about the parasites in the lungs must be accounted for solely on the basis of the organism's presence as a foreign body in the host tissue. At this time there was a second "shift to the left" in the peripheral blood stream, without any corresponding rise in the total leukocyte counts or marked variation in the relative percentages of the various types of leukocytes. Later, the host became more or less adjusted to the presence of these foreign bodies, as indicated by the change in the type of cell found about the organisms as they lie in the lung capillaries. The predominant cell changed to the eosinophile and, slightly later, the majority of the cells were of the lymphoid and plasma cell type. All these local changes occurred in the experimental animals with but slight change in the findings in the peripheral blood stream.

This local defense reaction on the part of the mammalian host to the invading *Schistosoma mansoni* is quite similar to that reported by Bachman and Rodríguez-Molina [30], working with *Trichinella spiralis* in hogs. Infection and subsequent reinfection was associated with a local reaction on the part of the host, without a general response, such as a rise in the number of eosinophiles in the peripheral blood or an increase in the precipitin titer. In none of our animals was there any possibility of previous infection with *Schistosoma mansoni*. Hence it may be argued that the animals on which blood studies were made were possibly resistant to the infection and that this resistance was mainly a local condition, with but slight peripheral blood-stream indication of the body's defensive activity. Such a supposition is given credence by the fact that none of our rabbits showed any evidence of allergic disease, such as might be indicated by diarrheic stools, loss of appetite or loss in weight.

That the monkeys showed severe reactions to the infection and that one (monkey no. 2) became very dehydrated and died of the disease, is to be explained on the basis of the monkey's low resistance to invasion by the parasite. Monkey no. 1, which possibly would have survived the infection, attempted some defense, as demonstrated by a peripheral eosinophilia which rose as high as 20 per cent on the 57th day after infection. This, however, was during the toxic stage of the disease, much later than the period of invasion, and was characterized by fever, dysentery and other toxic signs and symptoms. It merely signified that this animal

had more resistance than the one which succumbed, since the infection was no heavier in the former than in the latter.

An alternative explanation of this lack of general defense reaction on the part of the experimental host, as indicated in the picture of the blood stream, may be suggested. None of our animals were given an overwhelming inoculation. Hence it may be that there were not large enough numbers of the schistosomula to incite a general response great enough to be registered by a rise in the total leukocyte count. The local reaction in this case was simply the result of the localized filtering out of the leukocytic cells, quite similar to that phenomenon shown by Doan and Zerfas [31], who found that such local filtration in human cases of lobar pneumonia caused great variations in total leukocyte counts. In the case of the schistosomes, the toxic stimulus was only strong enough to incite granulopoesis to the extent that an increase in the number of young neutrophiles appeared in the blood stream, but the increased numbers of leukocytes were utilized locally. Hence there was no increase in the total leukocyte count.

Again, between the 35th and the 44th day, the number of young neutrophiles in the peripheral blood stream rose, likewise without any marked change in the total blood counts. This time the rise was more marked than before and occurred at the time when the parasites were beginning to mature and eggs were being discharged by the females. These eggs were certainly present in the portal blood stream as early as, or before, they were pased in the feces. Eggs which got free in the portal blood stream were filtered out in the intrahepatic capillaries of this system. In the liver they produced a very marked local leukocytic infiltration, first neutrophilic in type, later eosinophilic, still later, lymphoid and plasma cell in character, and, finally, characterized by fibrous tissue hyperplasia, with the production of pseudotubercles about the eggs. Eggs deposited in the intestinal wall, likewise, showed to some extent these local cellular changes.

That these eggs were sufficient to produce the marked acute local reaction and less marked peripheral blood stream response, was demonstrated by the fact that they contained living miracidia, which secreted lytic substances which exuded through the porous shell, in addition to their mere presence

as foreign bodies, producing marked irritation by reason of their pointed lateral spine. The absence of more marked general response was accounted for by the same factors which were active when the metacercariae were passing through the pulmonary blood stream. The finding of eggs in the feces of the monkeys between the 37th and the 44th day adds to the evidence that these eggs were primarily responsible for this reaction. When one considers the manner in which the eggs break through the intestinal wall and the location of the parasites in the extrahepatic portion of the portal system, it is quite certain that eggs began to reach the liver even before they were passed in the feces.

Later, this developing blood picture changed somewhat: all the acute reaction subsided, and the variations in the young forms of neutrophiles were no more than would be expected under normal conditions. A relative peripheral lymphocytosis appeared after this last local acute reaction. At this time the local reaction changed from neutrophilic to eosinophilic, with increasing numbers of lymphoid and plasma cells. The only blood stream response was this relative lymphocytosis, which was more marked prior to the 37th day, but remained slightly higher than normal throughout the period of the experiment. This later change indicated that the lesions were becoming chronic and that fibrous tissue proliferation was beginning.

In the animals which developed a significant peripheral eosinophilia (rabbits nos. 2 and 4 and monkey no. 1) the blood counts showed increasing numbers of eosinophiles, beginning on the 37th day in rabbit no. 2, on the 44th day in rabbit no. 4, and on the 56th day in monkey no. 1. The increase in eosinophiles was purely a relative thing, since no significant variations occurred in the total counts (*i. e.* the eosinophiles were increased at the expense of the neutrophiles). The most marked eosinophilia was developed on the 44th day in rabbit no. 4, in which the eosinophiles in the peripheral blood stream increased to 14 per cent from 5 per cent on the previous day. This is but seven days after the last peripheral increase in young neutrophiles in the blood, a response which was probably due to the initiation of oviposition in the portal system and the filtration of eggs into the wall of the intestine and the liver tissue. In view of the fact that the beginning of egg laying incites an adequate local re-

sponse to these irritating foreign bodies, it is suggested that with the passage of time and the maturing of more of the parasites, more eggs are deposited than can be combated by the local reaction. The first acute reaction subsides and a relative peripheral eosinophilia occurs. This presumptive relationship between the deposition of eggs and their filtration into the tissues of the intestinal wall and in the liver on the one hand, and the increase of eosinophiles on the other, was not so well defined in the other animals as in rabbit no. 4, but it followed in such close sequence that these two events must bear some intimate relationship one to the other. The possibility that changes in the biologic activity of the maturing parasites result in some modified secretion or excretion incident to their metabolism, which could incite the eosinophilic response, has not been demonstrated.

With the exception of monkey no. 1, at no time during the experiments did the Sia test for euglobulin in the blood become positive. In this one animal the positive test occurred on the 65th day, at which time the animal had a severe dehydrating diarrhea. In any event the eosinophilia had developed several days previously, *i. e.* on the 56th day. Thus there appears to be no evidence of correlation between the rise in euglobulins in the blood and the development of the eosinophilia.

The period in which our experimental animals developed their peripheral eosinophilia corresponded roughly to the period of active clinical schistosomiasis, characterized by toxic manifestation of fever and dysentery (Girges [32]). Both our monkeys developed a dysentery and fever, but only one developed a peripheral eosinophilia, so characteristic of this stage. In one case of clinical schistosomiasis, which was seen by us, the history indicated exposure some 50 or 60 days previously. This patient had a severe diarrhea and an eosinophilia of over 50 per cent. The diagnosis was confirmed by the finding of eggs in the stools.

In none of the animals was the total erythrocyte count lowered to any marked degree. The occasional finding of a nucleated red cell, polychromatophilia and slightly lowered erythrocyte counts in some of the animals was the only evidence present of blood destruction. In most of the animals the reticulocyte counts, when made, were not excessively high (1.8 per cent—5.4 per cent). However, at autopsy of

these animals during the active period of the disease, the fatty bone marrow of the femur was grossly hyperplastic, as indicated by its beefy red color. The rabbits used were quite young and healthy and their bone marrow response was, no doubt, entirely adequate to cope with the relatively light infection.

The degree of anemia in our experimental and clinical cases seemed to depend upon the severity of the infection rather than on the duration of the condition. None of our animals had a very heavy infection, consequently the anemia was not marked. In the human cases the average number of red cells found was 4,545,000. The hemoglobin was low in most of the cases and the color index markedly reduced. An average of 70 per cent hemoglobin and an average color index of .75 was found. However, this deficiency in hemoglobin and in the number of red cells can not be said to be entirely the result of the infection, because nutritional and other causes of anemia could not be eliminated. Most of the cases belonged to the lower classes. In the laborers in the *colonias* the anemia was most marked and in the higher classes the reduction in red cells and hemoglobin was very slight. The total leukocytes varied from 9,500 to 3,500 cells per cumm. The longer the duration of the disease, the greater the tendency there was toward a leukopenia, with a relative lymphocytosis. The smallest numbers of lymphocytes were found in the more recent cases, and the largest numbers in the late cases. Just the reverse was true of the eosinophilia, which showed a tendency to decrease as the duration of the disease increased. A number of the tests were positive for euglobulin which was evidently not related to the eosinophilia.

As the infections became more chronic, the polymorphonuclear neutrophilic leukocytes were diminished, while the monocytes were relatively increased. These monocytes in the human series averaged 8 per cent.

The Sia test for euglobulins was positive in 8 of the 11 human cases studied. It was recorded as + or — in one case, but this case had also been diagnosed as syphilis by the Wassermann reaction. Hence it is impossible to say whether or not the doubtful euglobulin reaction was caused by the lues or the schistosomiasis.

The blood pictures in these few cases were characteristic of the stage of fibrous tissue hyperplasia. During the later stages of the disease, fibrous tissue encapsulates the eggs which have been deposited in the bowel wall and liver, and the blood stream response is that usually seen in very chronic stages of diseases characterized by such pathology, namely a lymphocytosis with a reduction in neutrophiles.

On the whole, the blood studies on these human cases of schistosomiasis mansoni are the expected sequence in a helminthic infection, which has provoked an active hematopoietic response during the prepatent and early patent periods, but has resulted in an adjustment of the host tissue to the parasite as the infection became chronic.

SUMMARY AND CONCLUSIONS

1. We have studied for the first time in experimental rats, rabbits and monkeys the stage-by-stage migration of *Schistosoma mansoni* through the tissues, from the time the cercaria penetrates the skin until the adult female worms oviposit in the mesenteric venules. Later, we have shown how tissue reactions to the worms and the eggs may, to some extent, have changed the residence of the worms and have influenced their subsequent reactions.
2. In order that our findings might not be subject to misinterpretation, we have utilized an elaborate technic, particularly during the period of migration through the lungs. Only moderate numbers of cercariae were used, but colonies of active cercariae from individual snails were always pooled in order to ensure the presence of both males and females in the infections. The organs through which the worms migrated were isolated with particular care, and perfusions, chopped concentrates and stained sections were examined microscopically for evidences of the worms, or the lesions which they produced. All worms recovered were counted and classified according to their stages of development, as well as their location in the body.
3. Decaudated cercariae invade the skin when the water film begins to evaporate. This attack may, therefore, be interpreted as a protective mechanism by the para-

site. Invasion is accomplished by the boring action of the larva, supplemented by lytic substances poured out on the immediate skin surface by the penetration glands. Proof of this cytolytic action is furnished, not only by the rapid penetration through the outer resistent epidermal layers, but also by the depletion of the gland material immediately after arrival in the *rete mucosum* of the skin. This penetration usually occurs well within an hour and is frequently accompanied by an intense pruritus experienced by the host. Immediate vigorous scrubbing of the exposed skin of man with 70 per cent alcohol after accidental contact with *S. mansoni* cercariae affords complete protection.

4. Within 22 hours after inoculation by skin, the larvae may have reached the lungs *via* the right heart and pulmonary arteries, or they may have become temporarily lodged in peripheral lymph nodes. From this time through the eighth day many of them may be found in the pulmonary capillaries. In passing normally through the lungs they become greatly constricted in their transverse diameter, while the alveolar capillaries become greatly dilated. In this way they usually squeeze through the capillaries into pulmonary venules and are carried to the left heart and thence into the general circulation. In moderate infections larvae may occasionally break out of the lungs and be recovered in the pleural cavity. Our data, however, confirm those of Faust and Meleney on *Schistosoma japonicum,* that such larvae are trapped in this cavity and can neither penetrate farther, probably because of the depletion of the penetration glands, nor grow in this locality beyond the *epsilon* stage, because appropriate food is lacking.
5. Growth of the young worms depends on ingestion of blood. Our evidence indicates that feeding occurs only when the worms are in the intrahepatic portal system, which is reached by the mesenteric capillaries from the general circulation. Unlike the majority of *S. japonicum* larvae, those of *S. mansoni* which reach the hepatic portal filter or other capillary systems, instead

of lodging in these networks, squeeze through from one to several times and are carried again through the pulmonary capillaries. Such larvae as have previously been to the liver may be recognized by the presence of digested or digesting blood in their alimentary tract (*i. e.* they are black- or brown-gutted). Eventually, however, a relatively greater proportion of larvae from the inoculum accumulates in the intrahepatic portal vessel, where the larvae proceed with their development.

6. As soon as the worms have passed through their developmental period within the portal veins in the liver and have acquired sufficient strength, they migrate against the portal current out into the mesenteric venules. The site of their primary choice is the lower portion (ileo-colic branch) of the superior mesenteric vein and the colic branches of the superior and inferior mesenteric veins. In the terminal or subterminal venules at these sites they mate, and the females begin oviposition.
7. Four stages of development within the mammalian host have been recognized: (1) the metacercariae (*alpha* to *epsilon* stages), the usual forms found during the migration from the skin, through the lungs, to the liver; (2) juveniles (*xi* to *mu* stages), occasionally found in the pulmonary and general circulations, but most commonly recovered from the intrahepatic portal stream; (3) adolescents (*nu* to *chi* stages), the forms migrating from the intrahepatic portal vessels to the site of predilection in the mesenteric venules, and (4) adults (*psi* and *omega* stages), with fully formed and functioning sex organs. These stages parallel those of *Schistosoma japonicum* in their general metamorphosis.
8. In comparison with *Schistosoma japonicum, S. mansoni* has a "lag" in the time required for complete development. This delay is appreciable as early as the 70th hour after inoculation and increases to a maximum of 10+ days after 30 days development. This "lag" is due to the slowness with which the larvae accumulate in the liver, apparently their only feeding ground. It continues to maturity, so that the earliest time when

eggs appear in the stools in *S. mansoni* infection is 37–44 days, in contrast to 28 days in *S. japonicum.*

9. In tracing the successive stages of development of *Schistosoma mansoni* in the mammalian host, 24 separate stages have been recognized. These have been designated as *alpha* through *omega,* as in *S. japonicum.* The most significant modifications in the growing worms, in addition to increase in length, include the following: (1) change of the proboscis-like anterior end into a typical sucker at the beginning of the juvenile stage (*xi* stages); sexual differentiation, initiated about this same time (females become longer and narrower than the males); (3) growth of the gut around the ventral sucker, followed by the junction of the two furci behind the ventral sucker (between the *kappa-lambda* stages) and the continued elongation of this posterior median stem with the growth of the worms of both sexes; (4) formation of the gynecophoral canal of the male worm (about the *nu* stage) by the ventral infolding of the sides of the worm, thus providing a holding-organ for the female worm; (5) manifest elongation of the female worm, greatly in excess of the male, without essential increase in transverse diameter, and (6) maturity of the worms, with the differentiation of primary sex organs.

10. A study of the mature male worm has demonstrated the presence of 6 (?) to 9 testes (usually 8), with a seminal vesicle and short nonmuscular cirrus tube, anterior to the testes. These organs lie crowded together in the mid-plane, a short distance behind the ventral sucker. The primary female sex organs consist of paired vitelline follicles, extending from the subdistal to the mid-ovarian levels, with a common vitelline duct running anteriad to the oötype; an elongate, oval, slightly torted ovary, blind anterially, with a duct leading out and around on the dorsal side of the ovary and running anteriad to the oötype; a short crooked receptaculum seminis (probably of generic significance) arising from the proximal end of the oviduct; the oötype, surrounded by a cluster of glandular cells, and the rather long uterus, usually containing a single

lateral-spined egg, characteristically situated at the proximal end of the duct. The cirrus duct in the male and the uterus in the female open just behind the ventral sucker. In neither male nor female worm is there any well-developed sphincter at the external opening of the sexual canal. Both mature males and females are covered with minute spines; males are also provided with sessile papillae all over the body behind the ventral sucker, except within the gynecophoral canal.

11. Worms *in copula* were quite rare in our experimental hosts sacrificed after maturity of the parasites. Coupled worms were most common in the terminal or subterminal venules of the mesenteric system. It is suggested that the male serves as an anchor for the female, when she elongates her anterior end to deposit an egg in a small venule. Continuous insemination is unnecessary with a receptaculum seminis.
12. Although it is usual for each female to have only a single egg *in utero* at any one time, the rapidity with which eggs are deposited and infiltrated into the tissues indicates that as many as one hundred or more eggs are layed *per diem*. We believe that eggs of *S. mansoni* are deposited in the terminal or subterminal venules of the submucosa by the paired females, and not into the capillaries of the mucosa. From these venules eggs may pass through the muscularis mucosae into the base of the glans mucosae or into the *tunica propria*, escaping from the venule into the mucosa and breaking out into the intestinal lumen; they may break out of the vessel while still within the submucous coat; or they may be carried back to the hepatic filter by the blood stream. In case they break out of the venule in the submucosa they may pass through the tissues into the mucosa and eventually be evacuated; or they may become permanently lodged in the submucosa as centers of pseudotubercles. Daily and weekly egg counts of evacuated feces, checked by intestinal wall scrapings, indicate that only a small percentage of the eggs laid by the females are ever evacuated. As the infection becomes more chronic and tissue repair occurs, eggs in the feces gradually diminish in numbers.

13. Hematologic studies were conducted on four rabbits and two monkeys in the experimental series, in order to determine what response, if any, appeared in the general blood stream as a result of the migration and development of *Schistosoma mansoni* in the mammalian host. These studies included total erythrocyte and leukocyte counts, differential leukocyte counts, Schilling classification of the young neutrophilic leukocytes and Sia precipitation tests for euglobulin, both before and during the period of infection. The animals under investigation were controlled, as far as possible, to minimize variations in the leukocytes due to digestive and excitement leukocytosis. In order to link up these experimental cases with more chronic stages of the disease, eleven positive human cases were given hematologic examinations.
14. Increases in young neutrophilic leukocytes (*i. e.* stab forms, juveniles and myelocytes) were registered (1) during the period of invasion of the larvae through the skin, (2) at the time of their maximum accumulation in the lungs, and (3) with the initiation of oviposition by the mature female worms. These increases were relative and were never accompanied by an absolute leukocytosis.
15. There was no local reaction at the sites where the larvae entered the skin. On the other hand, during the passage of the metacercariae through the lungs, and, later, around the sites where eggs were infiltrated into the liver and the intestinal wall, there was first an intense response on the part of the neutrophilic leukocytes, which were replaced by successive invasions of eosinophiles, plasma cells and fibroblasts. Generalized eosinophilia developed in some of the animals toward the end of the prepatent period and at the beginning of the patent period. Its complete absence in one monkey is to be regarded as a lack of defensive response to the disease, which caused the death of the animal on the 55th day. In general, with the progress of the infection a relative peripheral lymphocytosis developed.
16. The degree of anemia in both the experimental and

clinical cases was dependent primarily on the severity of the infection rather than on the duration of the disease.

17. Only one of the experimental hosts had a positive Sia euglobulin reaction. This did not appear until some days after a significant eosinophilia had been registered. On the other hand, 8 of the 11 human cases examined had a positive euglobulin reaction, but there was no evidence of correlation between the intensity of the euglobulin reaction in the blood and the degree of eosinophilia.
18. The hematopoietic response in experimental and human infections of schistosomiasis mansoni is similar to that of other helminthiases, in which an early acute reaction is followed by gradual adjustment of the host tissues to the invading organism.

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TABLE No. 2, SHOWING BLOOD STUDIES ON RABBIT No. 1

Day	1*	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
Erythrocytes (in millions)	5.63	5.53	5.58	5.6	5.88	5.65	5.71	5.76	6.01	6.26	6.06	6.21	6.4	6.4	6.06	5.92	6.26	6.01	6.26	.....	.....	6.02	.....	.....	.....
Leukocytes (in thousands)	8.25	5.6	5.5	5.5	6.5	11.0	12.0	6.5	4.5	6.0	7.5	4.5	5.5	5.5	4.5	8.0	10.0	8.5	8.0	5.0	4.5	8.0	6.0	4.0	4.0
Percent Lymphocytes	58	52	60	62	55	63	51	55	73	67	72	61	56	44	69	66	58	53	61	52	71	70	61	57	66
Percent Monocytes	5	7	6	9	13	12	9	11	5	3	3	6	3	6	4	3	3	3	3	2	3	4	2	3	4
Percent Neutrophiles	31	36	30	27	27	24	37	31	21	28	24	30	40	47	26	29	37	43	28	45	25	25	35	39	26
Percent Eosinophiles	2	4	4	2	4	1	2	2	1	2	1	1	1	3	1	1	2	0	6	1	0	1	1	0	1
Percent Basophiles	1	1	0	0	1	0	1	1	0	0	0	0	0	0	0	1	0	1	2	0	1	0	2	1	3

Day	26†	27	28	29	30	31	32	33	34	35›	36	37	38›	39	40	41	42›	43	44	45	46	47	48	49	50
Erythrocytes. (in millions)	6.86	.....	5.63	.....	.....	.....	6.6	.....	.....	.....	6.6	.....	.....	6.68	.....	.....	6.23	.....	.....	.....	6.08	.....	.....	.....	.....
Leukocytes (in thousands)	8.0	7.0	6.0	7.0	7.5	.....	2.0	9.0	7.0	9.0	8.5	6.5	7.0	6.5	11.0	11.5	6.5	6.0	6.5	7.0	8.0	5.0	4.5	4.5	5.0
Percent Lymphocytes	53	60	60	40	44	.....	60	51	59	53	60	61	61	63	69	64	66	64	64	68	67	68	72	76	84
Percent Monocytes	3	2	3	6	7	.....	4	4	4	6	6	3	4	5	5	6	6	6	6	6	8	3	6	5	5
Percent Neutrophiles	42	36	35	50	39	.....	33	42	35	38	28	30	31	25	20	30	27	27	28	25	22	27	22	18	11
Percent Eosinophiles	1	1	0	2	7	.....	1	1	2	1	2	2	3	6	5	0	1	3	1	1	2	1	0	1	0
Percent Basophiles	1	1	2	2	3	.....	2	2	0	2	0	4	1	1	1	0	0	0	1	0	7	1	0	0	0

Day	51›	52	53	54	55	56	57	58	59	60	61	62›	63	64	65›	66	67	68	69	70 YZ
Erythrocytes (in millions)	.....	.....	.....	.....	.....	6.4	.....	.....	.....	.....	.....	6.32	.....	.....	.....	.....	.....	.....	.....	6.93
Leukocytes (in thousands)	5.5	4.5	5.0	7.5	6.5	5.5	5.0	.....	.....	.....	.....	5.5	.....	.....	.....	.....	.....	.....	.....	8.5
Percent Lymphocytes	74	80	73	79	66	70	63	60	60	65	58	55	56	65	63	54	59	68	58	54
Percent Monocytes	2	5	3	2	4	8	5	5	5	4	5	6	5	4	6	5	3	7	6	3
Percent Neutrophiles	23	14	24	18	28	19	37	31	29	27	29	34	32	28	25	37	29	23	27	38
Percent Eosinophiles	1	1	0	1	2	2	4	3	5	7	6	4	6	3	6	2	8	2	4	3
Percent Basophiles	0	0	0	0	0	1	1	1	1	1	2	1	0	0	0	2	1	0	5	2

* Inoculated
† Reinoculated
Y Reticulocytes, 3.9 per cent
Z Polychromatophilia
› Sia test for euglobulin negative