Brumpt (l. c., p. 264) has calculated that the females of *S. mansoni* lay from 157 to 191 eggs per day or 6 to 8 per hour. No evidence was furnished by this investigator as to the way in which this conclusion was reached. In an attempt to determine the amount of egg-laying by these worms in rhesus monkeys, we have estimated the total number of eggs evacuated daily, by counting all of the eggs in the first and last five per cent of a suspension of entire daily fecal samples, previously weighed, beginning at the end of the prepatent period. In one animal which died fifteen days after the first eggs were recovered in the feces, the total eggs in the dejecta were estimated to have varied daily from 113 to 5,890, with an average of 1,784. At autopsy of this host 562 female worms were recovered. In another monkey the daily egg estimates ranged from 320 to 3,750, with an average of 2,150. At autopsy only 36 female worms were recovered. Total egg estimates from a third animal, which is still living, were made daily during the first twelve days and subsequently at weekly intervals. In this animal the daily average for the first ten days was 679; for the following three months, 1,940; for the next three months, 1,011; and, more recently (three-months' average), 843. These data not only show a tremendous difference between the eggs *per* female worm recovered from the feces, but also a difference in the number of eggs evacuated over a period of several months. Furthermore, at autopsy of the first two animals, scrapings from the large bowel wall, near the sites of egg deposition, as distinguished from the lumen of the bowel, demonstrated the presence of tens of thousands of eggs within very limited areas (approximately 2 cm. in diameter). This observation lead us to believe that, even during the acute stage of schistosomiasis mansoni in the monkey, only a very small fraction of the eggs was evacuated from the intestinal wall. Similar scrapings from the upper ileum, jejunum and duodenum, when examined microscopically, indicated that relatively few eggs were deposited at these levels. This finding is in agreement with the observations on the gross and microscopic appearance of the bowel at these levels. Although our data do not allow of actual estimates of the egg-laying capacity of the female *S. mansoni* we are convinced that each mature worm probably lays one hundred to several hundred eggs *per diem*. While the

smaller number of eggs in the dejecta following the acute stage of the infection may conceivably be due to a slowing down in the egg-producing mechanism, it is much more likely the result of tissue repair in the bowel wall, which increases the difficulty of eggs breaking through into the intestinal lumen.

In our rabbits and monkeys only a small proportion of the adult egg-laying females resided in the terminal venules of the mesenteric system, and *none were in the capillaries of the mucosa or submucosa.* The great majority of them were found in the subterminal vessels and in the transverse anastomoses connecting one radicle with the next. In a typical case (one of the monkeys, 55th day sacrifice) 292 males and 207 females were recovered from the mesenteric system. Of this number only 79 (43 males and 36 females) were present in the terminal or subterminal venules coming from the submucosa; 70 of these worms were coupled. While it is probable that the male worm is useful in serving as an anchor for the female at the moment she is extending her anterior end into a small venule, preparatory to oviposition, and, therefore, can make little use of her own acetabula, we can not agree with Brumpt (l. c. p. 293) that the coupled male serves as the piston of a pump to produce a reverse blood current, to inject (or project) the eggs into the distal-most venules. However, the presence of the male may retard the normal coursing of the blood into the larger veins, thus expanding the terminal venules, so that the female may the more readily oviposit in the smaller vessels. The actual escape into the tissues of these eggs, which have been deposited in the lumen of the blood vessel, appears to be primarily mechanical, and is, no doubt, accelerated by the peristaltic movement of the bowel itself. The lateral glands or antero-lateral glands of the miracidium enclosed within the egg-shell may also play a part in this escape from the venule, infiltration into the bowel wall and, in some cases, escape into the intestinal lumen, just as they apparently do in the case of *Schistosoma japonicum* (Faust and Meleney [4], p. 18, Hoeppli [22]), but it has been shown (Faust and Hoffman [10]) that the lateral glands are less active in *S. mansoni* miracidia than they are in *S. japonicum,* and that the primary function of the antero-lateral glands is probably to lyse the tissues of the appropriate snail, when the mira-

cidium attacks this intermediate host. While the lateral spine of the egg may perforate the wall of a small venule or capillary, it is more likely to obstruct the progress of the egg in its escape from the bowel wall than to hasten its evacuation.

In order to obtain more information bearing on the passage of eggs of *S. mansoni* out of the terminal or sub-terminal venules, we have made a careful study of sections of various levels of the intestinal wall in the case of our monkeys. Having found no evidence whatsoever that eggs are deposited by female worms directly into the capillaries of the mucosa, we have considered five possible sequelae to egg deposition within the mesenteric venules of the submucosa: (1) the egg may pass from a venule directly *via* a distended capillary into the mucosa and be almost immediately discharged through the tissue into the intestinal lumen; (2) it may become lodged for a shorter or longer time in the mucosal layer, after having arrived directly *via* the blood stream (*i. e.* venule to capillary); (3) it may break out of the venule or capillary while still in the submucosa and gradually work its way through the tissues into the lumen; (4) it may become permanently lodged in the submucosa after escape from a nearby venule, and (5) it may be carried along with the mesenteric blood current and be filtered out in the liver. Our study of sections has provided definite evidence supporting the first four hypotheses. Since there were many more worms in the larger veins than in the terminal and subterminal vessels, it would be impossible to determine if eggs laid by females in or near the submucosa failed to be discharged into the intestinal wall, but were carried back to the liver. Presumably this is the case. In the rectum of the monkey sacrificed on the 55th day (Fig. 9) we found several eggs in distended venules and capillaries, in successive stages of progress from the submucosa through the muscularis mucosae into the tips of the interglandular tissues. In one capillary the spine of an egg had pierced the wall just beneath the muscularis mucosae. In numerous instances the eggs had escaped from capillaries in the *tunica propria* of the mucosa. In no instance was there any extensive hemorrhage near the eggs. In this respect the situation exactly parallels that of *S. japonicum* (Faust and Meleney [4], p. 185). In the same sections of rectum, eggs, which had undoubtedly left

the blood vessels deep in the submucosa, were passing through the substance of the muscularis mucosae into the mucosa, usually between the crypts, but occasionally into the base of the glands. In both of these modes of escape there were immature as well as mature eggs which were about to leave the mucosa; likewise, there were a few around which cellular infiltrations had already occurred, thus delaying the evacuation. Finally, in sections of the appendix of the 55th-day monkey as well as the 70th-day monkey, nests of eggs with extensive tissue reaction, essentially isolating the eggs, were found in the midst of the submucosa. We are convinced, therefore, that it is not necessary for the eggs of *Schistosoma mansoni* to be deposited into the capillaries of the mucosa layer, in order for them to escape, and we very much doubt if this commonly occurs. They may be carried out into the mucosa through the blood vessel or they may filter out through the stroma, but the great majority appear to be oviposited in the venules of the submucosa.

Hematologic studies

Daily blood studies were made on four of the rabbits and two of the monkeys. Rabbits, instead of dogs were used in this experimental work, since the dogs infected with *Schistosoma japonicum* by Faust and Meleney [4] failed to develop any significant eosinophilia. Our blood studies consisted in daily total leukocyte and erythrocyte counts on each of the animals for a period of seventeen to nineteen days. Thereafter, for thirty or more days, daily total leukocyte and weekly erythrocyte counts were done. Subsequently, until the end of the experiment, total leukocyte and erythrocyte counts were made at weekly intervals. A daily differential leukocyte count, including an estimation of the percentage of young neutrophilic leukocytes, based upon Schilling's [24] description of these forms, was made until the animal was sacrificed or moved to New Orleans. In every case, immediately before the animal was autopsied, a total erythrocyte and total differential leukocyte counts were done. An occasional reticulocyte count was made on some of the animals during the course of the experiment and always before they were sacrificed.

In addition to these numerical and morphologic studies

of the blood, after the thirtieth day of the infection precipitation tests for the presence of elevated euglobulins in the blood serum were performed after the method of Sia [25]. These tests were made at varying intervals of from two to seven days.

These hematologic data were obtained with the idea that they might serve as a check upon the condition of the animal under experiment, and to determine whether there was any general blood stream response to the parasite during its migration and development in the mammalian host. In the event of such a general response, our data might be helpful in clarifying the sequence of events in the development of the commonly observed blood picture in clinical schistosomiasis. Furthermore, it seemed advantageous to study the development of the characteristic peripheral eosinophilia, to see if there was any correlation between its appearance and the rise of euglobulins in the blood to such a level as to be detected by the Sia test. Finally, it was desirable to see whether or not the blood studies on these experimental animals were comparable to observations made by us in a few human cases in much later stages of the disease.

For the blood counts the standard diluting pipette was used and Toison's fluid was employed as a diluent. Only two pipettes were used, both of which delivered equal volumes of water. No effort was made to use the same pipette on each animal every day. After each blood count was made the pipettes were cleaned by washing successively with acetic acid, water, alcohol, and ether. The Toison's fluid was freshly prepared from chemically pure ingredients, and was discarded as soon as any growth of yeast cells appeared. For the total counts a Bausch and Lomb counting chamber with the Bass-Johns' ruling was employed. By the use of this type of counting chamber and Toison's fluid both total erythrocyte and leukocyte counts could be made upon the same preparation. The technic employed in making the counting chamber preparations, smears for differential counts and reticulocyte counts was that described by Bass and Johns [26]. Both Wright's and Leishman's stains were found quite satisfactory for the differential counts.

In collecting samples of blood from the rabbits for counting, the animal's ears were kept shaved and were swabbed with alcohol and allowed to dry before each sample was col-

lected. One of the ear vessels was then opened with a sharp lancet and the blood allowed to flow freely before any sample was taken into the diluting pipette. The smears for differential counts were made immediately after dilution of the blood in the pipettes. The amount of blood lost by the host at each sampling was negligible. The total counts were made within thirty minutes after dilution.

An effort was made to control the daily variations in the leukocyte counts incident to the daily rhythm of the cells, as demonstrated in man by Sabin, Cunningham, Doan and Kindwall [27], and in the rabbit by Pearce and Casey [28]. Cheng [29], working with the same strain of rabbits which we used in our experiments, has shown that by taking the blood at the same time every day this diurnal variation of the leukocytes is negligible. Furthermore, he has demonstrated that certain other factors cause variations in the total leukocyte counts in these animals, but that by observing certain precautions these variations may be controlled. The animals were kept in the laboratory and their food trays were always kept full; in this way the digestive leukocytosis was avoided. Each animal was removed from his cage and allowed to be quiet before any blood was taken. All samplings were made with the animals in the upright position.

The test for euglobulins in the blood was performed as follows: Six-tenths of a cubic centimeter of doubly distilled water (pH 7.1) was placed in a small test tube. Twenty cubic millimeters of blood were then withdrawn from the animal into a Sahli hemoglobin pipette and quickly discharged into the water. Observations were made immediately and at intervals up to an hour. A positive test consists in relatively rapid flocculation. The results are recorded as ++++, if the flocculant material settles out in 15 minutes; +++, if at the end of 30 minutes; ++, if at the end of 45 minutes, and +, if at the end of an hour or longer. This test has been shown by Sia and Wu [25a] to be entirely dependent upon the level of the euglobulin in the blood.

The various factors influencing the total leukocyte counts could not be so well controlled in the monkeys, because of the difficulty in handling them. The blood was never withdrawn immediately after feeding and was always taken in the morning, although the hours varied a great deal. The

animals were quite nervous from being caught and transferred to the laboratory. The blood samples were taken while the animals were held on their backs. The legs of the monkeys were kept shaved, and prior to each sampling were swabbed with seventy per cent alcohol. One of the superficial veins of the legs was opened, and blood was allowed to flow freely before dilutions or smears were made. The bleeding was stopped by pressure over the area, then the leg was swabbed again with alcohol. Both animals developed infection in the areas from which the blood was removed, but this was purely local and did not cause any variations in the blood counts.

Preliminary blood counts for three to five days were done in the case of each animal except rabbit no. 3. In general, the counts were done long enough before infection to establish more or less the normal total erythrocyte and leukocyte counts for each animal. As far as the differential counts were concerned, our findings are in essential agreement with the data of Cheng (l. c.). The lymphocytes and basophiles were relatively more numerous in the rabbit than in human blood, while the neutrophilic leukocytes were decreased. On the average, in this series of rabbits, the white cells were distributed as follows: lymphocytes, 60 per cent; monocytes, 5–9 per cent; neutrophiles, 30 per cent; basophiles, 3–5 per cent, and eosinophiles, 1–3 per cent.

There are certain morphologic differences between rabbit blood and human blood. The granules of the polymorphonuclear neutrophilic leukocyte take more of the acid stain, and appear as bright red granules in the cytoplasm. So marked is this tendency at times that the cell warrants the designation of "pseudoeosinophile". The true eosinophile of the rabbit can be differentiated easily from these cells on the basis of morphologic criteria. The neutrophilic granules are small, irregular in size, and relatively sparsely distributed through the cytoplasm. The nucleus is generally multi-lobed. The eosinophilic granules, on the other hand, take a great deal of the basic stain and appear darker than the human eosinophile. These granules are large and quite regular in size and shape, and are very numerous in the cytoplasm. The nucleus is bi- or tri-lobed and is never obscured by the cytoplasmic granules. The basophilic cells

have large irregular, deeply basophilic-staining granules, irregularly distributed through the cytoplasm, and often obscuring the nucleus. The agranulocytic leukocytes are quite comparable to those seen in human blood.

In estimating the age of the neutrophilic leukocytes, those cells were considered as adult which had either more than two lobes to the nucleus or just two lobes connected by a thin nuclear thread. All other forms were grouped by us as "young neutrophiles", since the leukocytic reaction was usually in the form of increased stab cells, occasionally juvenile cells, and rarely myelocytic cells. In these rabbits approximately 3 to 5 per cent of the total white cells consisted of young forms. The classification of all the younger forms of leukocytes as young cells, regardless of their age, was done in order to simplify the graphic representation of the neutrophilic response to the parasite.

In the monkeys the morphologic characteristics and the normal numerical values of the various white cells more nearly approximated those of human cells. The lymphocytes were slightly higher, averaging 44 per cent, and the neutrophiles somewhat lower, 47 per cent. The other cells were approximately the same as those found in human blood. The total white cell counts showed considerable variation, but were constant enough in individual animals to indicate any significant change from the norm. Each of the rabbits at autopsy was proved to be infected with *Schistosoma mansoni* and had no other parasites. The monkeys harbored several species of intestinal protozoa and *Strongyloides stercoralis,* but at the same time showed no marked blood changes. They had no infections other than the intestinal parasites and *Schistosoma mansoni.*

The results of the blood studies in the animals are presented in the following charts and tables, which are self-explanatory (charts 2–7, tables 2–7).

Eleven human cases of schistosomiasis were examined to note the relationship, if any, between the experimental blood pictures and those of clinical cases. This was in no way a clinical study of the disease, but was utilized solely for purposes of comparison. From this human series certain interesting observations were made. One patient, whose peripheral blood showed an eosinophilia over 50 per cent, had

a severe diarrhea, fever, loss of appetite and malaise, symptoms which were quite similar to those of monkey no. 1, which also registered a significant eosinophilia (See table 6). In these eleven cases no elaborate or complete studies were made. The duration of the disease was from one to eleven years, as determined from the history. Our hematologic findings are in close agreement with those of Girges [32], although too few patients were studied to warrant any general conclusions as to the diagnostic and clinical significance of the blood picture. Enough cases were studied, however, to demonstrate how the blood picture, which develops in the experimental animals, is related to that found in these rather late cases of human schistosomiasis. Our examinations are summarized in the following table (Table 8).

DISCUSSION

In viewing the mammalian phase of the life cycle of *Schistosoma mansoni* in its entirety, (including the penetration of the skin, the migration through the lungs, eventual accumulation of many of the young worms in the intrahepatic portal system and their development to adolescent stages in that location, their subsequent migration to the site of their adult predilection in the mesenteric system, and their eventual maturity, mating and the production of eggs by the females), we have been impressed, on the one hand, with their general conformity to the development of other mammalian schistosomes, and, on the other hand, with specific differences. Unfortunately, except for the work of Faust and Meleney [4] on *S. japonicum,* no complete study on the successive stages of development during the period of migration and maturity of mammalian schistosomes is available for comparison. Until similar investigation is conducted on *S. haematobium,* and preferably also *S. bovis* and *S. spindale,* deductions must necessarily be tentative.

The metacercarial-juvenile period

This period of migration and development includes the phase from penetration of the skin or buccal mucosa until the young worms begin to accumulate in numbers in the portal system. It is characterized by very rapid penetration of the outer layers of the skin or the buccal mucosa and

relatively rapid transit to the lungs. We have demonstrated the early arrival of the first metacercariae of *S. mansoni* in the lungs (at least within 22 hours after inoculation). Even lodgement in the peripheral lymph nodes was of very short duration, as indicated by the marked petechial hemorrhages of these glands in the path of progress within the first 3 days, and by the almost complete absence of metacercariae in these organs, as determined by microscopic examination of the concentrates of the minced tissues and of fixed sections. On the other hand, a considerable time was required for the worms to pass through the normal blood channels of the lungs. Although there was some evidence of escape of these larvae from pulmonary capillaries, even through the eighth day, the great majority of the young worms were slowly passing through the pulmonary arterioles and alveolar capillaries into the pulmonary veins. This was consistently demonstrated by the recovery of hundreds of worms in these sites in the lungs, tightly squeezed into greatly dilated arterioles and capillaries, usually without rupture of the walls of these vessels, and by their presence in appreciable numbers in the blood of the left heart. This passage through the pulmonary capillaries was made possible (1) by the capacity of the capillary walls to dilate tremendously, and (2) by the ability of the worms to elongate so that their transverse diameter was greatly reduced. Undoubtedly the proboscideal anterior end of the metacercaria was of considerable assistance in negotiating a path through the alveolar capillaries.

Once out of the pulmonary network and into the general circulation, the young worms were free to migrate to the terminal network of the systemic arterial circulation. In contrast to the lodgement of the young *S. japonicum* in such filter beds as the capillaries of the stomach wall and the kidneys and the production of extensive petechial hemorrhage in those locations, no such filtration of young *S. mansoni* took place. Even those individuals which reached the portal system, and, as a result of feeding, began to increase in size, had the capacity for several days to squeeze through the hepatic filter bed and usually returned to the lungs. While Faust and Meleney occasionally found black-gutted metacercariae of *S. japonicum* outside the portal system, it was a relatively uncommon finding; in *S. mansoni,* it was common.

Thus, though this difference between these two species is not absolute, *S. mansoni* unquestionably has a less specific adaptation for the portal blood stream during the earlier days of development than does *S. japonicum*. On the other hand, the ability of young *S. mansoni* worms to pass through capillary networks outside of the portal stream insures an eventually greater accumulation of larvae in this optimum location for development during the juvenile and adolescent periods.

Our study has convinced us, just as similar experimental evidence on *S. japonicum* convinced Faust and Meleney (l. c.), that metacercariae which get into the pleural cavity are in a blind location and can not develop into juveniles. They are unable to penetrate through the relatively resistent diaphragm, probably because their lytic glands have been exhausted. Associated with this finding is their inability to obtain appropriate nourishment in that cavity, or anywhere else in the body outside the portal blood stream. Just what the particular adaptation is, which limits their food supply to portal blood, is entirely unknown, but the fact remains. Individuals can not proceed in their growth beyond the *epsilon* stage without residing for some time in the portal vessels.

The adolescent period

While late juvenile stages (*i. e. iota* to *mu* stages) are apparently vigorous enough to migrate out of the liver against the incurrent portal blood, this migration appears to occur rarely before the end of this period. In our examination of mesenteric blood (*vide supra*) the earliest stages recovered (546 hours) were *mu, nu* and *xi,* and then only isolated examples. Later adolescent forms, from *nu* through *sigma* and *tau* stages of development, began to leave the liver for the mesenteric radicles. The earliest forms, like the more developed adolescents, accumulated first of all in the venules draining the region of the ileo-colic level. Later, when greater migrations occurred, probably due to congestion, they became more generally distributed throughout the mesenteric venules, from the duodenum to the rectum, and a few even wandered into the vesical plexus. We are certain, however, that the primary predilection of *S. mansoni* is for the posterior branches of the superior mesenteric and the

adjacent inferior mesenteric veins. This stands in marked contrast to *S. japonicum*, which chooses first of all the anterior branches of the superior mesenteric veins and later migrates farther down the mesenteric system; and to *S. haematobium*, which primarily inhabits the vesical plexus, although *en route* it may be found in the left colic branch of the inferior mesenteric and the hemorrhoidal veins. According to Fairley and Mackie [23] (p. 21) *S. spindale* has greatest concentration in the mesenteric veins, although it also resides in the gastric (40 per cent), splenic (36.6 per cent), and pancreatic veins (30 per cent), as well as in the pulmonary artery (26.6 per cent), right heart (13.3 per cent), inferior vena cava (10 per cent) and pelvic veins (10 per cent). Apparently *S. spindale* adults have a less specific predilection for any particular site than do any of the other three schistosome species considered.

Brumpt [21] (p. 278) has attempted to explain the distribution of mammalian schistosomes at different levels in the mesenteric veins as caused by the posture of the host. On the basis of our observations and the data in the literature, we find no justification for this hypothesis. In man, with upright posture, as well as in four-footed experimental mammals, and monkeys, which occupy an intermediate postural position, *S. mansoni* adolescents consistently seek out the mesenteric branches previously described. Similarly, in *S. japonicum* and *S. haematobium*, the sites are the same irrespective of the postural habits of the host. However, we have no alternative theories to present and are frank to admit that these predilections, wherever they occur, remain entirely unexplained.

The time element in the development of S. mansoni in the mammalian host.

We have previously commented on the slow migration of *S. mansoni* metacercariae through the lungs; likewise, the relatively long time required for the young worms to accumulate in the portal blood stream, due to their return from one to several times into the general circulation. In reality this greater wandering of the young pre-juvenile stages, as well as the early juveniles, has retarded growth approximately in proportion to the time spent outside the portal blood. Table 1 shows the respective stages of growth

and the tissue in which the young worms were recovered in our studies on *Schistosoma mansoni* and Faust and Meleney's studies on *S. japonicum* through the first 40 days in experimental rats (or, in *S. japonicum,* in mice). The symbols in parenthesis represent the approximate average of development at the particular time. Hence they may be used as the basic points for comparative curves of growth of the two species. Inspection indicates that the successive "lag" in development of *S. mansoni* in comparison with *S. japonicum* is about as follows: at 70 hours, the "lag" amounts to 24 hours; at 112 hours, 50 hours; at 166 hours, 72 hours; at 208 hours, 88 hours; at 304 hours, 136 hours; at 450 hours, 234 hours; at 546 hours, 234 hours; at 720 hours, 264 hours, and at 960 hours, 240 hours. Even the recovery of eggs in the stool of experimental and human hosts shows this same delay of 9 or more days. *S. spindale* apparently matures about the same time as *S. mansoni* (35th–40th day) and the eggs infiltrate into the tissues soon thereafter (Fairley and Mackie [23], p. 23). Whether this longer period required for development in *S. spindale* is due to slow accumulation of the pre-juvenile worms in the portal vessels is not answerable on the basis of published data. The first eggs of *S. haematobium* are discharged about six weeks after exposure of the experimental hosts (Manson-Bahr [19], p. 688), although in human cases six months may be required before eggs appear in the urine. This greater delay is, no doubt, due, at least in part, to the farther migration of these worms from the mesenteric veins into the pelvic plexuses and the longer time required for the eggs to infiltrate through the bladder wall.

The presence of adult mammalian schistosomes in the portal stream and in the lungs is more or less related to the ease with which these worms can travel along a relatively direct path from the seat of their major predilection. There is no evidence that the metacercariae lodge and develop in either of these sites, but rather, after accumulating and developing in the liver, and migrating out into the mesenteric venules or their immediate anastamoses, the adolescent or mature worms either actively migrate or are passively carried into the adjacent blood vessels and became lodged where the diameter of the vessel is too small to allow them to pass farther distad. Thus in *Schistosoma japonicum,* with a

normal concentration in the superior mesenteric veins, a very high proportion of mature worms in the living host is consistently found within the intra-hepatic portal system and only occasionally in the pulmonary arteries. In *S. mansoni* the number in the portal blood stream within the liver is also large, although usually much smaller than those present in the mesenteric veins; occasionally worms get to the pulmonary artery. In *S. spindale* (*vide* Fairley and Mackie [23]), with its wide distribution in the mesenteric and collateral veins, the number in the portal veins (93.3 per cent) is almost as great as in the mesenteric veins, yet the pulmonary arteries contain 26.6 per cent of the mesenteric yield. In *S. haematobium* the worms in the pelvic plexus are more or less isolated in a collateral circulation. The liver is, therefore, less commonly involved in schistosomiasis haematobia than it is in the intestinal schistosomiases and the lungs are more commonly a focus of blood-fluke infection. Once the worm has attained adolescence, there is every indication that it may continue to live and propagate outside of the site of its major preference, if only it arrives at that site.

Deposition and extrusion of eggs

We have previously described five ways in which the eggs of *S. mansoni,* deposited in the venules of the mesenteric system, may be disposed of. Extrusion into the intestinal lumen shortly after oviposition in the venules or capillaries of the submucosa is the most usual course in the early phase of patency. As tissue repair becomes more and more common, infiltration into the tissues with blockage by scar tissue in the mucous and submucous coats of the intestine and, soon thereafter, extensive cellular reaction around the eggs so disposed, tend to isolate the eggs more or less permanently in the submucosa. Again, they may be carried back to the liver, where they filter out and become permanently lodged.

Blockage by tissue repair in the mucosa and submucosa of the bowel wall possibly has some effect on the worms themselves, causing them to migrate away from the sites of original preference. In *S. mansoni* the worms migrate upward into the upper branches of the superior mesenteric veins; in *S. japonicum,* the migration is downward toward

the colon and rectum. In this change of location the worms are at times necessarily unattached to the walls of the vessels through which they are passing and thus may be carried passively in the portal stream to the liver. Thus, with the exception of the original choice of a site for maturing and oviposition, we find a reasonable explanation for the activities of the adult worms on the basis of their host-tissue relationship.

Hematologic findings

In considering the blood pictures of our infected rabbits and monkeys, it will be noted in all cases that, one or two days after the animals were inoculated, there appeared an increase in the number of young polymorphonuclear neutrophilic leukocytes in the peripheral blood, and that the number of these young neutrophiles dropped to normal figures again within two to three days. Moreover, in from four to eight days after the first increase in young neutrophiles, there occurred a second similar rise. This "shift to the left" was not accompanied by any change in the total leukocyte count, nor even in the relative number of polymorphonuclear neutrophilic leukocytes. Other than this slight and rather ephemeral "shift to the left", the blood picture remained essentially unchanged.

During this first period, in which the young neutrophiles were increased, the metacercariae were working their way out of the skin into the peripheral circulation, and migrating to the lungs, either directly or after passing through the peripheral lymph nodes. Later, the second "shift to the left" in the Schilling index occurred at a time when the schistosomula had accumulated in the lungs in greater numbers, and were beginning to arrive in the liver. Strangely enough, though these organisms penetrate the epidermis through lytic action produced by secretions of their penetration glands, as well as by the boring movements of their proboscis, no local inflammatory reaction was seen about any of these metacercariae in sections of the skin. No doubt the lytic substance provides the chemotactic stimulus to incite the first rise in the number of young neutrophiles in the blood. However, after this period, their migratory progress has been shown to be either mechanical or passive (*vide supra*). The acute local response of numerous neutrophilic leukocytes seen