efferent veins; they are thus able to pass to the lungs a second time. As early as the 10th day, round-celled, eosinophilic and histiocytic infiltration begins in the portal spaces surrounding parasitized veins and in the subintima of these veins. This infiltration is already quite distinct on the 20th day, and by this time has extended to involve unparasitized portal areas and the subintima of portal veins. Pigment first appears at this time within Kupffer cells and phagocytes of the portal spaces. Portal endophlebitis is a characteristic finding, and visible at its best about dead parasites, in which case there is extensive proliferation of epithelioid cells beneath the intima, as early as the 30th day, when schistosome ova are not yet to be found in the hepatic tissues. Large polyps are thus formed by infiltration of the intima, and these may lead to venous occlusion. Development of fibrous tissue is altogether absent during this period.

Splenic alterations during the period of migration of parasites consist of a slight acute splenic tumor from the 2nd to the 10th day, inclusive. Congestion of sinuses does not become distinct until the 30th day. Prominence of reticulum and endothelial cells starts at about the 8th day, while pigment is first visible on the 30th.

The gastro-intestinal tract appears to suffer very little during this early period, since the only findings were a few petechial hemorrhages in the cardia of the stomach on the 10th day and congestion of subserosal blood vessels of the small intestine beginning on the 20th.

In the kidneys, young parasites are able to pass along with the blood, causing very little damage, apart from marked dilatation of the glomerular capillaries through which they travel, followed by congestion, and occasional slight lesions of the cortex in the intertubular stroma.

During the period of invasion and migration of schistosomules and of their maturation in intrahepatic radicles of the portal vein, the skin, superficial lymph glands, lungs and liver are the organs and tissues mainly affected.

Second stage: The liver bears the brunt of the schistosomal infestation in this stage. Congestion, which was first noted on the 10th day after inoculation, progresses until by the 40th day the portal branches along the inferior margin of the lobes are engorged with blood and worms and become distinctly dilated. By the 50th day, very little hepatic tissue remains in these portions between the dilated veins. This dilatation later involves some of the sinusoids and eventually extends to the central or efferent vein. Although a single empty egg shell was found on the 40th day within the lumen of a portal vein, ova did not appear in the hepatic tissues until the 50th. Even at this early date, some of them were already surrounded by epithelioid cells and a peripheral zone consisting of a few concentrically arranged fibroblasts, but the majority lay in the immediate vicinity of interlobular veins and had excited, at the most, formation of foreign-body giant cells. Disintegration of egg shells began to be noticed on the 75th day. Pseudotubercles form but rarely about ova in the rabbit's liver. A faint nodulation of the surface of the organ became apparent grossly on the 30th day, but this was due to cellular infiltration and slight edema of the portal spaces, for fibrosis was not in evidence until the 75th day. This increase of fibrous tissue about the lobules was marked only about the dilated veins near the inferior margin, elsewhere being very slight. It did not affect all of the organ equally, becoming less noticeable towards the dome. The fibrous tissue was not especially concentrated in areas where ova were more numerous. The endophlebitis during this stage is more marked about dead worms, where the intima of the veins becomes greatly broadened in polypoid fashion, and not infrequently obstructs the lumen, particularly of the smaller vessels. Blackish pigment first appears on the 20th

day, but not until the 40th does it begin to accumulate to a notable extent, and forms prominent clumps in the Kupffer cells, in phagocytes of the portal spaces, in foreign-body giant cells surrounding ova, and in epithelioid cells beneath the intima of veins, as well as in pseudotubercles.

In the lungs, the more severe alterations during the second stage were not those dependent on deposition of ova, but on the accumulation of adult worms in pulmonary arteries and, to a lesser extent, in veins and alveolar capillaries. This resulted in marked damage to the wall with aneurysmal dilatation of blood vessels. Where worms had died, the wall of the blood vessel had been replaced by a layer of epithelioid cells or by fibrous tissue, and the surrounding pulmonary parenchyma presented extensive patches of pneumonia, in which eosinophils were the predominant cell. There were also hemorrhagic infarcts. The intima of blood vessels, especially when containing living worms, was infiltrated with round cells and eosinophils, at times leading to formation of intimal polyps. Ova occurred in small numbers throughout the lungs, but had only infrequently provoked formation of pseudotubercles.

The spleen presented moderate dilatation of sinuses after the 50th day. There was increased prominence of reticuloendothelial cells and increasing accumulation of pigment in reticulum cells of both the pulp and follicles after the 30th day. Ova and pseudotubercles did not occur.

The stomach and intestines exhibited no definite alterations until beginning deposition of ova. In the small intestine and appendix ova were first seen on the 50th day in quite large numbers, and occurred isolated and in small groups in the basal portions of the mucosa. They led to formation of pseudotubercles and eosinophilic infiltration, but no diffuse acute inflammatory changes. Congestion of some of the villi and occasional areas of hemorrhage into these structures were observed some time later. Changes in the colon were similar to the above, and more marked in the proximal portions. Ulceration of the mucosa did not occur.

II. The White Rat

Material and methods: Thirty-three young adult white rats were utilized. Infestation was brought about by immersion, as for most rabbits (*vide supra*), except that the total volume of tap water after addition of the cercariae was

400 to 800 cc. After immersion for 1 hour the animals were withdrawn and allowed to dry.

The rats were killed by ether anesthesia at intervals of 14, 24, 36, 48, 60 hours, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14, 15, 18, 20, 30, 40, 60, 71, 91, 158, 170, 180, 195, 210, 227, 240, 256, and 271 days.

A complete autopsy was performed immediately after death; the central nervous system and bone-marrow were not examined. The details of procedure were as for rabbits, and the tissues were handled in the same way.

Biopsies of the skin for study of changes incidental to penetration of the cercariae were not obtained.

Restlessness and evidences of irritation of the skin became evident soon after confinement of the animal in the inoculating jar. Rubbing of the paws against the nose and face was particularly active, and this went on for a few hours after withdrawal from the suspension of cercariae.

Close observation of the animals throughout the experimental period failed to reveal any changes in behavior or appearance that could be ascribed to schistosomiasis.

As in the case of the rabbits, no petechial hemorrhages were seen in the subcutaneous or cutaneous tissues, muscles or serous membranes, exception made of the animal sacrificed on the 3rd day, which presented a few in the deeper portions of the skin covering the right thigh.

Lymph glands:

Gross external examination of the knee, inguinal and axial lymph nodes revealed changes in the 4-day animal only, the inguinal lymph glands on the left side of this rat being slightly enlarged and hemorrhagic.

Description of microscopic appearances is based on a single section of each gland removed. Slight recent hemorrhage had taken place into the peripheral sinus of an axial gland 24 hours after inoculation, but no parasites were in evidence.

At 36 hours one schistosomule was present in the peripheral sinus of an inguinal lymph gland. The parasite was perfectly preserved, and had provoked no hemorrhage or cellular reaction. In the axial nodes, the peripheral sinus was broadened and hemorrhagic, and there was beginning phagocytosis of erythrocytes by macrophages. A few eosinophils and numerous lymphocytes had invaded the sinus.

On the 3rd day two parasites were found in the peripheral sinus of a knee gland, and there were small points of hemorrhage and slight increase in macrophages along this sinus.

Slight hemorrhage had taken place in the peripheral sinus of the axial and inguinal nodes, but there were no parasites.

Changes in the lymph nodes were at their height on the 4th day. The nodes of the knee presented fairly extensive hemorrhage and active phagocytosis of red blood cells in the peripheral and medullary sinuses, with occasional eosinophils in these areas. The same alterations obtained in the inguinal nodes where, in addition, several parasites were found. Usually a single parasite was seen in each gland, excepting one section that contained three. They were situated for the most part in the peripheral sinus, but in one gland a parasite had penetrated the lymphoid tissues. Only one parasite was in process of disintegration, and even this one had excited no leukocytic infiltration. Changes in the axial nodes were as above, except that there were no schistosomules.

Well-preserved parasites were again found in the peripheral sinus of an axial node and in the lymphoid tissues of an inguinal gland on the 7th day, one occurring in each situation. Another parasite had penetrated the lymphoid tissue of an axial gland on the 8th day, and still another, a medullary sinus of a node of the knee on the 10th day. It is interesting that the 20-day rat exhibited a well-preserved parasite with its gut loaded with golden-yellow pigment resembling hemosiderin, in a sinus halfway between capsule and hilus. It is difficult to explain the presence of this parasite, which had already fed on blood, in a peripheral node at this time. Presumably, it had lodged there from the arterial circulation, after having passed out of the liver.

Slight hemorrhage and some phagocytosis of erythrocytes could still be observed until the 15th day. Pseudoeosinophils were rather numerous in the peripheral sinus of an axial node on the 9th day, together with increased numbers of macrophages, eosinophils and plasma cells, but the pseudoeosinophilic infiltration did not occur in any other animal. Some increase of plasma cells occurred diffusely from the 6th to the 13th day. Slight hyperplasia of the lymphoid tissues was noted from the 7th to the 15th day.

In a popliteal gland of the 12-day rat, a microscopic nodule of epithelioid cells was found growing on the inner aspect of the capsule and projecting into the peripheral sinus. In the center of this pseudotubercle was a group of eosinophils that surrounded a narrow tubular structure containing

hemosiderin and probably representing a degenerated parasite.

In the rat sacrificed 256 days after infestation, a section of the nodes of the knee disclosed a pseudotubercle in the periglandular tissues, at some distance from the capsule. In the center were two large fusiform spaces without ova, surrounded by foreign-body giant cells and epithelioid cells; around the periphery was a narrow zone of round cells. The fusiform spaces may have contained ova that had apparently strayed with the circulation to this region.

Lungs:

A single bright red petechia was found on the pleural aspect of each lung as early as 14 hours after inoculation. These increased to 4 or 5 on each organ at 24 hours, but none were evident at 36 and 48 hours. At 60 hours 2 or 3 such hemorrhages were observed, and the same number obtained at 3, 4 and 5 days. Double that number was found on the 6th and 7th days, while on the 8th there were quite numerous, dark red petechiae distributed throughout all lobes, but more notably in the postero-lateral portions. The 9th day there were no more than 10 on each side, and some of these were beginning to assume a brownish color. After this day they rapidly diminished in number. Some, however, were found as late as the 40th day, but at this time were extremely faint and had obviously developed some time previously. Small bluish-red patches were present at 60 days. At 71 days the lungs were normal, but infestation of this animal seems to have been very mild. Some 10 petechiae were seen beneath the pleura in each lung on the 91st day and approximately the same number at 240 and 256 days; these were bright red and of recent origin. On the 170th day an area of congestion measuring 1 cm. in principal diameter appeared in the right lower lobe.

In the lungs of animals sacrificed on the 180th and 227th day were patches of consolidation proved microscopically to be areas of pneumonia having no relation to the schistosomal infestation. Gross dilatation of pulmonary blood vessels by schistosome worms, and areas of pneumonia or infarction provoked by these parasites, were not observed in the white rat.

Histologically, pulmonary alterations were noted first on the 4th day, when there appeared occasional minute foci of hemorrhage into the air sacs. Young parasites were visible within alveolar capillaries in some of these areas of hemorrhage, and also at other points where no extravasation of erythrocytes had taken place. About a few of the parasites there was a slight increase in the number of nuclei of the alveolar walls, apparently from proliferation of histiocytes, and not from accumulation of leukocytes. Most of the parasites, however, had provoked no reaction on the part of the surrounding tissues, and one was seen within an otherwise

unaltered air sac. The extravasated erythrocytes in some of the alveoli were being engulfed by macrophages.

By the 6th day, the pulmonary tissues were diffusely congested, particularly about hemorrhagic alveoli. Small groups of air sacs showed slight but distinct broadening of their walls due to increase of cells with oval-shaped vesicular nuclei, apparently histiocytes. Parasites were not infrequently found within capillaries in the above areas of alveolar thickening, and one had found its way to an air sac, where it was surrounded by loosely arranged epithelioid cells. A few of the smaller blood vessels were surrounded by pseudoeosinophils. In one section was a fairly large patch beneath the pleura in which the walls of air sacs were broadened by congestion and by accumulation of lymphoid cells and histiocytes. Most of the alveoli in this area contained numbers of large mononuclear cells, lymphocytes and rare pseudoeosinophils and erythrocytes. About some of the blood vessels in this field were prominent collars of lymphoid and plasma cells, and fewer histiocytes, some of which were undergoing mitotic division. No parasites could be found in this area, and the pathogenesis of the lesion remains obscure, although the histologic appearances were rather suggestive of a schistosomal etiology.

On the 8th day the focal areas of septal thickening had become more distinct, and about a few schistosomules lying within alveoli, small nodules composed of epithelioid cells had developed, accompanied by lymphocytes and eosinophils.

By the 9th day, most of the parasites contained abundant brown pigment in their intestinal tracts—this was first observed as early as the 7th day in a single parasite. The diffuse congestion of alveolar walls observed on the 6th day had by this time disappeared, being limited to small areas where hemorrhage had taken place or where young parasites were passing along capillaries. Pseudoeosinophils and eosinophils were grouping themselves about small arteries and bronchi in larger numbers.

Twelve days after infestation there was marked edema about blood vessels and some bronchi, with sparse to moderately dense infiltration by eosinophils. Groups of air sacs were filled with epithelioid cells and eosinophils, and at times large foreign-body giant cells and syncytia had developed, partly surrounding disintegrating parasites (Figs. 43 and 44).

There were occasional fairly distinct pseudotubercles composed of epithelioid and foreign-body giant cells about parasites, but without peripheral fibrosis. In some of these nodules the constituent cells were loosely arranged, star-shaped and suggestive of a fibroblastic nature. Young capillaries were developing in these foci and hemosiderin-laden phagocytes were in evidence in these areas and in the neighboring alveolar walls. These lesions apparently represented organizing areas of hemorrhage. Some of the young parasites within alveolar capillaries were undergoing degeneration without exciting any reaction on the part of the neighboring tissues.

In the lungs of the 13-day animal some of the groups of alveoli showing focal accumulation of histiocytes or formation of epithelioid cells within their lumen were in contact with the pleura, which had responded with the proliferation of histiocytic elements beneath the mesothelial layer, forming a delicate plaque of thickening.

The above described changes consisting of focal broadening and congestion of alveolar walls, of hemorrhage into air sacs, of epithelioid and giant cell reaction within alveoli, and of perivascular edema and leukocytic infiltration, were less noticeable on the 15th day, and by the 18th, were in frank regression.

On the 20th day, some edema could still be observed about blood vessels, with persisting, fairly dense infiltration by eosinophils, round cells and large mononuclears. The foci of alveolar thickening were very scanty, but occasional small groups of alveoli contained red blood cells, lymphocytes and large mononuclears, and there were young parasites with pigmented intestines in the alveolar capillaries in relation to these lesions.

One month after inoculation there were none of the above alterations. Occasional young worms occurred in pulmonary arteries of rather small size, and very shrunken ones, showing pyknosis of their cell nuclei, lay in air sacs. It is to be observed that the intestines of the parasites found within air sacs were free of pigment, while those of worms lying in pulmonary arteries were black with it, suggesting that the former had not passed through the liver, at least recently, and that they had been trapped in the lungs during their first and only passage through these organs.

On the 60th day, there was infiltration with round cells and eosinophils about many of the smaller arteries and in occasional alveolar septa. Pseudotubercles composed of epithelioid cells, with abundant blackish pigment towards the center and eosinophils at the periphery, were occasionally observed. Other pseudotubercles contained no pigment. A necrotic parasite lay in the midst of a small group of collapsed alveoli surrounded by eosinophils; its gut was black with pigment. Ova were not encountered in relation to the pseudotubercles, and it seems more probable that the latter had developed about parasites.

At 70 days, a parasite containing no pigment was to be seen in an alveolar capillary. Other schistosomal alterations consisted only of the presence of pseudotubercles and of slight eosinophilic infiltration about a few blood vessels. In addition, there was an acute suppurative bronchitis and peribronchitis with early pneumonia, apparently of bacterial origin.

The 91-day rat presented numerous small foci of infiltration about blood vessels of small caliber and in alveolar walls with plasma cells, lymphocytes, eosinophils and histiocytes. The reaction in the alveolar walls could often be traced to empty schistosome egg shells. A partly necrotic worm was surrounded by very large epithelioid and foreign-body giant cells that contained dark brownish pigment (Fig. 45). There were small areas of hemorrhage into alveoli.

On the 158th day the alterations were fundamentally similar. One or two living worms were found within branches of the pulmonary artery, the walls of which were entirely normal, but the perivascular tissues were edematous and overrun by eosinophils. Monocytes laden with blackish pigment had gathered about another artery that contained a living worm; the adjacent alveolar walls were sparsely infiltrated with eosinophils.

Similar changes as in the 158-day rat obtained at 170, 180, 195, and 210 days. On the 227th day one section through the margin of the lung showed foci of calcification suggesting, because of their contorted cylindrical outline, that schistosome worms had been present here, and these were surrounded by a sparse infiltration with round cells and a few eosinophils (Fig. 46).

At 240 days no worms or ova were encountered. A few

pseudotubercles were present, and there were rare groups of pigment-laden phagocytes and a few round cells about blood vessels.

At 271 days there was slight round-celled and eosinophilic reaction about a few small and medium-sized arteries. There were worms with pyknotic nuclei in a large branch of the pulmonary artery. No ova or pseudotubercles could be found.

Liver:

A few fine petechial hemorrhages first appeared beneath the capsule on the 9th day, but these did not become really numerous until the 14th, at which time they were quite evenly distributed throughout the various lobes at a distance of approximately 0.5 cm. from one another. By the 18th day petechial hemorrhages were faint and very scanty. At 20 days minute yellow specks, representing worms, began to appear along the inferior margin of the lobes, and congestion was noticeable, especially near this edge. At 60 days the liver surface was very finely nodular and here and there were minute yellow points. The cut surface had a greyish cast from deposition of pigment. At 91 days the surface was smooth, but here and there near the inferior margin were dark blue and blackish patches that, on section, proved to be dilated venous channels containing much dark blood and numerous schistosome worms. Minute pale yellow or grey nodules were scattered over the surface, near and along the inferior edge. These alterations were somewhat more marked at subsequent periods up to the 195th day, when nodularity of the surface again became evident in addition to the other changes. From this time until the 271st day, when the period of observation came to an end, no further progress took place.

Seven to eight sections of liver were obtained from each animal at autopsy for histologic study, but none of the blocks was cut serially. The first microscopic alteration was found on the 8th day after inoculation and consisted of small groups of lymphoid and large mononuclear cells slightly distending the sinusoids in places; one gained the impression that the latter were derived from Kupffer cells. At 9 days two young parasites without pigment in their intestinal tubes were discovered lying in sinusoids, unaccompanied by leukocytes. A moderate infiltration with lymphoid cells and a few eosin-

ophils had taken place about unparasitezed portal veins. The 10th day there were, in addition, rare slightly dilated sinusoids containing erythrocytes, eosinophils and larger histioid elements.

On the 12th day the Kupffer cells in general were more prominent that usual, dilated sinusoids were more frequently seen, and infiltration about portal veins had become a much more prominent feature, having extended even to the finer venous radicles; the larger portal areas were somewhat edematous. In some areas the infiltrating cells had invaded small portions of the adjacent liver lobules, with replacement of a few hepatic cells. Several young parasites with abundant pigment in their guts were seen in portal branches, and a few non-pigmented ones in the sinusoids, where they were at times surrounded by a few round cells (Fig. 47).

On the 15th day the infiltration of portal spaces was the principal feature, with eosinophils predominating, and lesser numbers of lymphocytes and large mononuclear cells. A non-pigmented parasite was still found in a sinusoid. The Kupffer cells near some of the portal areas contained dark brown granules of pigment for the first time.

At 20 days the cellular infiltration had extended to the subintima of the portal veins, producing slight broadening of this layer. Phagocytes in portal areas contained a small amount of pigment. Portal spaces in which the veins contained no worms were nevertheless infiltrated with cells. In the parenchyma, which until now had been normal, were microscopic foci of hyaline necrosis of liver cells, while the Kupffer cells bordering on them stood out well-preserved; the sinusoids in these portions contained large mononuclear cells and eosinophils.

Thirty days after infestation the larger portal veins were filled with worms, and occasional portal spaces showed increase of fibrous connective tissue in addition to cellular infiltration. The pigment within Kupffer cells was more abundant. Small areas of necrosis of liver cells were again observed.

At 40 days there was as yet no definite cirrhosis and the changes were more or less as above. Some of the parasitized veins, however, were distinctly dilated. A dead worm within a portal vein was completely surrounded by rather a broad zone of large, pale epithelioid cells developing in the

intima, and some of which contained brown pigment, while numbers of eosinophils had collected immediately about the necrotic parasite. Schistosome egg shells first appeared in this animal, but only one was found; it was surrounded by a foreign-body giant cell and round cells.

The 60-day liver showed definite fibrosis of the portal spaces, with extension of the connective tissue in a delicate band completely about the periphery of the lobules (Fig. 48); this gave the sections a checkered appearance recalling the normal structure of the pig's liver. The fibrosis was most marked about the larger portal veins, where there was in addition fairly marked edema and infiltration by eosinophils and fewer lymphocytes. Small groups of liver cells had here and there become surrounded by the fibrous tissue to form pseudolobules. Marked dilatation of portal veins was again noted, especially along the inferior margin of the organ, where also a single pseudotubercle, composed of epithelioid cells and a fibrous peripheral layer, was found. No ova were discovered in any section.

Ninety-one days after infestation the fibrosis was more advanced, and the larger portal areas were overrun by very numerous plasma cells, lymphocytes, eosinophils and phagocytic cells laden with dark brownish schistosomal pigment. Numerous schistosome egg shells had found their way to the fibrous tissue surrounding portal veins, where some lay in the center of a fibrous nodule (Fig. 49) and others in pseudotubercles (Fig. 50) composed of foreign-body giant cells, epithelioid cells, and a peripheral zone of fibrosis. The pigment was forming solid clumps in the portal spaces and Kupffer cells, and was quite abundant within the foreign-body giant cells of the pseudotubercles. The ova were found not only in the portal spaces but also in the proximal portions of the sinusoids, in which location they had only rarely excited pseudotubercle formation. The portions of the sinusoids bordering on the portal spaces had often undergone dilatation and congestion. Dilatation of the veins near the inferior margin of the lobes (Fig. 51) had advanced, so that in places the appearance was very close to that of a cavernous hemangioma. Numerous schistosome worms had made their habitat in these veins, and not infrequently were found in copula.

On the 158th day there was no diffuse cirrhosis observable,

although the portal veins were heavily parasitized. Cellular infiltration of the portal spaces was, however, slightly heavier than at the previous period, and egg shells were found quite as frequently.

At 170 days the picture was essentially the same, except that a fine fibrosis was again noted about the lobules towards the dome.

Hepatic changes were most advanced 195 days after inoculation, but all features were essentially as already described; no further progress was noted after this period. The perilobular fibrosis was always less marked towards the dome of the organ. After this period, the pseudotubercles showed a distinct tendency to replacement of epithelioid cells by the fibrous connective tissue of the periphery.

Proliferation of bile ducts was observed only in the rat sacrificed 271 days after inoculation, but limited to portions along the inferior margin of the lobes and for a short distance above it. This was particularly noticeable in the fibrous tissue that separated dilated veins from one another. The hepatic parenchyma had disappeared almost completely from these portions.

Spleen:

The weight and size of this organ failed to reveal departures from the normal that could have been considered significant. Pigmentation of the pulp was the only alteration observed grossly. This was first noted 60 days after infestation, and consisted of a dark bluish or purplish cast to the pulp, in contrast to the normal bright red color.

A single section of the whole length of the organ through its center was utilized for microscopic study.

Increased activity of the lymphoid follicles began at 10 days. On the 12th the cells of the reticulum of the pulp and those lining the sinuses seemed slightly more prominent than normally. These alterations, however, were rather vague and could not be observed in several of the animals.

Pigment first made its appearance on the 30th day, when it was found in finely divided form in reticulum cells of the pulp and within macrophages. Congestion of the sinuses became evident on the 40th day, at which time pigment was also appearing in the central portions of the hyperplastic follicles.

Congestion and somewhat diminished cellularity of the

pulp, hyperplasia of the lymphoid follicles, which at times were composed mainly of medium-sized and large lymphocytes, and increasing accumulation of pigment in both pulp and follicles (Fig. 52), constituted the maximum of splenic alterations, as seen in animals of subsequent periods. The morbid changes did not appear to be continuously progressive, but this may only mean that some of the rats sacrificed at a later period were more lightly infested than others killed at an earlier date.

At 271 days, which was the longest period in the series, congestion and dilatation of sinuses were distinct and more marked than in any other rat, and the pigment was very abundant and formed prominent intracellular clumps. On the other hand, the follicles showed no increased activity.

In none of the sections were ova or pseudotubercles seen in the splenic tissues, nor were worms found at any time within intrasplenic veins.

Gastro-intestinal tract:

On the 8th day after infestation, 8 to 10 bright red petechial hemorrhages occurred evenly distributed throughout the mucosa of the stomach, and a single one on the 9th day. No other alterations were noted grossly in the stomach, and the small and large intestines remained entirely unaltered throughout the experimental period.

The histologic appearance was equally unimpressive throughout the whole period of observation comprising 271 days.

Stomach:

Slight to moderate infiltration of the basal portions of the mucosa and submucosa with eosinophils first appeared 20 days after inoculation. This was again seen in 8 different animals after the 40th day, although neither ova nor worms could ever be demonstrated.

Intestines:

No microscopic departures from the normal were evident, apart from occasional infiltration of the mucosa with eosinophils. Neither worms nor ova could be found in any section.

Kidneys:

Petechial hemorrhages were never observed in these organs. In no animal were there gross alterations that could be referred to the schistosomiasis.

A lymph node in the hilus of one kidney showed, 36 hours after infestation, groups of macrophages laden with fresh

erythrocytes, as well as free red blood cells in the peripheral sinus. This was again noted on the 4th day.

From the 7th to the 15th day, inclusive, young parasites were occasionally found within glomerular capillaries which had become greatly overdistended (Fig. 53). In a few instances, this had caused enlargement of the endothelial and epithelial cells of the capillary, with pyknosis of their nuclei. Once there was sparse eosinophilic infiltration about the glomerulus. In the 12-day rat, there was some proliferation of the cells of the capsule opposite the obstructed capillary, with formation of a small mound that projected into the capsular space. Rare glomeruli showed collapse of their tufts, in some of which was a small amount of pinkish fibrinoid material; there was slight infiltration of these glomeruli with fragmented leukocytes. In the 10-day rat a few atrophic and distorted tubules were found in the immediate neighborhood of a glomerulus with collapsed tufts. A few red blood cells had entered the lumen of these tubules, within one of which was a well-preserved young parasite. A few eosinophils were infiltrating the stroma between the affected tubules. In one rat, rare ischemic glomeruli were surrounded by a few collapsed tubules, in which the epithelial cells were large, pale and probably fatty. Once or twice young parasites were found within capillaries in the intertubular stroma of the cortex (Fig. 54). In the 15-day rat there were several ischemic glomeruli in which the tufts exhibited swollen nuclei. One of these tufts had become adherent to the capsule.

On the 20th day one schistosomule was found distending a glomerular capillary tuft which was otherwise unaltered. In the renal stroma were two or three small foci of infiltration with eosinophils and slight increase in histiocytes.

After the 20th day, no more parasites or lesions were found in the kidneys. An occasional atrophied glomerulus was in evidence, but we cannot attribute this to the schistosomal infestation with any certainty, for they may also be seen in normal rats.

Pancreas:

No gross alterations were noticed in this organ. Microscopically, in the 12-day rat there was a pancreatic capillary with faintly staining necrotic wall and conglutinated erythrocytes within the lumen. Adjacent to this part of the

capillary was a minute focus of histioid cell reaction and infiltration by eosinophils. At 195 days, there was a similar focus of histiocytes and eosinophils, but no damaged blood vessels. Schistosome ova and pseudotubercles were never in evidence.

Thymus:

Three petechial hemorrhages were present beneath the capsule covering the anterior aspect of the gland on the 60th hour after inoculation, and an equal number on the 8th and 13th days.

Microscopically, minute foci of extravasation of red blood cells were encountered in the above animals and in the 3-day one, but no parasites and no cell reaction were in evidence.

Suprarenal and submaxillary glands, urinary bladder, internal genitalia, esophagus, deep cervival lymph glands:

No pathologic changes that could be ascribed to schistosomiasis were found in these organs.

Summary of pathologic findings in the white rat:

First stage: The superficial lymph glands draining the portal of entry of the schistosomal infestation responded to passage of the parasites with little more than hemorrhage, sparse eosinophilic infiltration and mobilization of macrophages into the sinuses. Once there was an acute inflammatory response as in rabbits.

The lungs reacted to the presence of young parasites much as in the rabbit, there being foci of congestion of the alveolar walls, points of broadening due to endothelial proliferation and cellular infiltration, and areas of hemorrhage into alveoli. In addition, large syncytia and foreign-body giant cells often developed about parasites that had wandered into air sacs.

In the liver, although parasites were not found until the 9th day, groups of round cells could already be seen in the sinusoids on the 8th. Round-celled and eosinophilic infiltration of portal spaces began on the 9th day about unparasitized veins. Fine granules of blackish pigment appeared in Kupffer cells near portal spaces on the 15th day, and in phagocytes about portal veins on the 20th. Slight portal fibrosis made its onset on the 30th day. Small foci of

necrosis of liver cells were observed at 20 and 30 days. Dilatation of veins at the inferior margin began to be distinct 40 days after inoculation.

The spleen showed some hyperplasia of lymph follicles after the 12th day, while deposition of pigment in reticulum cells and macrophages began on the 30th.

In the kidneys, young parasites were encountered in glomerular capillaries from the 7th to the 20th day. At times this led to slight localized enlargement of epithelial and endothelial cells of the affected tufts and adjacent portions of the glomerular capsule. Collapsed renal tubules in relation to ischemic glomeruli were also part of the damage produced by the wandering parasites; one of these was indeed found within a tubule in such an area.

Second stage: This was not as severe in the rats as in the rabbits.

The lungs again showed adult worms in the pulmonary arteries, but not to the same extent as in rabbits, and without marked dilatation of the vessels or destruction of their walls. Necrotic worms were not infrequently found after the 60th day in alveoli and large blood vessels, and were surrounded by eosinophils or epithelioid cells or both. Ova did not appear until the 90th day, and about them as they lay in alveolar capillaries were small groups of round cells, eosinophils and histiocytes, but no distinct pseudotubercles developed.

A single ovum was found in the liver on the 40th day, but ova did not occur in numbers until the 90th. Fibrosis, however, was by this time quite marked and, as in the rabbit, proceeded towards the dome from the margins. Dilatation of veins was never as distinct as in the rabbit, though presenting much the same features. Endophlebitis was not marked, and there were no polypoid projections from the intima. Formation of pseudotubercles about ova, increasingly denser infiltration of portal spaces with round cells and eosinophils, and increasing deposition of pigment in the Kupffer cells, completed the picture in this stage. The hepatic changes became stationary after the 195th day.

In the spleen, congestion and dilatation of sinuses, deposition of pigment in reticulo-endothelial cells of the pulp and follicles, and hyperplasia of the latter progressed until the

170th day. After this time the only change observable was the more massive clumping of pigment.

Ova were never found in the kidneys, and the slight changes noted during the first stage of infestation underwent complete regression, for no alterations were encountered in the second stage.

The gastro-intestinal tract remained normal throughout the period of observation.

DISCUSSION

Our data concerning the route followed by the young schistosome parasites from the portal of entry to the intrahepatic branches of the portal vein corroborate the results obtained recently by Faust, Jones and Hoffman (*l. c.*), who utilized an altogether different method of study. This route seems to be exclusively intravascular from the skin via lymphatics to the regional lymph glands, and via blood vessels to the lungs. Most of the parasites manage to pass through the lymph nodes, for only rarely were disintegrating schistosomules encountered in these structures. From the nodes they escape with the lymph and, providing they are not held up and destroyed while on their way, are ultimately transported to the subclavian vein and so to the lungs.

In view of the extreme rarity with which parasites were found within blood vessels in the skin, it seems probable that the route followed to the lungs is mainly the lymphatic one.

In the lungs the parasites maintain their intravascular localization, entering air sacs only exceptionally. When passing into air sacs, they disintegrate and are disposed of by phagocytes and giant cells. In their progress along blood vessels, they may obstruct alveolar capillaries, but for the most part are able to pass out of these organs with the blood. This will take them to the left side of the heart, whence they must be widely disseminated throughout the host with the arterial blood. We found no evidence in substantiation of Narabayashi's [11] and Sueyasu's [12] claim for *S. japonicum* that young parasites reach the liver by direct wandering through the pulmonary tissues, pleura and diaphragm.

In our material, gross evidence of this widespread dissemination was very scanty. It might be expected, as a result of the transportation of young parasites to various organs and tissues, that petechial hemorrhages would often

occur in the latter, as happens in the lungs, but this was not forthcoming. The only organs other than the lungs that exhibited petechiae during the period of wandering were the thymus, stomach and liver, and serial sections of the thymus failed to demonstrate that the petechial hemorrhages were due to the passage of schistosomules. For this reason we have come to believe that caution is necessary in interpreting petechiae, for in many instances they may be caused by factors other than obstruction of blood vessels by parasites.

There were, however, certain slight focal changes in the interstitial tissues of the myocardium and kidneys in rabbits, suggestive of the passage of young parasites; and the actual finding of schistosomules distending glomerular capillaries in both rabbits and rats, in most instances without provoking any hemorrhage, leaves little doubt that they are transported to various organs during this period. Actual proof of this has been offered by Faust, Jones and Hoffman (*l. c.*) with their perfusion experiments. It seems as if the great distensibility of capillaries and the elasticity of the young parasites would in most instances allow of their passage without much visible damage to either, except in the lungs, where the loose texture of the organ may favor the development of hemorrhages.

How the parasites eventually reach the intrahepatic branches of the portal vein could not be directly ascertained in the course of our studies, but it seems that they do so, as indicated by Miyagawa and Takemoto [13], Faust and Meleney [14] for *S. japonicum,* by passing from the arterial to the venous side of the circulation in those organs whose venous return is tributary to the portal vein.

The tissue alterations observed during the first stage of the disease depend for their localization on the route followed by the parasites, as above outlined, and are probably determined by the following factors: (1) Obstruction of capillaries by schistosomules, and their occasional passage outside of blood vessels; (2) the liberation by living parasites of noxious substances, be they products of metabolism or true toxins; (3) the liberation from dead parasites of products of their disintegration, and (4) the extrusion of pigment elaborated in the intestinal tract of the worms from ingested blood.

The immediate reaction provoked by the cercariae in the skin and regional lymph nodes of the rabbit consisted of an

evanescent infiltration by pseudoeosinophils. We thought it possible that this leukocytic infiltration might be due to bacteria carried in with the cercariae, rather than to the parasites themselves, but no microörganisms were found in sections of skin and lymph nodes stained by the Gram and Giemsa methods.

The young parasites provoke the formation of petechial hemorrhages, whenever they obstruct capillaries sufficiently to bring about their rupture. In many such instances the obstruction is probably temporary and the parasite manages to continue on its way. When escaping into air sacs, the parasites act as foreign bodies and provoke the accumulation of phagocytes, which may coalesce to form rudimentary foreign-body giant cells. In the liver, the young parasites are responsible for the round-celled and eosinophilic infiltration of the portal spaces, multiplication of Kupffer cells at the points of obstruction in the sinusoids, and polypoid endophlebitis of portal veins in the rabbits.

The cellular infiltration of the intima of portal veins within the liver and of portal spaces, as well as the fibrosis, extends to portions of the organ where parasites and ova are not found. These alterations make their appearance before the beginning of deposition of ova, and their genesis is best explained by the supposition that certain noxious substances elaborated by the parasites are set free in the circulation. The increased prominence of reticulo-endothelial cells of the spleen, before the beginning of deposition of pigment, might be due to the same cause.

Beginning 30 days after inoculation, there is a change in the character of the tissue changes that seems principally dependent on (1) the presence of adult worms within blood vessels; (2) the extrusion of increasingly larger quantities of pigment by the parasites; (3) the deposition of ova and (4) the liberation of noxious substances by living and dead adult worms.

The cellular infiltration of portal spaces and the polypoid endophlebitis of intrahepatic branches of the portal vein make their appearance while the parasites are still young, but reach their height after full maturation of the worms. Since these alterations are always more marked towards the inferior margin of the liver, where worms are most abundant,

and since they have their inception prior to extrusion of ova, it is evident that they result from the presence of worms, probably through the liberation of noxious substances by the parasites.

The presence of very large numbers of worms in the portal branches along the inferior margin of the liver and in the pulmonary arteries leads to great dilatation of these vessels. This is probably aided by weakening of the blood vascular walls because of the inflammatory changes which always precede and accompany the dilatation, and which result in progressive attenuation of the muscle layer, thinning and destruction of elastic fibers.

It seems most probable that the adult worms found within branches of the pulmonary arteries reach that location by direct passage through the dilated sinusoids and efferent veins of the liver, rather than through pelvic anastomoses between the inferior hemorrhoidal plexus and the inferior vena cava.

It is furthermore probable that parasites may be able to remain in the lungs and there mature, for in a few instances they were encountered in pulmonary blood vessels prior to the time when marked dilatation of portal veins and sinusoids becomes evident. These parasites were distinctly stunted and underdeveloped, as compared with those found within the portal and mesenteric veins of the same animal. However, the number of worms whose presence in the lungs could be explained in this manner was always very limited.

The cellular reaction provoked by young and adult living parasites is mainly round-celled (lymphocytes, plasma cells) and eosinophilic. About dead adult worms, the cellular response is predominantly eosinophilic and histiocytic, and there is abundant proliferation of epithelioid cells that completely surround the necrotic parasites. Epithelioid cells, however, at times form about living adult parasites and rarely about young ones. Eosinophils become more numerous in the lesions of all organs after the 30th to the 40th day, when parasites reach their full development.

When first reaching the tissues, the ova excite a slight infiltration with lymphocytes, plasma cells and a few eosinophils. Foreign-body giant cells appear next, and lastly epithelioid cells may accumulate about the ovum and form

the fully developed pseudotubercle. Except in the intestines, pseudotubercles were a very infrequent occurrence, and the amount of cellular reaction about ova was in general not marked; this was particularly observed in the liver. It is to be noted that, in the rat and rabbit, the embryo dies very shortly after deposition of the ovum, for in all organs, save the intestines, it was most rare to find any but empty egg shells. We incline to believe that of the two components—embryo and shell—the former is essential to the development of a pseudotubercle, and that it is for this reason that in our material little more than a foreign-body reaction developed about these entities. Apparently there is a substance common to young and adult parasites, as well as to embryos, which has the property of stimulating the formation of epithelioid cells.

The rôle played by schistosome ova in the pathogenesis of the hepatic fibrosis is not clear. While there is always some proliferation of fibrous connective about the few pseudotubercles developing in this organ, the fibrosis is for the most part diffuse along portal spaces, irrespective of whether there are ova or not, and in such tissues as the pulmonary and intestinal no fibrous connective forms. We are inclined, therefore, to believe that whatever toxic substances are responsible for the diffuse cellular infiltration of these areas also provoke the fibrosis, and that irritation by ova plays a minor rôle in these animals. Unisexual experimental infestations would be necessary for a finer analysis of this point.

The hepatic alterations, as seen in the rabbit and white rat, lack some of the characteristics of a true cirrhosis: there is scanty destruction of liver cells, practically no formation of pseudolobules, and no diffuse proliferation of bile ducts. Furthermore, the process starts along the inferior margin and then gradually extends towards the dome.

Schistosomal changes in the intestines of the rabbit consist of the formation of pseudotubercles and eosinophilic infiltration, but even though ova may be quite numerous, there are no acute inflammatory changes, no formation of granulation tissue, and no fibrosis of the submucosa or ulceration of the mucosa, as in man and monkeys. It seems as if ova were quite unable to traverse the intestinal mucosa in this animal.

In the white rat, worms or ova were never encountered in the intestinal wall, even though 15 to 20 blocks from various levels of the small and large intestine were examined for each animal. This might mean that adult worms in this species prefer veins other than the finer mesenteric radicles for oviposition, and that the portal vein and its intrahepatic branches are the habitat of choice in this animal. However, Lutz (*l. c.*), Brumpt[15] and others have seen ova and lesions in the intestine of rats; we cannot explain the discrepancy between their findings and ours.

Observations made while studying sections of liver and small intestine appear to us to be of importance in understanding the mechanism of extrusion of ova into the tissues. Ova or shells that had come to lie against the endothelial lining of capillaries and very small veins were several times seen in the act of being covered by cells continuous with those lining the blood vessel. This is the first step in the process by means of which the ova are excluded from the circulation and immobilized, while still lying within the basement membrane of the capillary. A few leukocytes soon gather about the ovum, and giant cells quickly envelop it. The next step, which must be rupture of the basement membrane of the capillary, was not directly observed, but is probably readily brought about by pressure of the ovum, as shown in Figure 41, aided in some instances by its spine, and by the slight inflammatory reaction which it provokes. The rôle played by the ova is a passive one. These observations afford an explanation of the way in which ova, such as those of *S. japonicum,* might come to pass into the tissues, even though their spine is so stunted as to be quite ineffective in piercing the blood vascular wall.

No complete pathological data are available on the early period of wandering of the schistosome parasites prior to their colonization of the portal and mesenteric veins of man and monkeys, but there being no fundamental anatomical differences between the blood and lymph circulation in these two species on the one hand, and that of rabbits and white rats on the other, there is no valid reason to suppose that the route followed by the parasite in the former animals should be very dissimilar to what obtains in the lower species. It might, therefore, be expected, that the lesions occurring

during this early stage in the higher animals above mentioned are similar in their localization, and perhaps also in their character, to those that we have described for the rabbit and white rat.

Pons and Hoffman [16], Girges [17, 18] and others have described a period of fever and eosinophilia as occurring in man for a number of days and even for several weeks, beginning 40 or 50 days after infestation. This time marks the attainment of sexual maturity by the schistosome worms and the beginning deposition of ova in the tissues. We noted in our experimental animals that, after attainment of adult size, many of the worms die and begin to disintegrate. At the same time, the embryos that are being deposited with the ova in the tissues are also dying and being absorbed. The absorption of products of disintegration of both worms and ova by an already sensitized host probably accounts for the period of fever and eosinophilia, while the local irritation produced by the ova, and the inflammatory changes taking place about them, may also play a part. Faust, Jones and Hoffman (*l. c.*) have explained the eosinophilia by them observed in a few experimental animals at the beginning of oviposition as due to the "local response to these irritating foreign bodies [the ova]". These authors minimize the probable rôle of the maturing parasites, and do not consider the possible effect of absorption of products of disintegration of dead worms and embryos by an already sensitized host.

The second stage of the disease, as above described for our experimental animals, differs in several important respects from the corresponding stage of the infestation as seen in our human autopsy material and in monkeys infested in the laboratory. In the latter two species, the intestinal changes are more marked; the spleen participates in the pathological picture to a much greater extent; and the hepatic cirrhosis differs in being more diffuse, in not showing a particular predilection for the inferior margin of the organ, and in not being accompanied by the marked venous and sinusoidal dilatation that is so prominent a feature of hepatic schistosomiasis of the rabbit and white rat, particularly of the former. It is our impression, also, that ova are of greater relative importance in the pathogenesis of human

schistosomal lesions than in the lower animals by us studied. Although certain variations are to be expected in the reaction of different hosts to a given pathogenic agent, it remains to be seen whether some of these differences cannot be explained—as far as man is concerned, at least—by the fact that our animals were subjected to a single, moderately heavy infestation, while the disease in the human subject usually is the result of repeated exposure and extends throughout more prolonged periods of time.

CONCLUSIONS

1. Penetration of cercariae of *S. mansoni* through the skin of the rabbit takes place mainly between the openings of hair follicles, and not down these structures.

2. The young parasites leave the skin mainly by way of the lymphatic channels.

3. The route followed by young parasites from the portal of entry to their definitive localization in branches of the mesenteric and portal veins is exclusively intravascular.

4. Young parasites are able to pass along the hepatic circulation and out of the liver for a second circuit of the lungs.

5. The initial cellular response on the part of the rabbit to invasion by cercariae is with pseudoeosinophilic infiltration of the corium and regional lymph glands.

6. During the first 10 days after inoculation there is a general response on the part of the rabbit in the form of increased production of pseudoeosinophils in the bone-marrow and a slight acute splenic tumor.

7. Morbid changes during the period of wandering of the schistosomules affect mainly the lungs, liver and kidneys, and are due in part to obstruction of capillaries and the occasional passage outside them of the parasites, and in part to the discharge of noxious substances.

8. None of the lesions provoked by immature parasites during their passage through various organs results in permanent damage, except for atrophy of occasional glomeruli.

9. The usual cellular reaction to the presence of young and adult parasites and to ova is with infiltration by lymphocytes, plasma cells, eosinophils and histiocytes. Eosinophils

predominate after the 30th to the 40th day, which marks the attainment of full development by the parasites.

10. Young parasites, mature living and dead worms, and ova may excite the formation of epithelioid cells. This response is characteristically seen about dead adult parasites.

11. A pseudotubercle begins as a slight infiltration of small round cells and eosinophils, followed by formation of foreign-body giant cells about which epithelioid cells then develop.

12. Most of the morbid alterations seen during the course of the disease are the result of the presence of the parasites themselves, acting by mechanical damage, by the liberation of noxious substances and products of disintegration, and by the extrusion of pigment.

13. In the rabbit and white rat, schistosome ova play a relatively minor rôle in the evolution of morbid alterations.

14. Tissue changes in rabbits after maturation of the parasites affect mainly the liver, lungs, intestines and mesenteric lymph glands. In the white rat, the intestinal tract is little, if at all, involved and the disease is mainly hepatic.

15. In the rabbit, the disease is mainly characterized by the blood vascular changes, with marked dilatation, polypoid endophlebitis and endarteritis, and extensive epithelioid cell reaction about dead worms.

16. Splenic changes are of the nature of a general response to the parasitic infestation and to the deposition of pigment.

17. Localization of adult worms in branches of the pulmonary arteries probably results from passage of parasites out of the liver by way of the dilated intrahepatic portal veins, sinusoids and efferent veins.

18. Young worms may remain in the lungs and there develop, though imperfectly.

19. Hepatic fibrosis appears to be secondary mainly to the presence of parasites and their products, and to a lesser extent, to the deposition of ova.

20. The mode of extrusion of ova appears to be as follows: (*a*) Adhesion of the ovum to the inner lining of the capillary; (*b*) immobilization and exclusion from the blood current by growth of endothelial cells of the inner lining of the capillary over the ovum, and (*c*) disruption of the base-

ment membrane of the capillary by pressure of the ovum aided by the inflammatory reaction which it provokes.

21. Schistosomiasis in the rabbit and white rat differs in various important respects from the disease as seen in man.

The author is greatly indebted to Professor William A. Hoffman and his assistant, Mr. J. L. Janer, for the experimental inoculation of the animals utilized for this study.

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DESCRIPTION OF FIGURES

All photographs are of rabbit tissues stained with hematoxylin and eosin, unless otherwise specified.

FIG. 1. Young parasite in lymphatic of corium. Penetration appears to have been obliquely through opening of hair follicle. 4 hours. 400X

FIG. 2. Young parasite within hair follicle. 9 hours. 400X

FIG. 3. Young parasite still within epidermis, along which it has bored horizontally. Size of penetration tunnel in part probably an artifact. 4 hours. 400X

FIG. 4. Young parasite within lymphatic deeper in corium. Edema of dermis. 4 hours. 320X

DESCRIPCION DE LAS LAMINAS

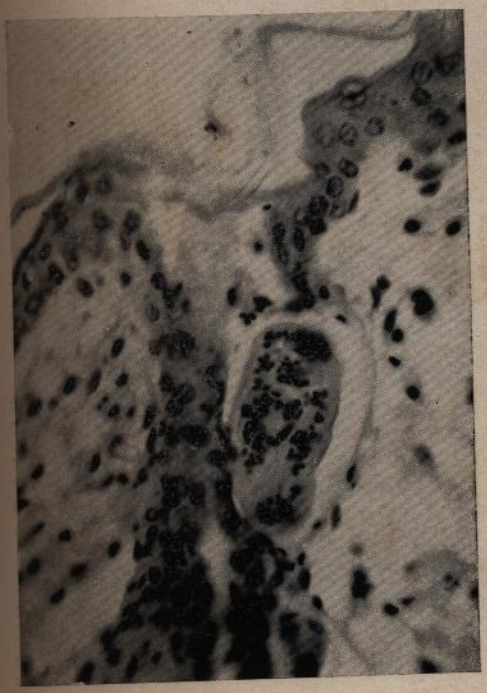
Todas las láminas son de cortes de tejidos del conejo teñidos con hematoxilina y eosina, a menos que se advierta otra cosa.

LÁMINA 1. *Esquistosómulo en un linfático del corion, habiendo al parecer penetrado oblicuamente por la apertura del folículo piloso. 4 horas. 400X*

LÁMINA 2. *Esquistosómulo dentro de un folículo piloso. 9 horas. 400X*

LÁMINA 3. *Esquistosómulo en vías de penetración a lo largo de la epidermis. El tamaño del túnel producido por el parásito quizá se haya exagerado en el proceso de preparación de los tejidos. 4 horas. 400X*

LÁMINA 4. *Esquistosómulo en un linfático de las profundidades del corion; ligero edema en su vecindad. 4 horas. 320X*



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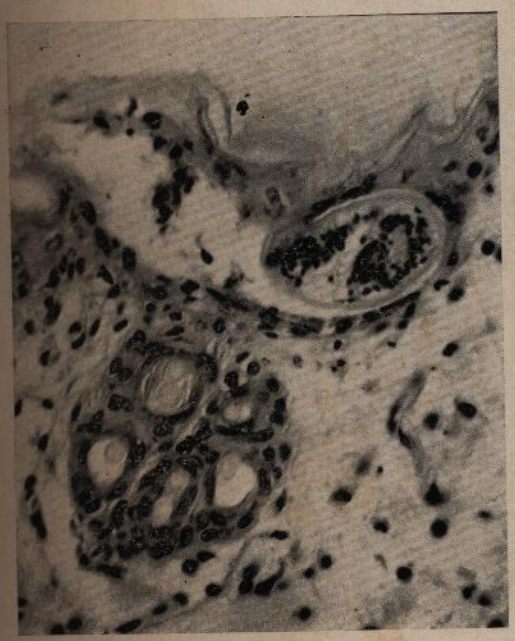

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PATHOLOGY OF SCHISTOSOMIASIS MANSONI

FIG. 5. Young parasites in lymphatics of papillary plexus next to opening of hair follicles. Focus of pseudoeosinophilic infiltration between the parasites, and edema of corium. 4 hours. 400X

FIG. 6. Intense pseudoeosinophilic infiltration about necrotic parasite in corium. 8 hours. 400X

FIG. 7. Young parasite in marginal sinus of popliteal lymph gland. 25 hours. 450X

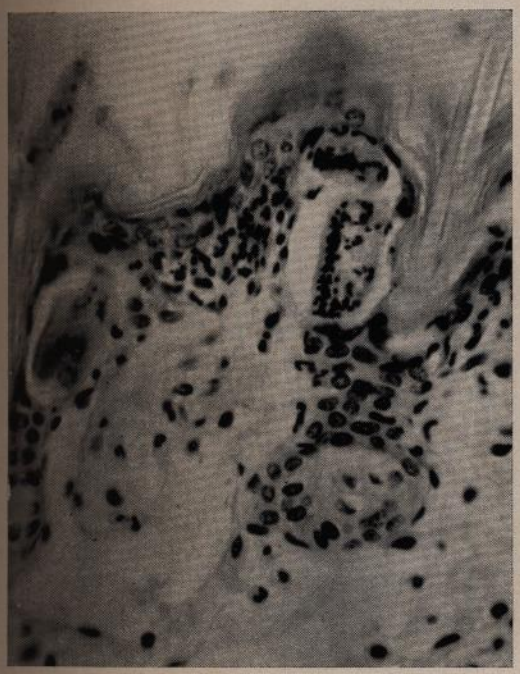
FIG. 8. Young parasite in medullary sinus of popliteal lymph gland. 25 hours. 450X

LÁMINA 5. *Parásitos jóvenes en linfáticos del plexo papilar en la inmediata vecindad de folículos pilosos; foco de infiltración seudoeosinófila entre los vermes, con edema del corion. 4 horas. 400X*

LÁMINA 6. *Intensa infiltración por seudoeosinófilos en el corion, en derredor de un verme joven necrosado. 8 horas. 400X*

LÁMINA 7. *Verme joven en el seno marginal de un ganglio popliteo. 25 horas. 450X*

LÁMINA 8. *Verme joven en un seno medular de un ganglio popliteo. 25 horas. 450X*



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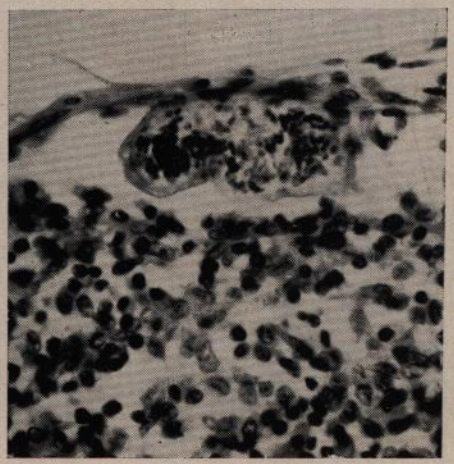

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FIG. 9. Young parasite in inguinal node entering lymphoid tissues from marginal sinus. 25 hours. 400X

FIG. 10. Diffuse pseudoeosinophilic infiltration of popliteal lymph node. 13 hours. 400X

FIG. 11. Focus of broadening of alveolar walls due to eosinophilic and round-celled infiltration about alveolar capillary previously occupied by young parasite. 49 hours. 400X

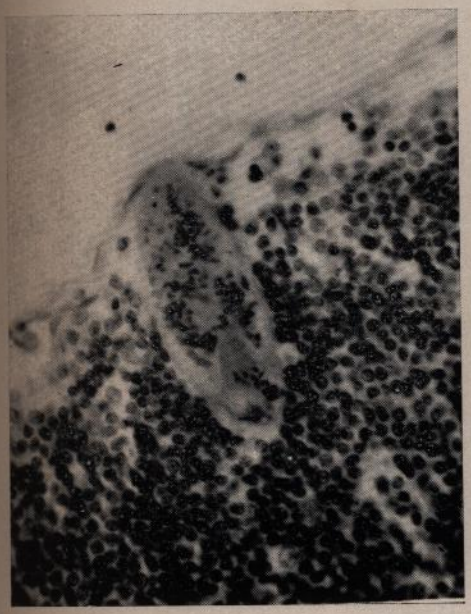
FIG. 12. Young parasite within alveolar capillary; pyknosis of endothelial cells, but no leukocytic infiltration. 4 days. 430X

LÁMINA 9. *Parásito joven pasando del seno marginal a los tejidos linfoides de un ganglio inguinal. 25 horas. 400X*

LÁMINA 10. *Infiltración difusa de un ganglio popliteo por seudo-eosinófilos. 13 horas. 400X*

LÁMINA 11. *Foco de engrosamiento de las paredes alveolares por infiltración con eosinófilos y células redondas, en derredor de un capilar previamente obstruído por un verme joven. 49 horas. 400X*

LÁMINA 12. *Parásito joven dentro de un capilar alveolar; picnosis de las células endoteliales, pero sin infiltración leucocitaria. 4 días. 430X*



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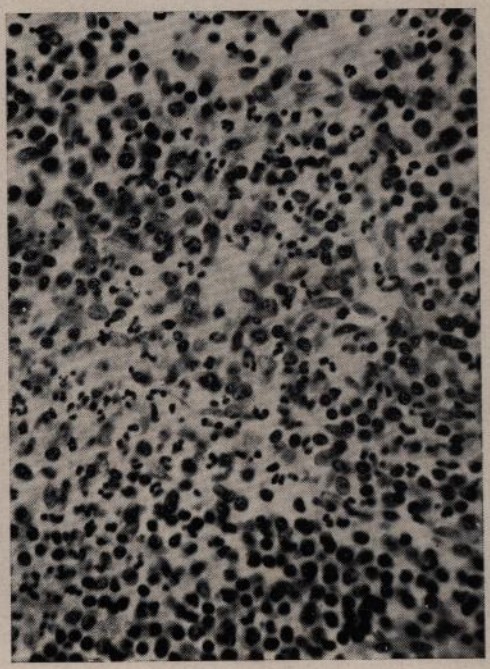

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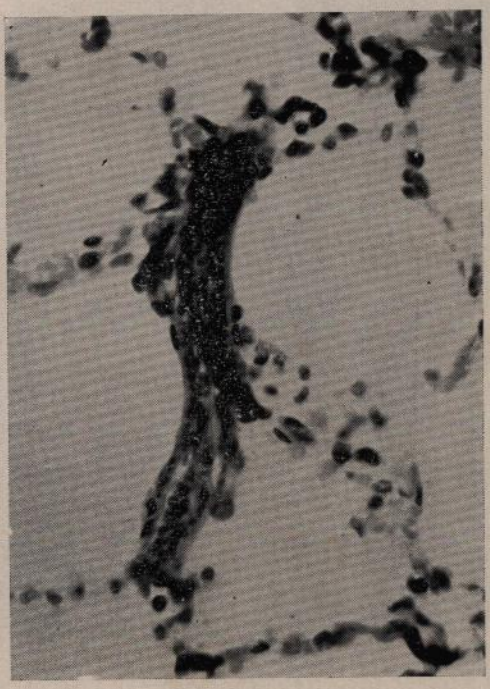

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FIG. 13. Young parasite within subpleural capillary surrounded by round cells and eosinophils. Slight thickening of pleura. Note pyknosis of endothelial cells of capillary. 5 days. 430X

FIG. 14. Star-shaped focus of congestion and round-celled infiltration about disintegrating schistosomule in alveolar capillary of lung. 5 days. 400X

FIG. 15. Eosinophilic infiltration of alveolar walls and spaces; large syncytium within acinus. Arrow points to disintegrating parasite in air sac. 50 days. 150X

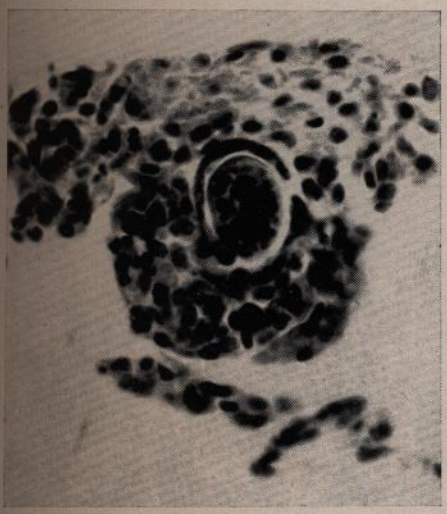
FIG. 16. Polyp composed of epithelioid cells and occasional giant cells, extending from intima of pulmonary vein to fill lumen. Round-celled and eosinophilic infiltration of surrounding tissues. 50 days. 150X

LÁMINA 13. *Verme joven rodeado de células redondas dentro de un capilar debajo de la pleura, ligeramente engrosada. Picnosis del revestimiento endotelial del vaso. 5 días. 430X*

LÁMINA 14. *Foco de congestión pulmonar en forma de estrella con esquistosómulo desintegrándose en su centro; infiltración con células redondas. 5 días. 400X*

LÁMINA 15. *Infiltración con eosinófilos en las paredes alveolares y acini. La flecha señala un verme en proceso de desintegración situado dentro de un acini. Nótese la gran célula sincitial. 50 días. 150X*

LÁMINA 16. *Pólipo compuesto de células epitelioides y alguna que otra célula gigante, extendiéndose a partir de la íntima de una vena pulmonar hasta ocupar su luz. Infiltración de los tejidos vecinos por células redondas y eosinófilos. 50 días. 150X*



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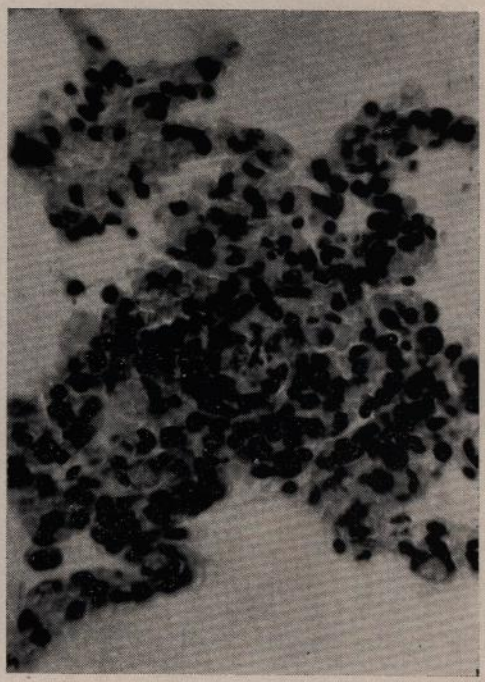

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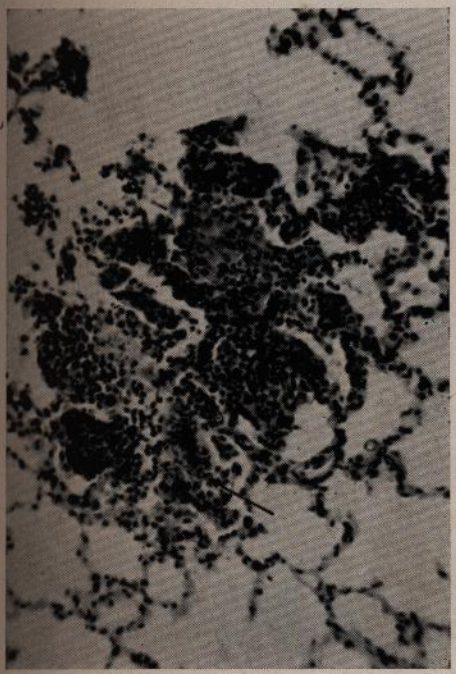

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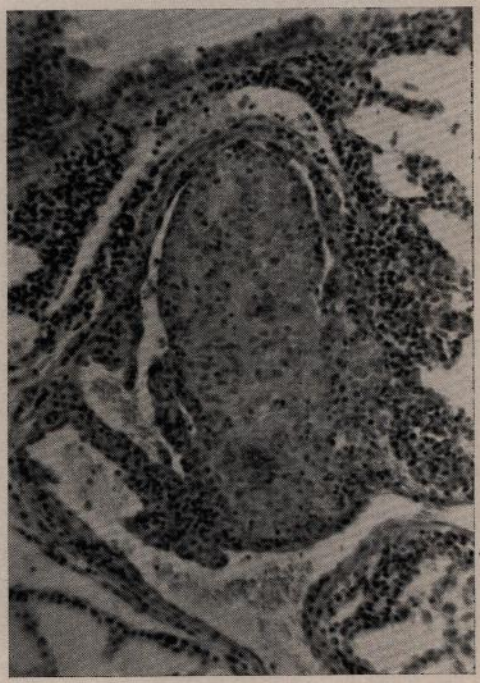

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FIG. 17. Focus of eosinophilic infiltration about empty egg shell in lung. 120 days. 150X

FIG. 18. Below, dilated pulmonary blood vessel full of necrotic worms. Marked attenuation of vascular wall. Eosinophilic infiltration and necrosis of surrounding parenchyma. Beneath pleura, dilated alveoli lined by cubical epithelium. Thickening of pleura to the right. 75 days. 100X

FIG. 19. Large dilated artery containing dead worms, some calcified, surrounded by clumps of eosinophils. Thickening of elastic membrane in places; thinning and fragmentation in others. Small blood vessel at top shows filling of lumen with mass of epithelioid cells; the central clump of pigment probably represents remnants of worm. Weigert's elastica-saffranin. 75 days. 100X

LÁMINA 17. *Foco de infiltración eosinófila en el pulmón en derredor de una cubierta ovular. 120 días. 150X*

LÁMINA 18. *En la parte inferior: vaso pulmonar dilatado y repleto de vermes muertos; notable adelgazamiento de las paredes vasculares e infiltración eosinófila y necrosis del parenquima pulmonar. Por debajo de la pleura vénse alveolos dilatados y revestidos de epitelio cuboide. 75 días. 100X*

LÁMINA 19. *Arteria pulmonar dilatada conteniendo vermes muertos, algunos calcificados, rodeados por grupos de eosinófilos. Engrosamiento de la túnica elástica en algunos parajes; fragmentación y adelgazamiento en otros. Hacia el borde superior de la lámina, pequeño vaso sanguíneo con su luz obstruída por células epitelioides; el pigmento en el centro parece provenir de los restos de un verme. Tinte de Weigert para elástica, con safranina. 75 días. 100X*

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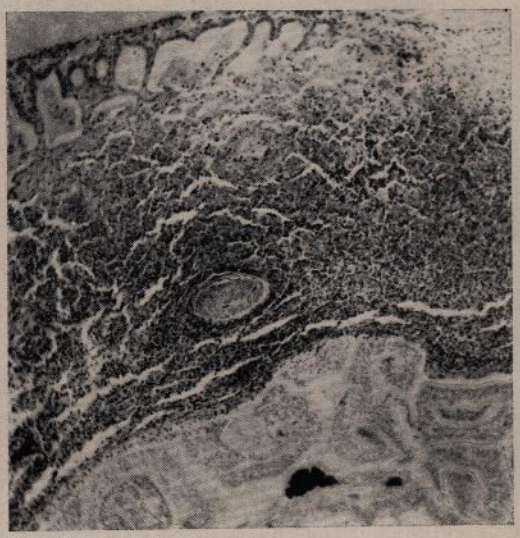

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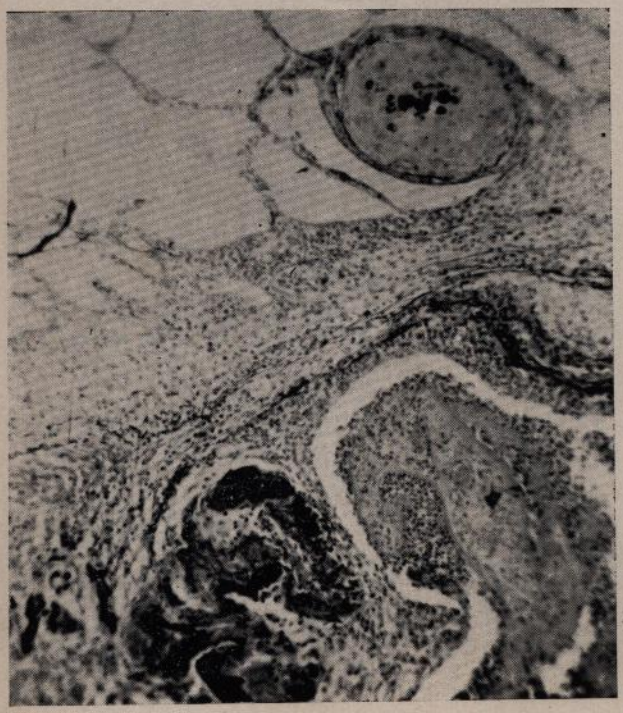

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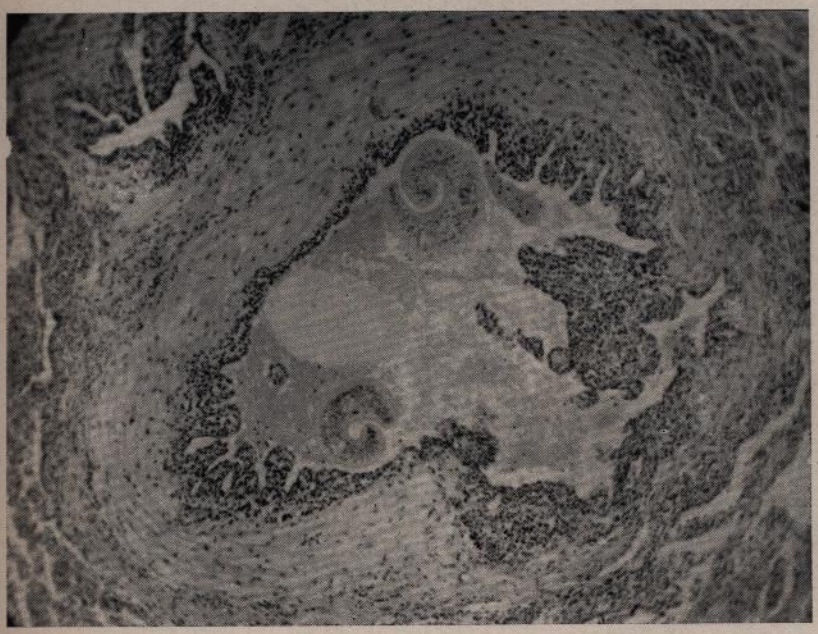
FIG. 20. Dilated pulmonary artery containing 2 living worms. Great hypertrophy and edema of muscle coat. Eosinophilic infiltration of intima with formation of small polyps. 120 days. 80X

FIG. 21. Obstruction of lumen of pulmonary blood vessel by polyp composed of epithelioid cells. In center, eosinophilic infiltration about disintegrating parasite; pigmented tubular space at lower end of intravascular mass represents intestinal tube of worm. 120 days. 100X

LÁMINA 20. *Arteria pulmonar dilatada conteniendo dos vermes vivos. Hipertrofia y edema de la túnica media e infiltración eosinófila de la íntima con formación de pequeños pólipos. 120 días. 80X*

LÁMINA 21. *Pólipo compuesto de células epitelioides obstruyendo el lumen de un vaso pulmonar. Al centro, infiltración eosinófila alrededor de un parásito casi totalmente desintegrado. 120 días. 100X*



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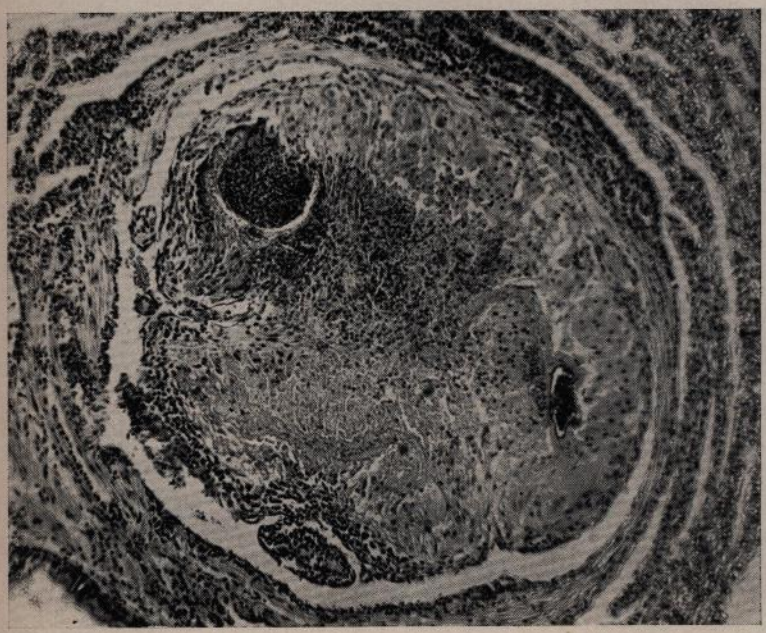

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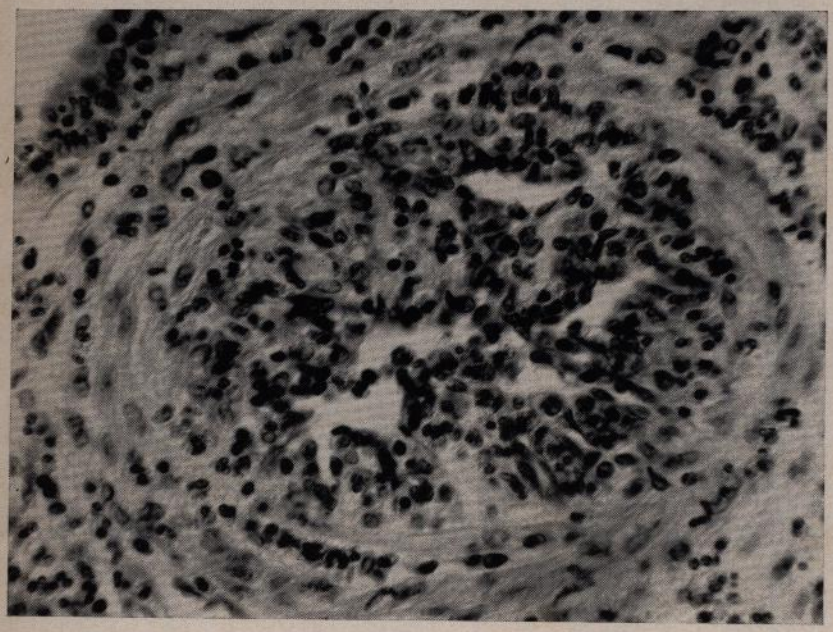
FIG. 22. Polypoid endarteritis of medium-sized pulmonary artery. 75 days. 400X

FIG. 23. Well-preserved parasite in pulmonary artery; eccentric endarteritis due to infiltration with eosinophils and lymphocytes. Hypertrophy of media and eosinophilic infiltration of perivascular tissues. 75 days. 150X

LÁMINA 22. *Endarteritis poliposa de una arteria pulmonar de mediano calibre. 75 días. 400X*

LÁMINA 23. *Verme vivo en una arteria pulmonar; endarteritis excéntrica por infiltración con eosinófilos y linfocitos; hipertrofia de la túnica media e infiltración eosinófila de los tejidos perivasculares. 75 días. 150X*



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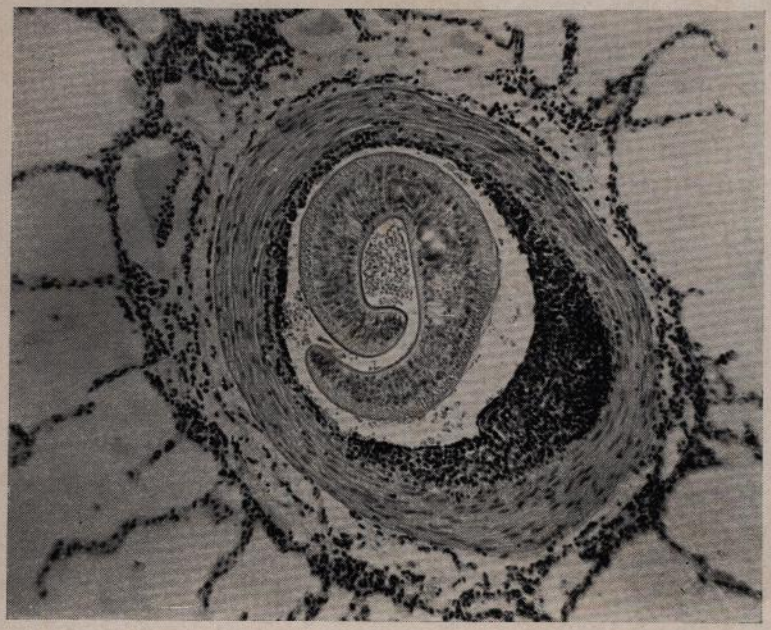

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FIG. 24. Stunted living worms in alveolar capillaries. Infiltration of alveolar septa with eosinophils. 75 days. 100X

FIG. 25. Focus of necrosis and eosinophilic infiltration about dead worm in lung. 120 days. 80X

FIG. 26. Replacement of wall of pulmonary blood vessel by epithelioid cells; dead worms and eosinophils in center. Note absence of epithelioid cell reaction about living worms to right. 120 days. 100X

LÁMINA 24. *Vermes pobremente desarrollados dentro de capilares alveolares; infiltración con eosinófilos. 75 días. 100X*

LÁMINA 25. *Foco de necrosis e infiltración eosinófila en el pulmón en derredor de un verme muerto. 120 días. 80X*

LÁMINA 26. *Reemplazamiento de la pared de un vaso sanguíneo pulmonar por células epitelioides; al centro, vermes muertos y eosinófilos. Nótese que no hay células epitelioides en derredor de los vermes vivos en los vasos sanguíneos a la derecha de la lámina. 120 días. 100X*

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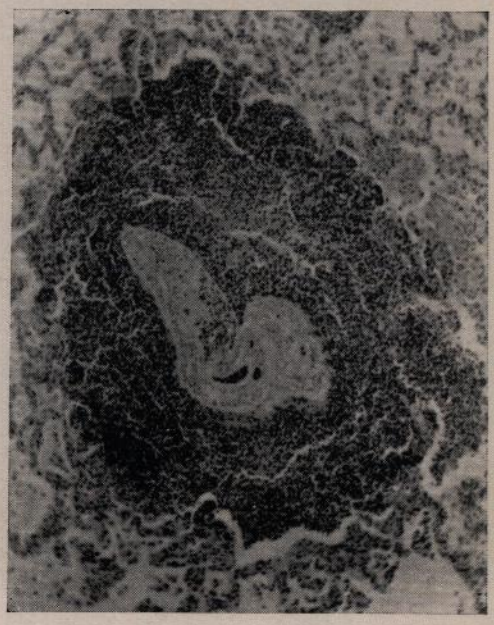

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FIG. 27. Cirrhosis of liver at 120 days. Larger nodules represent dilated veins. Note localization of process along inferior margin.

LÁMINA 27. *Hígado cirrótico a los 120 días de la inoculación. Los nódulos más grandes representan venas dilatadas y tortuosas. Nótese la localización del proceso a lo largo del margen inferior de la víscera.*

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FIG. 28. Schistosomule in intrahepatic portal radicle. Beginning round-celled infiltration of portal space. 10 days. 430X

FIG. 29. Schistosomule in hepatic sinusoid. 10 days. 450X

FIG. 30. Schistosomule in efferent vein of liver. 10 days. 360X

FIG. 31. Beginning polypoid endophlebitis of intrahepatic portal radicle. 20 days. 360X

LÁMINA 28. *Esquistosómulo en una vena interlobulillar; iníciase la infiltración del espacio periportal con células redondas. 10 días. 430X*

LÁMINA 29. *Esquistosómulo en un sinusoide hepático. 10 días. 450X*

LÁMINA 30. *Esquistosómulo en una vena eferente del hígado. 10 días. 360X*

LÁMINA 31. *Comienzo de la endoflebitis poliposa en una vena portal intrahepática. 20 días. 360X*

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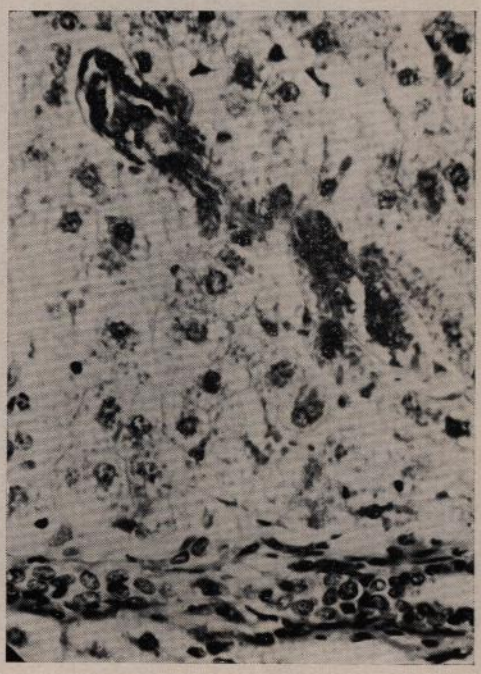

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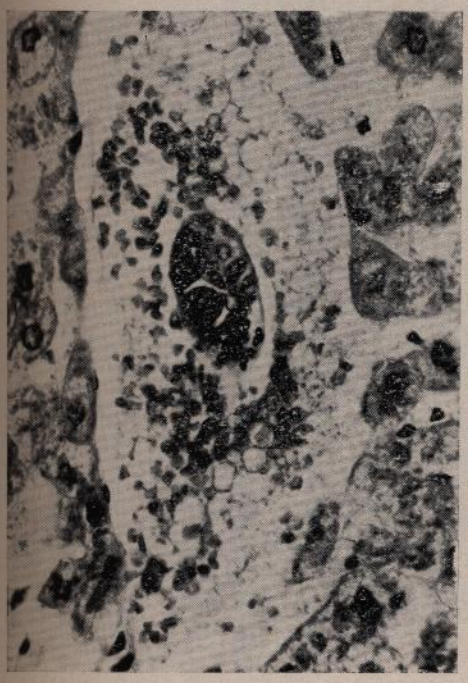

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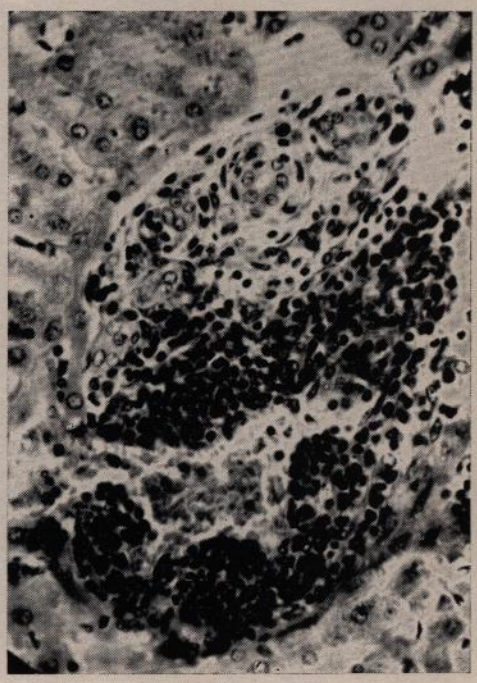

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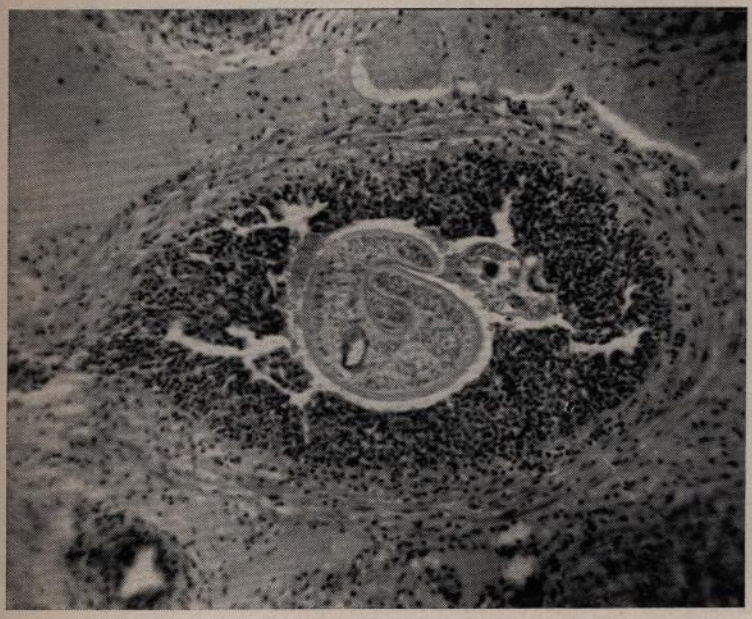
FIG. 32. Polypoid endophlebitis of portal vein about living parasites. Note marked dilatation of lymphatics about vein. 30 days. 100X

FIG. 33. Pseudotubercle about ovum in portal space. Note intimal polyp in small vein at top and cellular infiltration. 50 days. 100X

LÁMINA 32. *Endoflebitis poliposa de una vena portal intrahepática en derredor de vermes vivos. Nótese la gran dilatación de los linfáticos alrededor de la vena. 30 días. 100X*

LÁMINA 33. *Seudotubérculo en derredor de un huevecillo. Pequeña proyección poliposa en una venilla hacia la parte superior de la lámina. Infiltración del espacio de Kiernan con células redondas y eosinófilos. 50 días. 100X*



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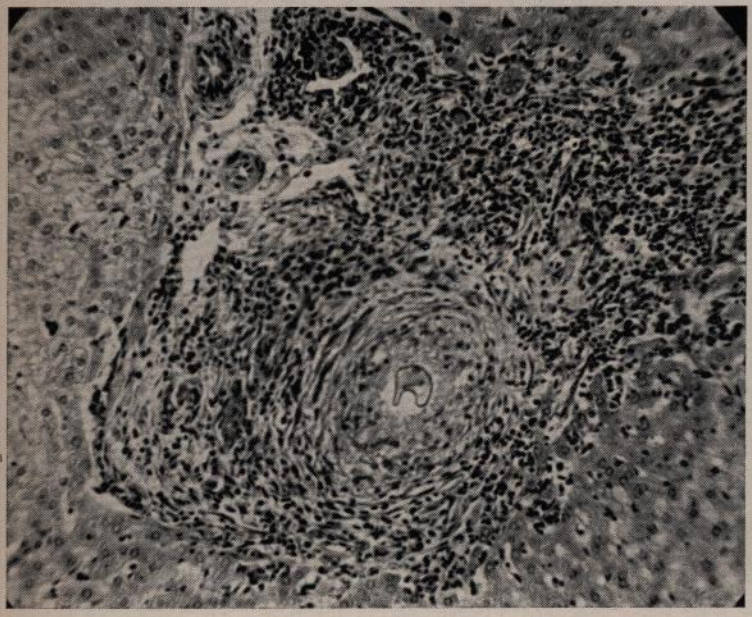

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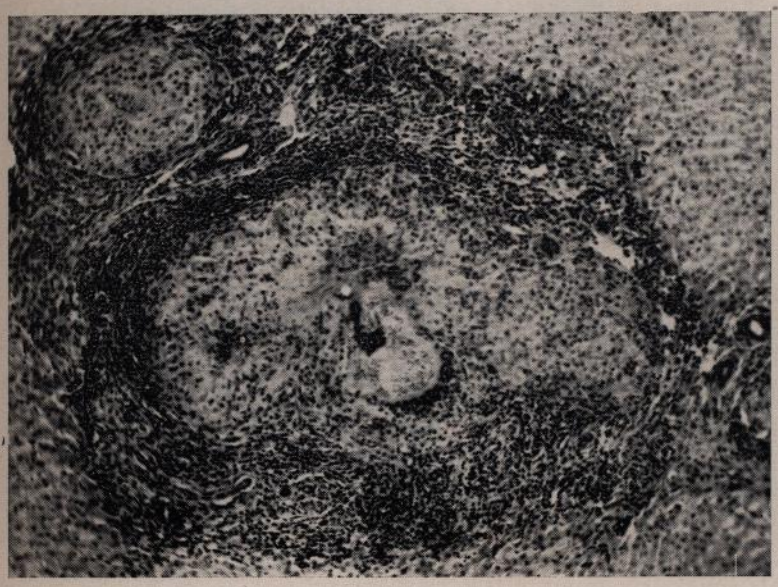
FIG. 34. Complete replacement of wall, and filling of lumen, of portal vein by epithelioid cells. Necrotic worm in center. Intense round-celled and eosinophilic infiltration of portal space. 50 days. 80X

FIG. 35. Dilatation of portal vein and polypoid endophlebitis. Ova and small pseudotubercles in some of intimal polyps. 50 days. 80X

LÁMINA 34. *Reemplazamiento total de la pared de una vena portal intrahepática por células epitelioides que han llegado a obstruir el lumen; al centro, verme muerto. Infiltración intensa del espacio periportal con células redondas y eosinófilos. 50 días. 80X*

LÁMINA 35. *Dilatación de una vena portal y endoflebitis poliposa de la misma. Huevecillos y pequeños seudotubérculos en algunos de los pólipos de la íntima. 50 días. 80X*



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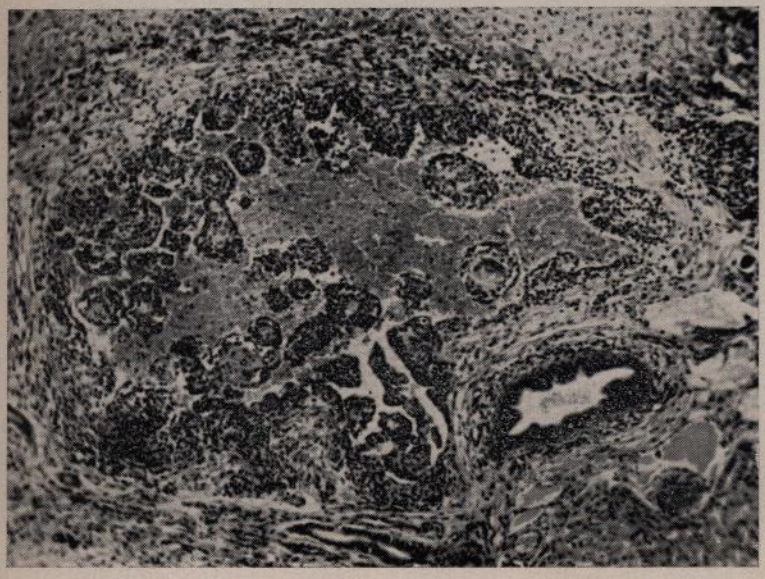

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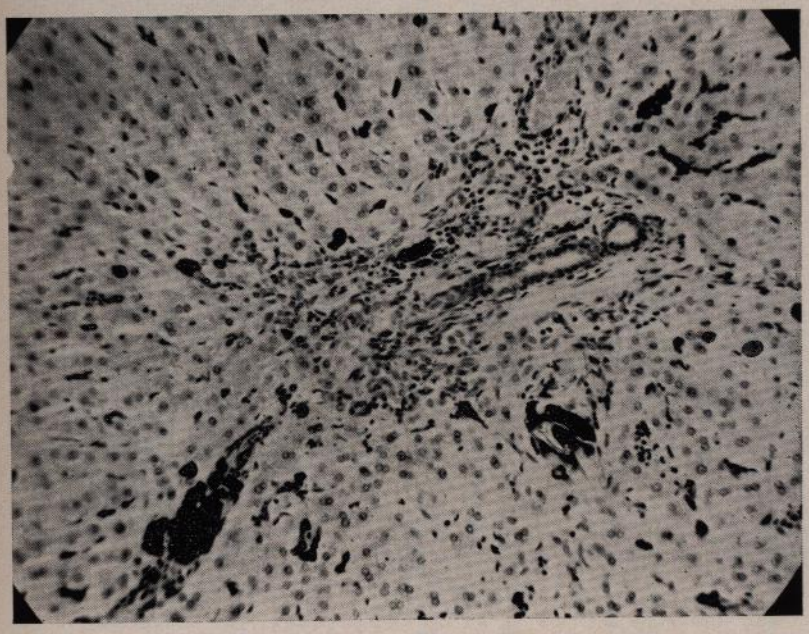
FIG. 36. Pigment within phagocytes of portal space and neighboring Kupffer cells. The larger masses below center of field are in foreign-body giant cells surrounding ova. 150 days. 150X

FIG. 37. One ovum lies free in lumen of interlobular venule and still contains an embryo. The egg shell below is being covered by endothelium continuous with that of capillary lining, but is still within basement membrane. Note cell infiltration about egg shell. 87 days. 496X

LÁMINA 36. *Fagocitosis del pigmento en los espacios portales y células de Kupffer más cercanas. Los grandes grumos hacia la parte inferior de la lámina están situados dentro de células gigantes alrededor de huevecillos. 150 días. 150X*

LÁMINA 37. *Un huevecillo con su embrión dentro de la luz de un capilar interlobulillar y una cubierta ovular que está siendo revestida por el endotelio capilar, pero que aún no ha perforado la membrana basal. Nótese que ya hay infiltración celular en derredor de la cubierta. 87 días. 496X*



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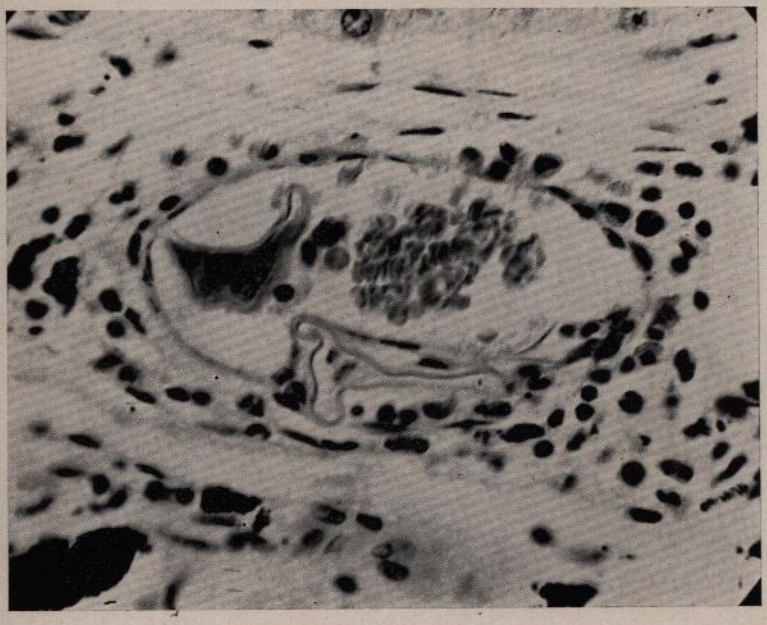

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FIG. 38. Group of egg shells within interlobular venule of liver completely covered by endothelium but still within basement membrane. 150 days. 400X

FIG. 39. Male and female worm in copula in submucosal venule of small intestine. 75 days. 100X

FIG. 40. Pseudotubercle about egg shells in submucosa of small intestine. 150 days. 150X

LÁMINA 38. *Grupo de cubiertas ovulares situadas dentro de un vaso interlobulillar del hígado y revestido por endotelio, pero sin perforar la membrana basal. 150 días. 400X*

LÁMINA 39. *Vermes acoplados en una venilla de la submucosa del intestino delgado. 75 días. 100X*

LÁMINA 40. *Cubiertas ovulares en un seudotubérculo de la submucosa del intestino delgado. 150 días. 150X*

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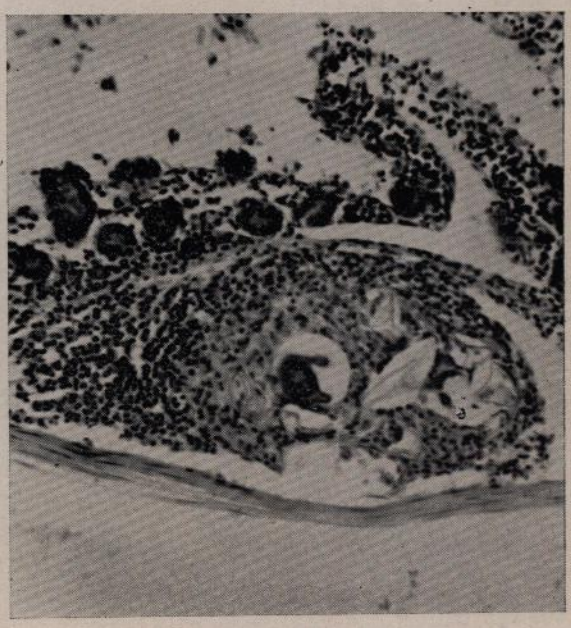

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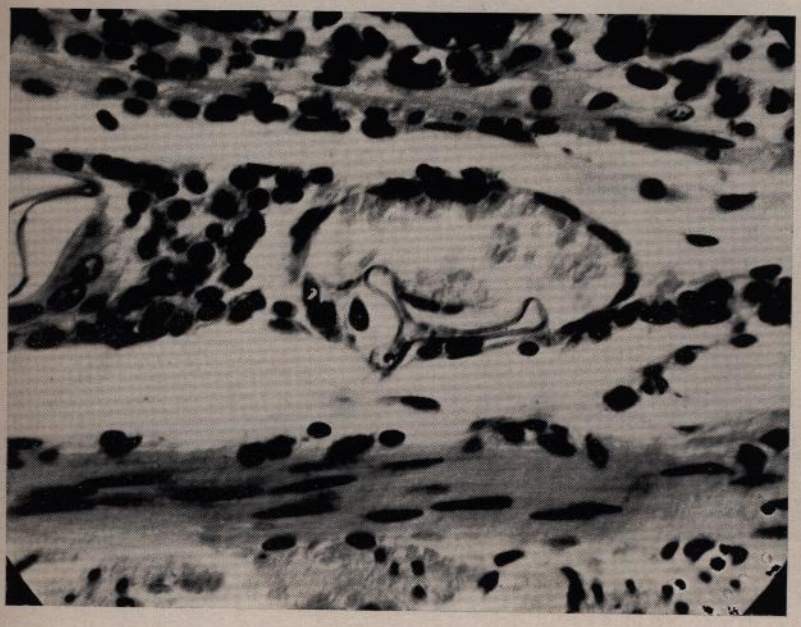
FIG. 41. Egg shell in submucosa of small intestine lying between basement membrane of venule and endothelial cells which have not yet completely covered it. Note few round cells about shell, and that the latter is about to perforate basement membrane. 150 days. 400X

FIG. 42. Group of egg shells within venule of submucosa of small intestine completely covered by endothelium, but still within basement membrane of capillary. 150 days. 496X

LÁMINA 41. *Huevo en la submucosa del intestino delgado, situado entre la membrana basal de un vaso capilar y las células endoteliales que se extienden sobre él para cubrirlo. Nótese acumulación de células redondas en torno al huevo, próximo a perforar la membrana basal. 150 días. 400X*

LÁMINA 42. *Grupo de cubiertas ovulares dentro de una venilla de la submucosa del intestino delgado, totalmente recubiertas por endotelio, pero todavía dentro de la membrana basal del capilar. 150 días. 496X*



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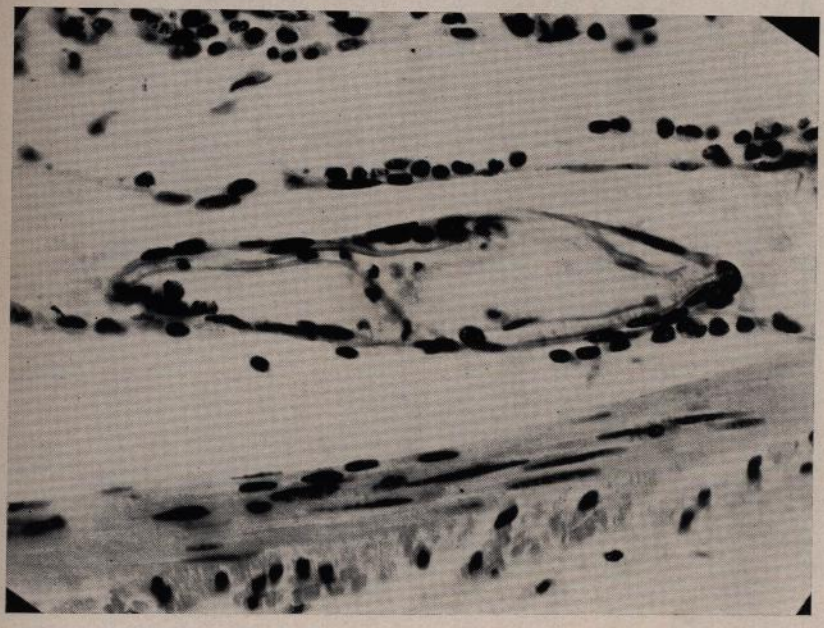

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FIG. 43. Large syncytium within pulmonary alveolus. White rat. 12 days. 310X

FIG. 44. Formation of giant cells in lung. Young schistosome parasite in lower right hand corner. White rat. 12 days. 310X

FIG. 45. Pseudotubercle developing in lung about adult parasite. Note pigment within epithelioid cells. White rat. 91 days. 150X

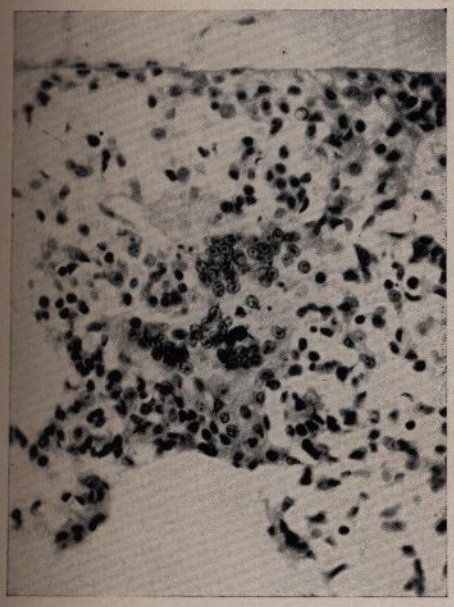
FIG. 46. Calcified schistosome parasites in margin of lung. White rat. 227 days. 80X

LÁMINA 43. *Gran célula sincitial dentro de un alveolo pulmonar. Rata albina. 12 días. 310X*

LÁMINA 44. *Formación de células gigantes en el pulmón. La flecha señala un parásito joven. Rata albina. 12 días. 310X*

LÁMINA 45. *Seudotubérculo formado en el pulmón alrededor de un parásito adulto. Nótese el pigmento dentro de algunas células epitelioides. Rata albina. 91 días. 150X*

LÁMINA 46. *Parásitos calcificados en el borde de un pulmón. Rata albina. 227 días. 80X*



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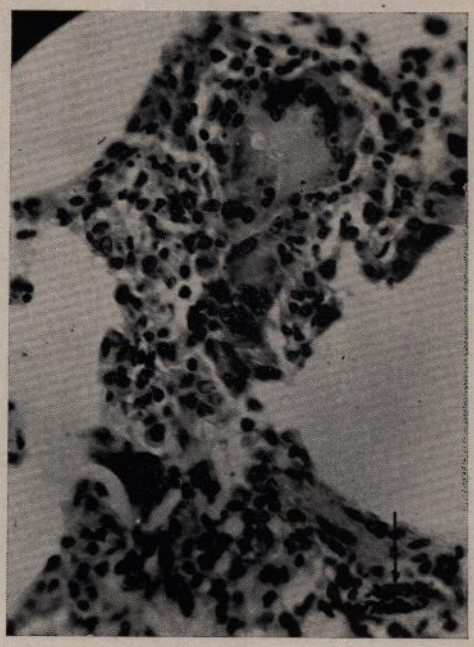

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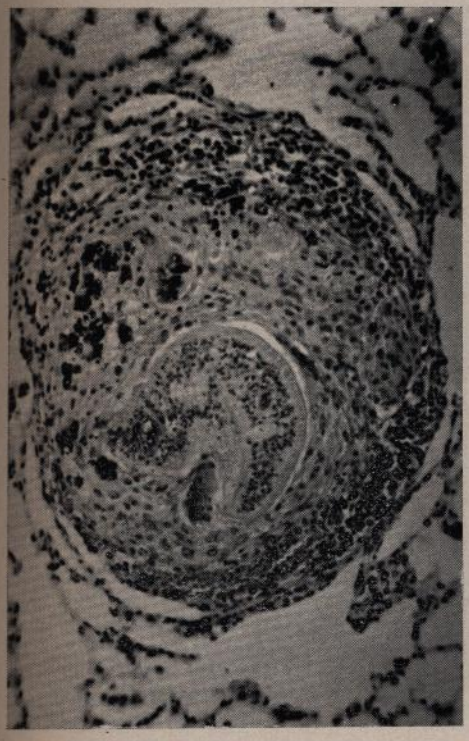

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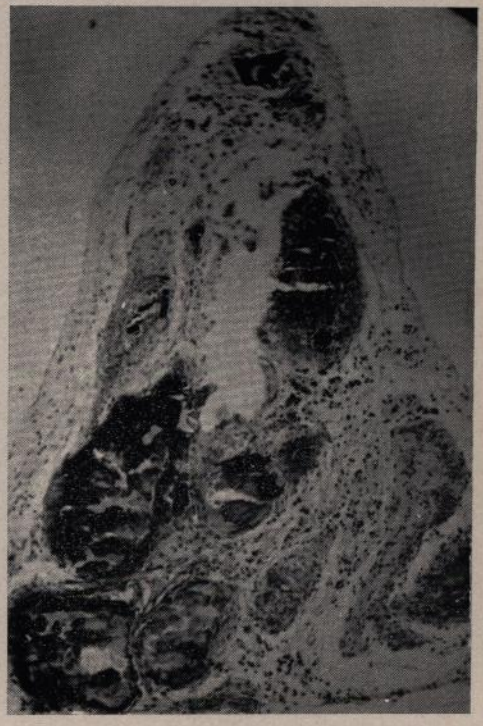

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FIG. 47. Focus of round-celled and eosinophilic infiltration about young parasite in hepatic sinusoid. White rat. 12 days. 310X

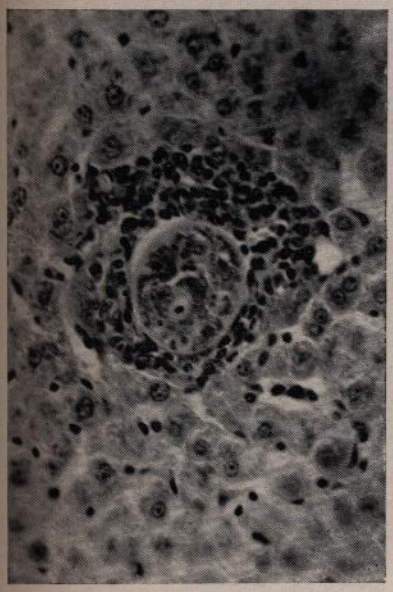
FIG. 48. Delicate diffuse fibrosis with formation of pseudolobules towards dome of liver. White rat. 271 days. 80X

FIG. 49. Fibrotic nodule developing in portal space about ova. White rat. 271 days. 150X

LÁMINA 47. *Foco de infiltración por células redondas y eosinófilos alrededor de un parásito joven situado en un sinusoide hepático. Rata albina. 12 días. 310X*

LÁMINA 48. *Ligera fibrosis con formación de seudolobulillos hacia la convexidad superior del hígado. Rata albina. 271 días. 80X*

LÁMINA 49. *Nódulo fibroso en un espacio periportal rodeando huevecillos. Rata albina. 271 días. 150X*



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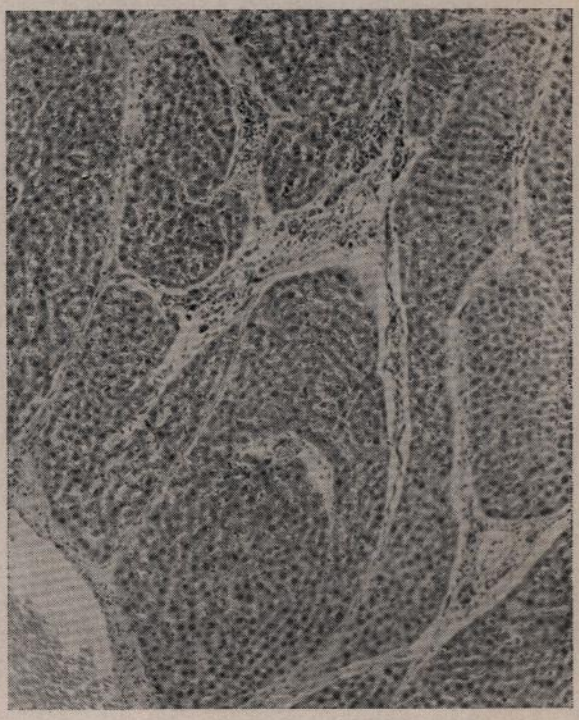

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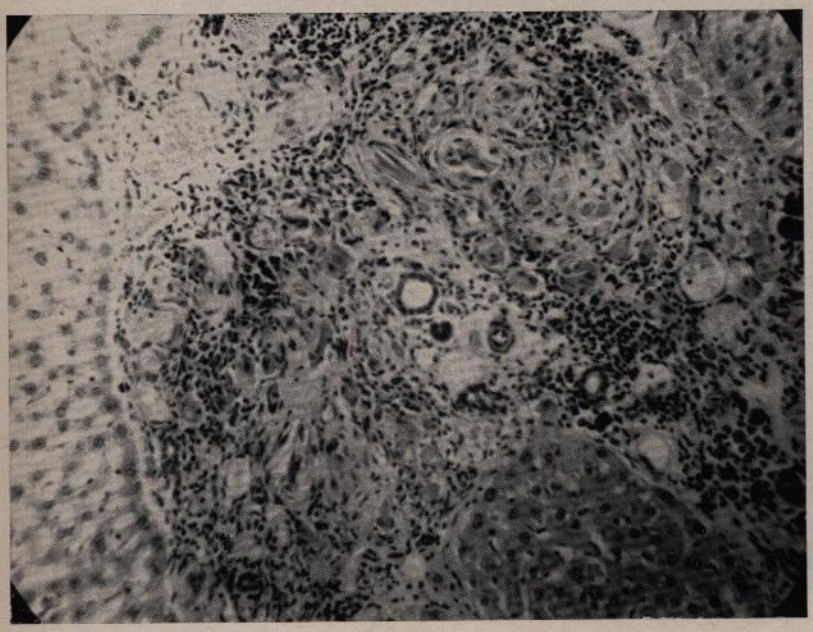

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FIG. 50. Pseudotubercle of liver with ovum in center. White rat. 271 days. 496X

FIG. 51. Great dilatation of portal veins filled with worms in inferior margin of liver. Note pseudotubercle to the right. White rat. 271 days. 80X

LÁMINA 50. *Seudotubérculo del hígado con un huevecillo al centro. Rata albina. 271 días. 496X*

LÁMINA 51. *Gran dilatación de las venas portales repletas de vermes en el borde inferior del hígado. Nótese dos seudotubérculos a la derecha. Rata albina. 271 días. 80X*

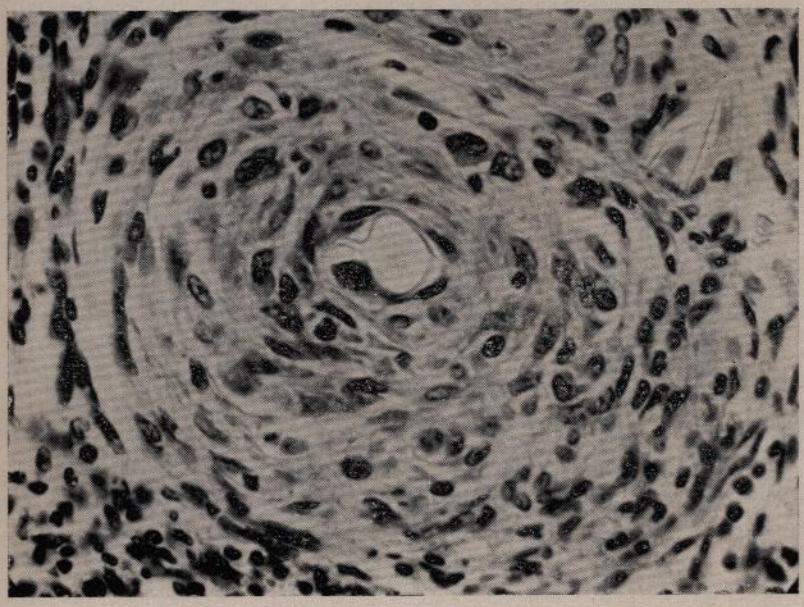

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FIG. 52 Pigment in germinal center of hyperplastic splenic follicle. White rat. 91 days. 496X

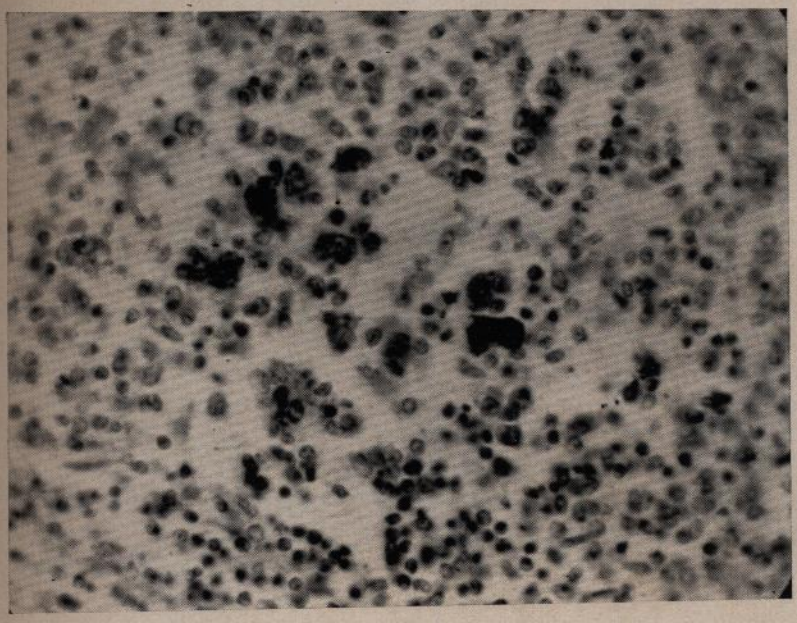
FIG. 53. Young parasite distending glomerular capillary. Note absence of hemorrhage or cell reaction. White rat. 7 days. 496X

FIG. 54. Young parasite within capillary of intertubular stroma of kidney. Sparse infiltration with round cells and eosinophils. White rat. 7 days. 496X

LÁMINA 52. *Pigmento depositado en el centro germinativo de un folículo esplénico hiperplásico. Rata albina. 91 días. 496X*

LÁMINA 53. *Parásito joven distendiendo un asa capilar de un glomérulo. Nótese que no ha habido hemorragia ni reacción celular. Rata albina. 7 días. 496X*

LÁMINA 54. *Parásito joven dentro de un capilar del estroma intertubular del riñón. Escasa infiltración con células redondas y eosinófilos. Rata albina. 7 días. 496X*



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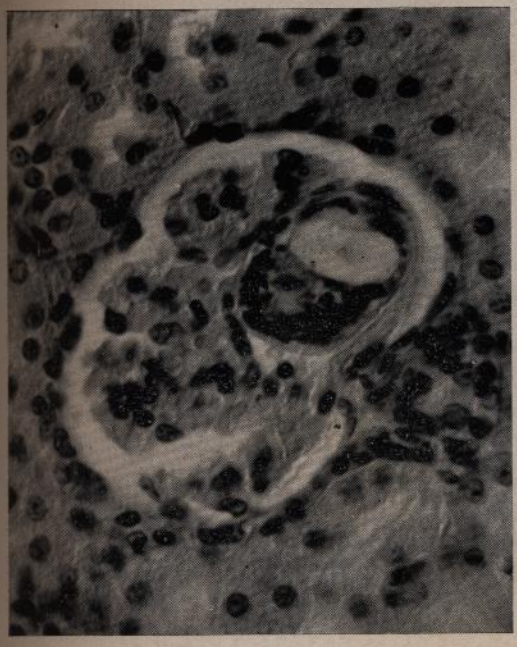

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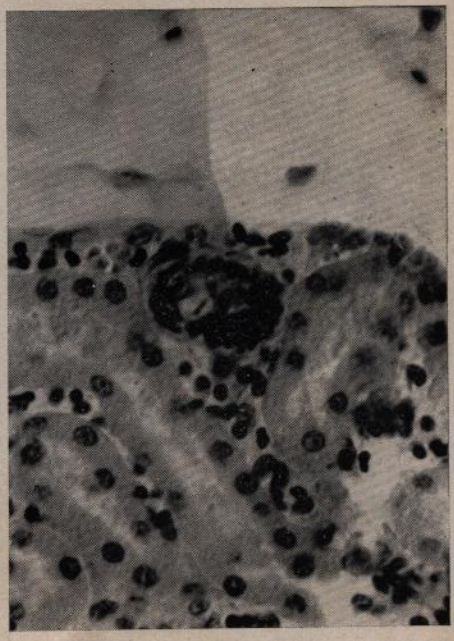

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