THE HISTOPATHOLOGY OF SWIMMERS' ITCH

I. The Skin Lesions of Schistosomatium douthitti and Gigantobilharzia huronensis in the Unsensitized Mouse*

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In 1928, Cort[1] demonstrated that non-human schistosome cercariae are capable of producing dermatitis in man. Since then, many species of avian and mammalian schistosomes have been shown to produce similar lesions, to which Cort gave the name, swimmers' itch. The gross lesions, as they appear in man and various species of experimental animals, have been well described, but the microscopic features of the host response have been the subject of only a few reports.

Vogel[2] (1930), working with *Cercaria pseudocellata,* described the response in human tissue taken for biopsy 24 hours after exposure. He noted moderate edema in the epidermis and a minimal cellular response consisting of neutrophils and lymphocytes. Dead cercariae were present in the epidermis.

Brackett[3] (1940), also reporting from human biopsy specimens, described the picture 29 hours after exposure to *C. stagnicolae,* and 50 hours after exposure to *C. elvae.* He noted marked edema and a neutrophilic response in the 29-hour biopsy material and a marked cellular exudate consisting principally of eosinophils and lymphocytes in that obtained at 50 hours.

Macfarlane[4] (1949), utilizing *C. longicauda,* described the host reaction from a series of human biopsies. In unsensitized individuals he found a mild response to the cercariae, consisting of edema, parakeratosis, and a lymphocytic exudate in the dermis. He was able to trace the fate of the cercariae from the time they first attacked the epidermis until they were killed and sloughed in an epithelial plaque with the stratum corneum about 2 weeks after exposure.

The response of the sensitized individuals in Macfarlane's series[4] showed edema and a massive lymphocytic exudate in both the dermis and epidermis. This reaction occurred in a much shorter period than did the milder response of the unsensitized persons.

In none of these three studies could the authors find any evidence that the cercariae had been able to penetrate the basal cell layer of the epidermis.

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Olivier and Weinstein[5] (1953) described the tissue response of rabbits to both *Trichobilharzia ocellata* and *T. stagnicolae.* The reaction of the rabbit to the two cercariae was similar, although more intense in the case of *T. ocellata.* The response of unsensitized rabbits was so minimal as not to be evident 48 hours after exposure. Living cercariae were observed in both the dermis and the epidermis. The response of the sensitized rabbits to these cercariae was intense and it consisted principally of leukocytes. The authors concluded that the cercariae may be destroyed by an undesignated humoral factor, by the cellular response, or by both.

Olivier[6] (1953) noted pulmonary hemorrhages in rabbits, mice, and several other laboratory animals that had been exposed to *T. ocellata,* demonstrating that avian schistosomes could proceed in mammals to a further stage of their life cycle than had been hitherto reported. Earlier, Penner[7] (1941) had shown that *Schistosomatium douthitti,* a parasite of muskrats and mice, could produce pulmonary hemorrhages in monkeys.

The gross lesions produced by schistosomes in abnormal hosts are apparently indistinguishable from one another, but the microscopic descriptions of these same lesions are too few to permit such a generalization. Furthermore, the exact method by which the host overcomes the cercariae is known only when the parasites are intraepidermal in location.

The present paper describes the response of the unsensitized white mouse to two species of schistosomes: *S. douthitti,* which is known to reach maturity in the mouse, and *Gigantobilharzia huronensis,* which has been described from several species of birds.[8]

Materials and Methods

Cercariae of *S. douthitti* and *G. huronensis* were used to infect white mice. Naturally infected *Lymnaea stagnalis,* collected from the muskrat farm of Mr. Charles Sagers of Fox Lake, Wisconsin, were the source of *S. douthitti;* and naturally infected *Physa gyrina,* collected from the Huron River near Ann Arbor, Michigan, were the source of *G. huronensis.* These snails were maintained in laboratory aquaria, to which calcium carbonate and lettuce were added periodically.

S. douthitti cercariae were collected by placing one or two *L. stagnalis* into a small glass vial, and the vial was then put in a darkened room. The cercariae, which are negatively phototropic, would begin to emerge from the snails, and within a short time they could be observed hanging from the surface film of water. Using a small hair loop, the

cercariae were picked off the surface film, were counted under a dissecting microscope, and were transferred to a 5 by 10 mm. glass vial. A mouse was anesthetized with phenobarbital and was taped to a small board. Its left ear was then dipped into the water containing the cercariae. The exposure of each mouse was to 100 ± 10 cercariae and was limited to 30 minutes.

The cercariae of *G. huronensis* are positively phototropic, and normally emerge from the snail in the early morning. These cercariae were collected by placing three or four *P. gyrina* into a small glass vial, and this vial was then placed in a darkened room for 24 to 30 hours prior to an exposure. The vials were then placed in a lighted room, at which time the cercariae would begin to emerge. These cercariae were surface hangers also, and were prepared for exposure in the manner described for *S. douthitti.*

At various intervals from the time of exposure, the mice were killed with phenobarbital and necropsied. The left ear and the internal organs were preserved in formalin. These tissues were prepared for microscopic examination by standard techniques and were sectioned at 5 μ. The ears were serially sectioned. All tissues were stained with hematoxylin and eosin and were mounted in Canada balsam.

Results

The Skin Lesions of S. douthitti

The gross pathologic features, as they appear in man and various species of experimental animals, have been well described by many investigators.[9] In the white mouse the cercariae of *S. douthitti* produced a maculopapular eruption. The macules were 0.3 mm. in diameter and appeared 5 to 10 minutes after an exposure. The papules appeared 30 to 60 minutes after exposure and disappeared completely during the third day following an exposure. At the height of the dermatitis the papules were 4 mm. in diameter and were surrounded by an erythematous ring approximately 5 mm. in diameter. If more than two or three cercariae had penetrated in close approximation, the epithelium would slough off, leaving an ulcer.

The microscopic picture of the host response varied with the fate of the cercariae. Many cercariae were able to penetrate only to the prickle-cell layer of the epithelium, where they produced intercellular and intracellular edema (Fig. 2). Occasionally there was also a minimal neutrophilic reaction in the dermis beneath, but usually there was none. The presence of the parasite seemed to induce hyperkeratosis of the epithelium beneath it (Fig. 2), resulting in the extrusion of the

cercaria with the exfoliating stratum corneum. Dead cercariae were seen in an epithelial plaque, forming part of the stratum corneum, within 90 minutes after exposure. This process was not observed after the third day following exposure.

Cercariae were observed to have penetrated into the dermis either directly through the basal layer of the epidermis (Fig. 3), or through the canal of the hair shaft into the sebaceous gland (Fig. 4) and thence into the dermis. In either case there was minimal neutrophilic response in the dermis in the immediate vicinity of the cercaria. When an ulcer had been produced by the entrance of several parasites within a small area of skin, there was a heavy neutrophilic response in the dermis, and often localized areas of hemorrhage (Fig. 5).

As soon as the cercariae had penetrated the dermis and subcutaneous tissues, tissue histiocytes began to accumulate in the vicinity of the parasites and to form a capsule around them (Figs. 6 to 8). Histiocytes were first observed about 12 hours after exposure. They reached maximum numbers about 4 days following exposure, after which cercariae were no longer seen in sections of the skin. The neutrophilic response remained moderate for as long as 3 weeks after exposure, whereas the histiocytic response subsided shortly after the cercariae disappeared from the skin and subcutaneous tissues.

A small number of living cercariae were observed in venules which were surrounded by minimal collections of both neutrophils and histiocytes (Figs. 9 and 10). Hemorrhage was observed throughout the site of the cercaria in these instances, as a result of the parasite's entry into the venule. The cecae of these cercariae were filled with golden-yellow or brown granules, the product of the parasite's metabolism.

The Skin Lesions of G. huronensis

In the majority of cases there were no gross lesions evident following exposure to *G. huronensis*. Infrequently, red macules about 0.3 mm. in diameter were observed. These appeared within 5 or 10 minutes and disappeared within 1 hour.

As with *S. douthitti,* these cercariae were observed to penetrate the dermis either directly through the basal cell layer of the epidermis or through the pilar apparatus into the sebaceous gland.

Microscopic sections showed that the cercariae were able to penetrate through the epidermis very rapidly. Living cercariae were observed in the subcutaneous tissues as soon as 15 minutes after exposure (Fig. 11). At this time they were beginning to be surrounded by tissue histiocytes, and there was a moderate histiocytic response throughout

the section. Within a very short time the cercariae were encapsulated by several layers of histiocytes in a manner similar to the process observed with *S. douthitti.* This local reaction persisted for 1 or 2 days, until the cercariae in the dermis and subcutaneous tissues were clearly dying or dead. It then disappeared quickly.

There was a minimal neutrophilic reaction noted 1 hour after exposure. This increased in intensity, reaching a maximum degree 1 day following exposure (Fig. 12). It gradually subsided, but it was still present 16 days after exposure.

A few living cercariae were observed in epidermal burrows without any sign of host reaction; and only one dead cercaria was seen in an epithelial plaque. No dead cercariae were observed within epithelial burrows. It was concluded, therefore, that practically all the cercariae that had attacked the skin had been able to penetrate the epidermis and to invade the subcutaneous tissues. This is in agreement with the minimal gross lesions.

Discussion

On the basis of the knowledge then available to him, Cort[9] (1950) stated that the dermatitis (in man) "produced by one species of non-human schistosome cercariae does not differ from that produced by any other." This is true in regard to the gross appearance of the dermatitis. Macfarlane[4] and Olivier[10] were able to demonstrate that the difference in the degree of the host response, and hence of the gross appearance of the lesions, was due solely to the previous degree of sensitization to schistosome cercariae which the host had experienced.

The investigations of Vogel,[2] Brackett,[3] and Macfarlane,[4] as well as the findings described in the present paper, all indicate that the cercariae which remain intra-epidermal cause a localized area of edema in the epithelial cells. This edema results in the development of a papule, which disappears as soon as the dead cercaria in the epithelial plaque is sloughed off with the stratum corneum. If the cercariae are able to penetrate through the epidermis, as in the case of *G. huronensis,* no papular dermatitis will be present. Upon the first exposure to schistosome cercariae, humans usually do not develop a dermatitis. It can be presumed that in these instances the cercariae are able to invade the subcutaneous tissues. Pulmonary migration of the non-human schistosomes in an unsensitized person, as suggested earlier by Olivier and Weinstein,[5] must be considered as a very distinct possibility.

As soon as the cercariae enter the dermis and subcutaneous tissues, there is an immediate local response by tissue histiocytes. The histiocytes serve to wall off the parasite, much as inert foreign bodies are

enveloped. The systemic response of the neutrophils is a more slowly developing process, and it becomes maximal only after a sufficient time has elapsed for the histiocytes completely to encapsulate the cercariae. The isolation of the cercariae in the subcutaneous tissues from their source of food contributes to the death of the parasites. The neutrophils then phagocytize the dead cercariae.

Living cercariae which have succeeded in entering venules were observed to induce a minimal reaction of histiocytes and neutrophils around the vessel. This is not an indication that the cercariae were dead, but rather that they had achieved this stage of their life cycle without succumbing to the host response.

Summary

The response of the unsensitized white mouse to cercariae of *Schistosomatium douthitti* and of *Gigantobilharzia huronensis* is very similar. The development of papules is caused by epithelial edema due to the cercariae which remain within the epidermis. Disappearance of the papules coincides with the extrusion of these dead cercariae in the stratum corneum.

The earliest demonstrable tissue reaction against cercariae in the dermis and subcutaneous tissues is a local accumulation of histiocytes. These histiocytes serve to encapsulate the parasites. Somewhat later there is a generalized neutrophilic response, which becomes maximal when the cercariae have become completely encapsulated. Phagocytosis of the parasites then ensues. Evidence of the inflammatory response was observed 3 weeks following exposure.

Addendum

After this paper had been accepted for publication, a similar study with *S. douthitti* was reported by Kagan and Meranze.[11]

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[*Illustrations follow*]

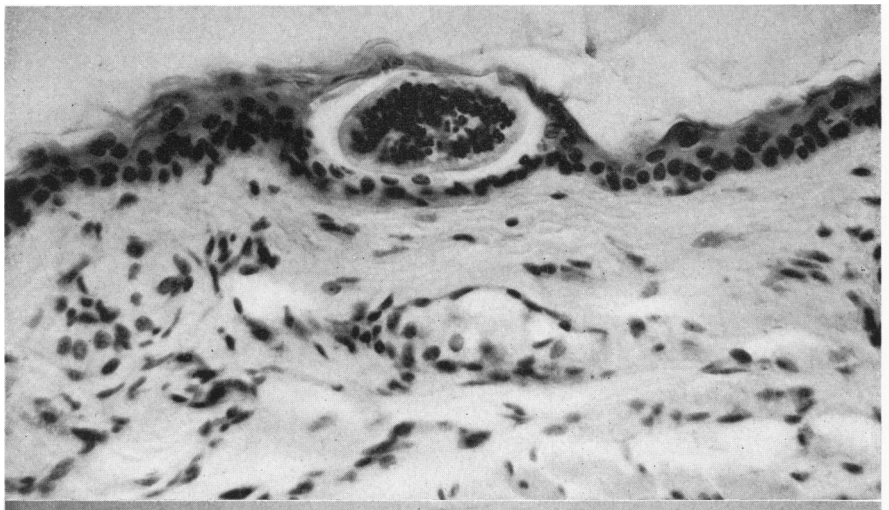
LEGENDS FOR FIGURES

All photographs were taken from sections of skin which were fixed in formalin and stained with hematoxylin and eosin. The magnification of Figures 1 to 4 and 6 to 12 is 275 ×, and that of Figure 5 is 140 ×. Figures 1 to 10 are after exposure to *Schistosomatium douthitti* and Figures 11 and 12 are after exposure to *Gigantobilharzia huronensis.*

FIG. 1. Living cercaria in epidermal burrow (2 hours after exposure). No evidence of host reaction.

FIG. 2. Dead cercaria in epidermal plaque (90 minutes after exposure) with moderate neutrophilic and very minimal histiocytic response in dermis. The epidermis is hyperkeratotic beneath the parasite.

FIG. 3. Living cercaria (2 hours after exposure) penetrating into the dermis directly through the epidermis. No host reaction is present.



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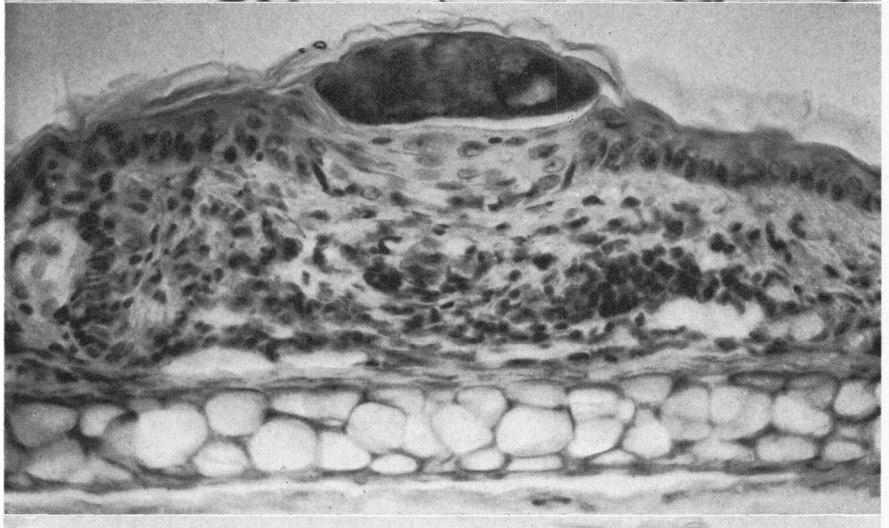

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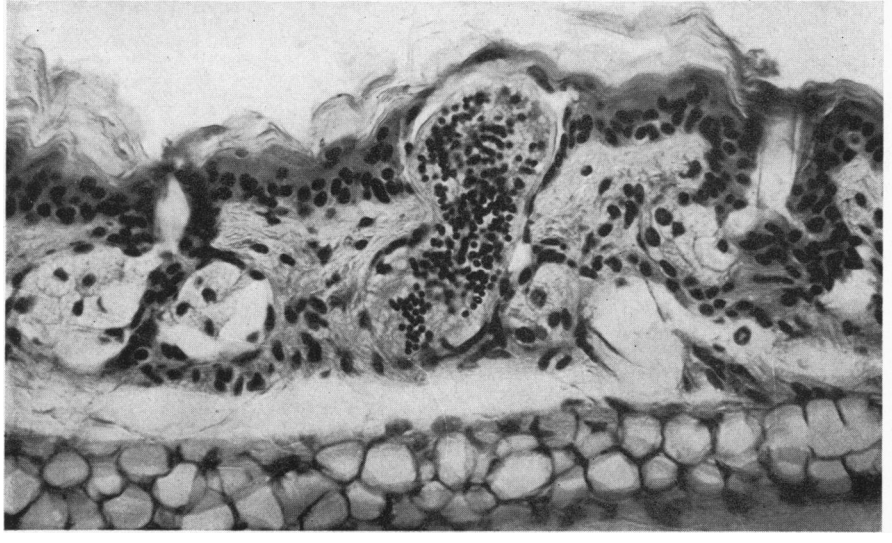

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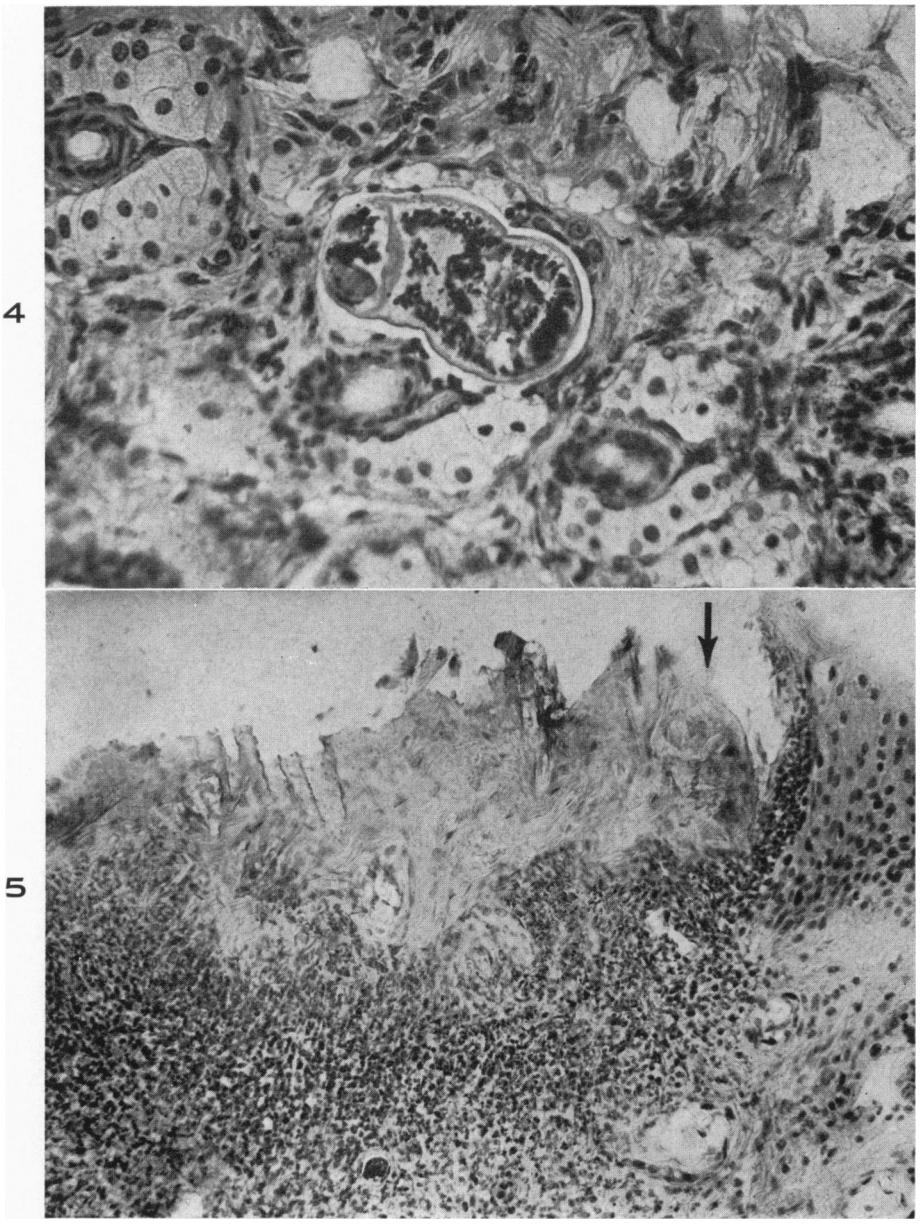
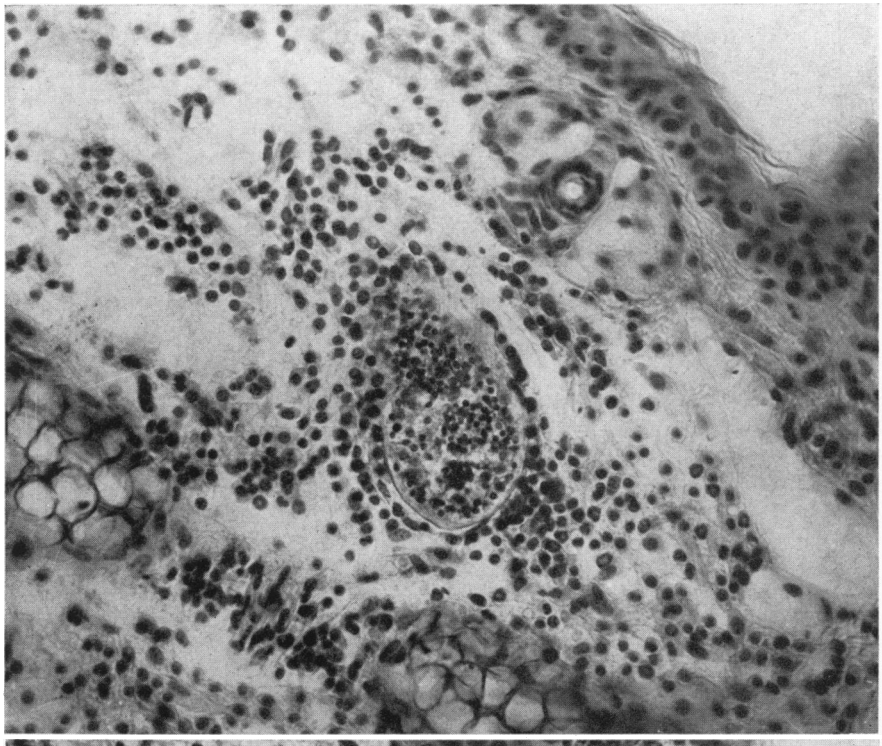


FIG. 4. Living cercaria (30 minutes after exposure) in sebaceous gland, without evidence of host reaction.

FIG. 5. Ulcer (20 hours after exposure) with heavy neutrophilic and minimal histiocytic reaction in dermis. There is a dead cercaria (arrow) in the base of the ulcer.

FIG. 6. Living cercaria (20 hours after exposure) with histiocytes beginning to surround it. Moderate neutrophilic and histiocytic reaction in the section.

FIG. 7. Dead cercaria (30 hours after exposure) in a later stage of encapsulation. Moderate neutrophilic and histiocytic reaction in the section.



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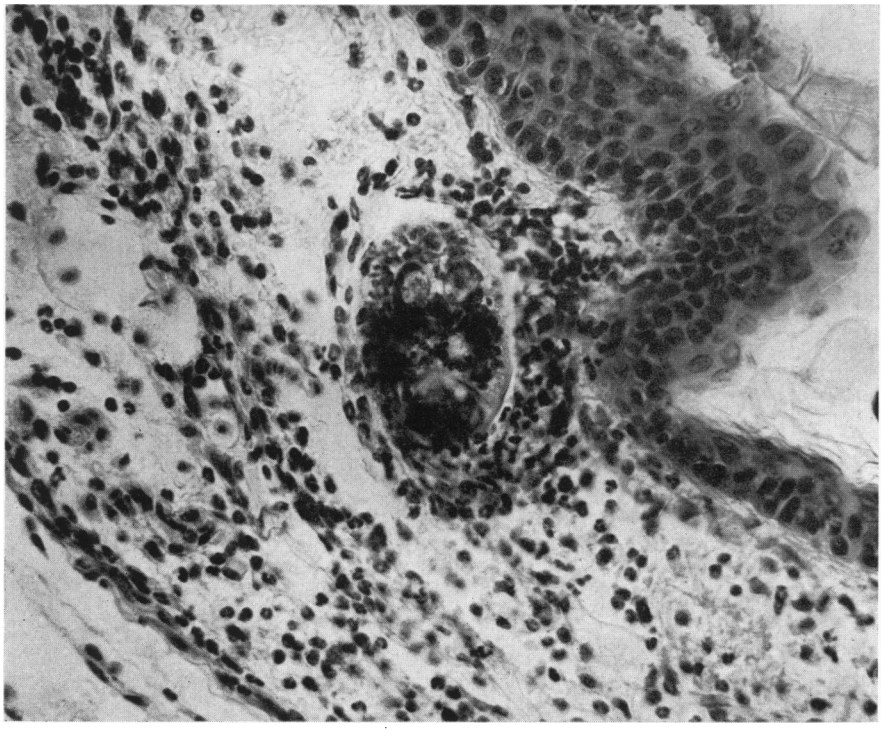

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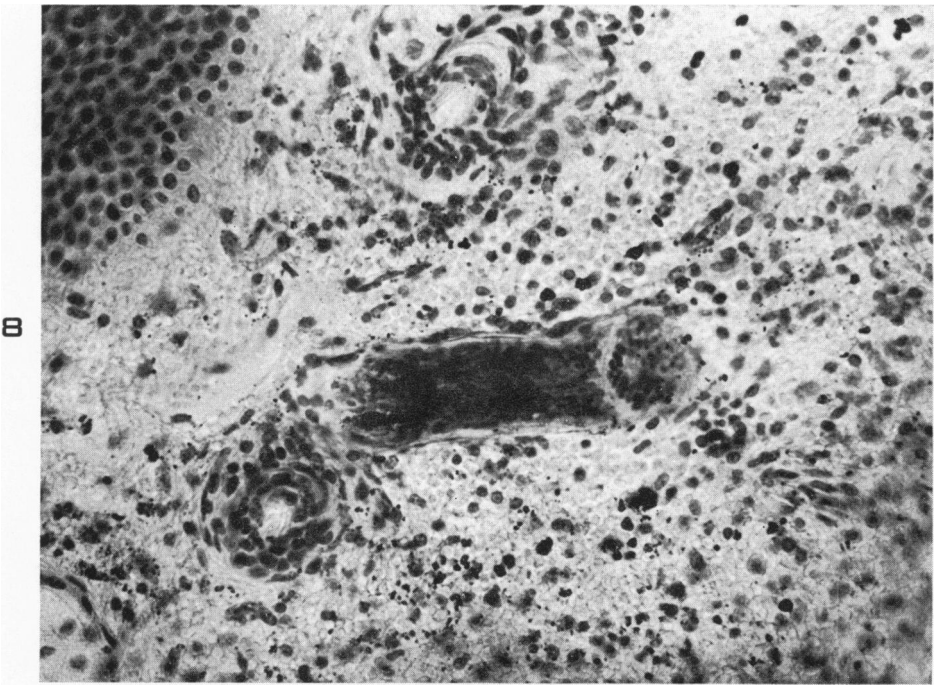
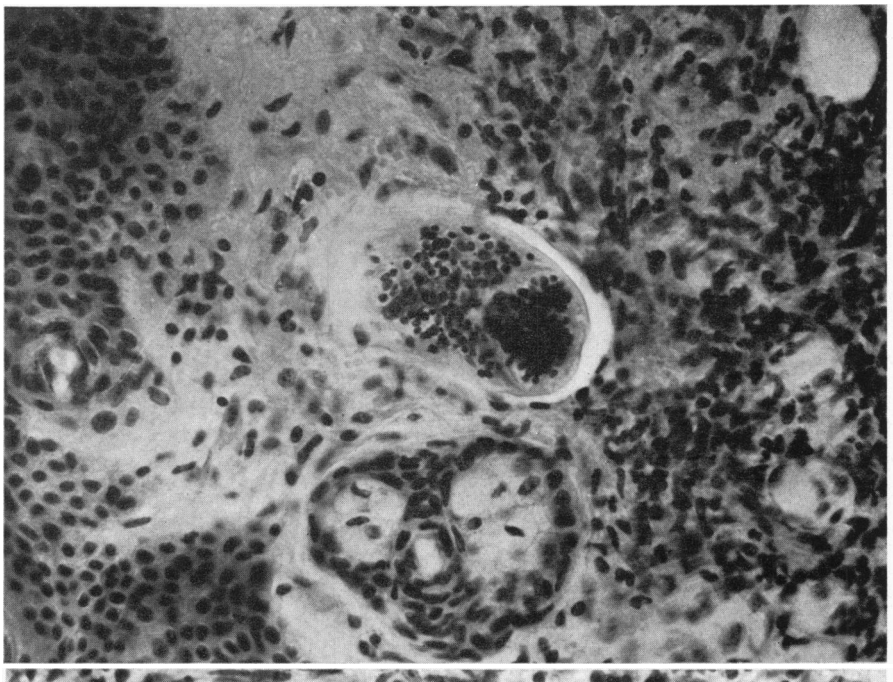


FIG. 8. Dead cercaria (30 hours after exposure) with a moderate neutrophilic and histiocytic reaction. Hemorrhage is present, and the cecae of the parasite are filled with pigment granules.

FIG. 9. Living cercaria (4 days after exposure) within a venule. Mild neutrophilic and histiocytic reaction in the section.

FIG. 10. Living cercaria (4 days after exposure) within a venule. Moderate neutrophilic and minimal histiocytic reaction around the venule.



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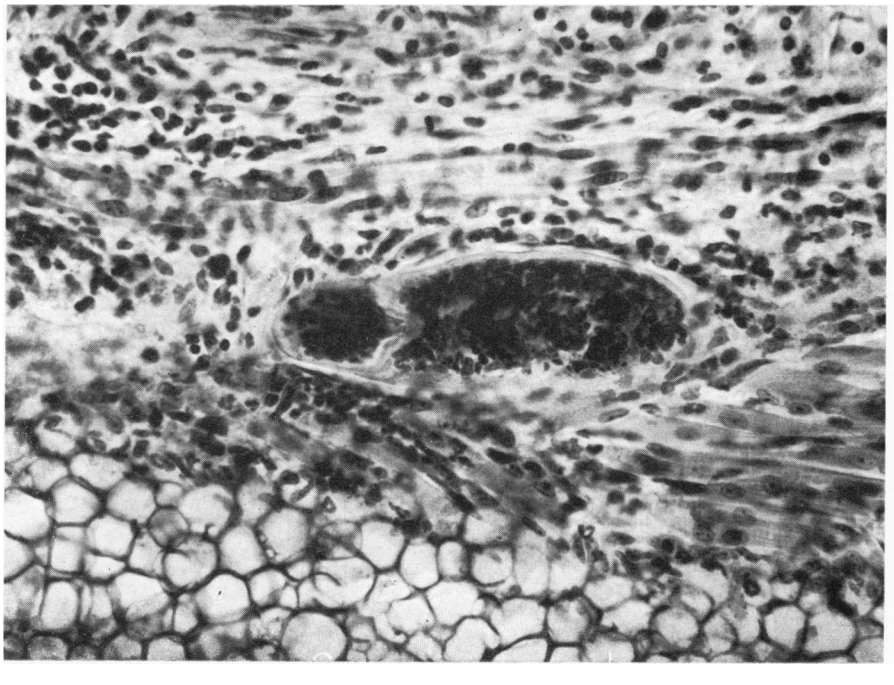

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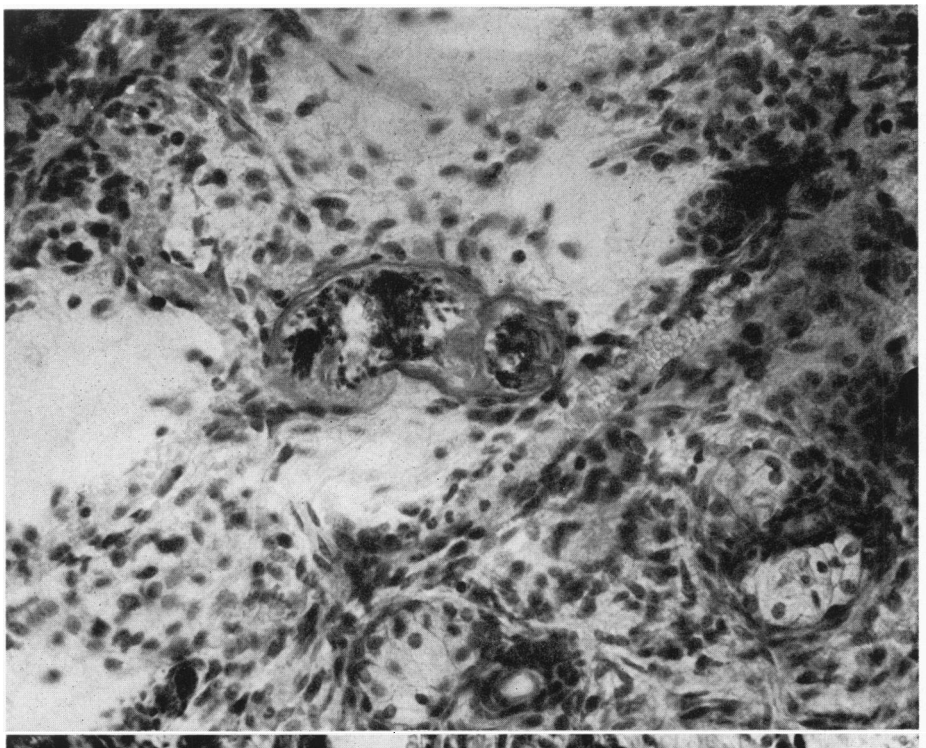
FIG. 11. Living cercaria (15 minutes after exposure) with a minimal histiocytic reaction around the parasite. There is no evidence of a neutrophilic response at this time.

FIG. 12. In the lower center of the field there is a dead cercaria in the subcutaneous tissues (1 day after exposure), with a heavy neutrophilic and moderate histiocytic reaction. The parasite is phagocytized.



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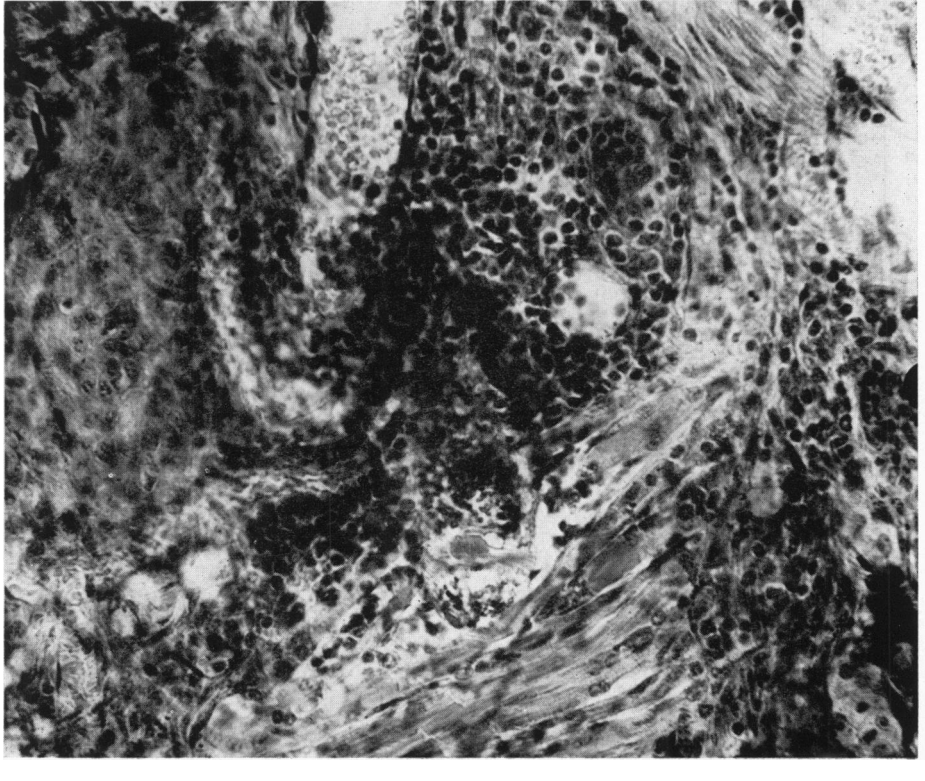

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