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CUTANEOUS HOOKWORM RESERVOIR*

ORVILLE J. STONE, M.D. AND CAROLYN J. WILLIS, M.A.

We wish to present data which we feel indicate that the skin can serve as a reservoir for *Ancylostoma braziliense* larvae and that these larvae can later become active. Admittedly, the circumstances preceding these observations are not entirely identical with natural infection. However, the fact that this phenomenon can occur under any circumstance is of importance.

It was previously considered a fact that the third stage animal hookworm larvae which produce creeping eruption do not progress in development in the skin of man. There was an *in vitro* test system for screening drugs based on the assumption that no change occurred in the larvae after they invaded the skin. After systemic thiabendazole was introduced as a cure for creeping eruption (1, 2), *in vitro* testing showed that it had no effect on the larvae (3). Based on the assumption that the test was not a duplication of biologic circumstances, studies were undertaken on factors influencing the progression of the larvae. It was shown that exposure to carbon dioxide would cause exsheathment of the larvae (3). This was important because the sheath is impermeable to most substances except water and gases. However, even after exsheathment the larvae were not susceptible to high concentrations of thiabendazole. Further studies showed that after the larvae underwent 72 hours of development in the intestine of a dog (4), they became susceptible to thiabendazole. The authors concluded that the best explanation for the discrepancy between clinical effectiveness of thiabendazole and its inability to kill the third stage exsheathed larvae was to assume that the larvae progressed partially in development. In retrospect, it is fairly logical that the larvae could not secrete proteolytic enzymes while inside an impermeable cuticle. It has also been suggested that these "creeping" larvae move through the epidermis but do not invade because they secrete proteolytic enzymes but no collagenase-like enzymes (4). During any one exposure, it is also probable that some of the larvae do invade even though they do not progress in development (5, 6). It is even possible that freezing therapy may simply drive in the larvae. There is no proof that freezing kills or removes the larvae.

This paper reports a third course of development. The larvae can remain in the skin and later become active. It is not an uncommon clinical experience to note the development of a new lesion several days after the onset of creeping eruption. The appearance of late-starting lesions has sometimes been interpreted as a re-infection.

MATERIALS AND METHODS

Both of the authors began repeatedly exposing themselves to *Ancylostoma caninum* larvae in September, 1963. Small numbers (3 to 5) of larvae were used at first, but later, larger numbers (25 to 50) were applied. These studies were done in an air conditioned room and multiple methods of application were attempted. By means of magnification, the larvae were observed to enter the skin. In no instance was there development of the papule said to be characteristic of *A. caninum* infection. In two instances, a single, small area of erythema developed and lasted less than 24 hours. They developed 24 hours after exposure and were gone by 48 hours. The source of *A. caninum* larvae was multiple cats and dogs who were sacrificed for identification of the adults in the intestines.

In 1965, we had opportunity to obtain a cat and two kittens from under a house where a natural infection of "creeping" type lesions had occurred. The kittens were sacrificed, and between the two of them (adult hookworms pooled), had only three *A. braziliense* but many *A. caninum*. Stool from the mature cat produced larvae which induced creeping eruption. Dr. Ashton Cuckler, Merck Sharp and Dohme, fed the larvae to wormed puppies and developed a pure strain of *A. braziliense*. The authors, over a six-month period, again began studies on themselves and developed typical creeping lesions. Both authors had some lesions almost continually over a six-month period.

For an experimental study with thiabendazole in dimethylsulfoxide, each author was exposed to 250 *A. braziliense* larvae under a heating pad.

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* From the Department of Dermatology, The University of Texas Medical Branch, Galveston, Texas 77550 J. Fred Mullins, M.D., Professor and Chairman.

The dimethylsulfoxide was withdrawn from investigative use before the study could be initiated. One of the authors had 22 lesions and took thiabendazole* 1.5 gm twice daily for two days with complete clearing. The other author had four lesions and followed the natural course of the lesions which spontaneously cleared over a five-week period. All work with hookworm larvae was discontinued and there was no contact with the area where an infected animal was housed. In the areas of previous exposure, the authors began to occasionally develop erythematous, pruritic papules and distinct creeping tracts. The area was entirely normal between lesions. Only those lesions in which there was no question as to diagnosis and where actual movement occurred are being reported. The author who took thiabendazole developed lesions at the following rate, dated from time of initial exposure: 33 days (lasted 5 days, 4 cm); 49 days (lasted 3 days, 4.5 cm); 58 days (5 days, 5 cm); 103 days (3 days, 3 cm); 139 days (4 days, 3.5 cm). The author who took no medication developed a lesion at 163 days. It lasted 5 days and moved 7 cm. The multiple lesions on the one author developed far enough apart on the forearm to suggest that they were separate larvae. All lesions were typical for pruritus and serpiginous course. A prisoner volunteer had a similar recurrence, but we do not consider him a qualified observer. He had no previous known exposure other than to 250 larvae at one time.

DISCUSSION

Fullerborn [reviewed in Chandler (7)] injected larvae of *Uncinaria stenocephala* (European dog hookworm) into its specific host, the dog. Most of the larvae migrated by lymph and the blood vessels for a normal life cycle, but some "strayed." The straying larvae were found embedded in fat, nerves, and musculature, but some were also found wandering in the superficial layers of the skin. The complexity of the host-parasite relationship for hookworm larvae in their normal and abnormal host has recently been reviewed (8).

Fullerborn showed that the larvae could remain in the tissues, but we know of no data showing that they can later become active. If a small number of human hookworm larvae in the skin of man became active and moved into blood vessels, there would be no signs or symptoms. The fact that we were dealing with larvae that "creep" allowed us to make our observations.

We can only speculate as to the way in which the larvae were able to remain inactive. They may have been active previously, but we doubt this. We feel that it is more likely that they were inactive until they eventually began movement. They could have even remained in their sheath for a long period, even though most larvae rapidly exsheath. They could not remain in the epidermis in an inactive form, as they would be moved outward with epithelial growth. They could survive in an inactive form below the basal cell layer, or perhaps more likely, in the follicles.

The main clinical significance of this data is in relation to human hookworm disease. The possibility of a cutaneous reservoir adds to the complexity of this major health problem. Our clinical experience with the use of thiabendazole in the therapy of creeping eruption is excellent, but some larvae are occasionally present after therapy. Some of the larvae may have been just becoming active, and therefore were unaffected by therapy. It is not uncommon to see new lesions develop over a period of several days after a single exposure.

The fact that the actively creeping larvae become permeable to thiabendazole or ingest it suggests to us that the larvae are receiving nutrition from the host. Even though hookworm larvae contain large amounts of stored food, we believe the amount of proteolytic enzyme secreted would rapidly deplete the parasite's food stores if it did not receive nutrition from the host.

Even though the late-developing larvae moved for only a short time and a short distance, it would have been enough activity to get an invading type of larvae into a blood vessel. Once reaching the blood vessel, the course of human hookworm larvae is largely a mechanical phenomenon and requires little effort on the part of the parasite (9).

SUMMARY

The authors have observed that animal hookworm larvae can remain in the skin of man without producing signs or symptoms. These larvae can later become active and serve as a reservoir for creeping eruption, and of more importance, perhaps the skin can serve as a reservoir for human hookworm disease.

REFERENCES

1. Stone, O. J. and Mullins, J. F.: First use of thiabendazole in creeping eruption. Texas Rep. Biol. Med.. *21:* 422–424. (Fall) 1963.

* Mintezol—Merck Sharp & Dohme.

2. Stone, O. J. and Mullins, J. F.: Thiabendazole effectiveness in creeping eruption. Arch Derm., *91:* 427–429 (May) 1965.
3. Stone, O. J., Mullins, J. F. and Willis, C. J.: In vitro studies on Ancylostoma caninum with thiabendazole with observations on larval exsheathment. JID., *44:* 256–258, 1965.
4. Stone, O. J., Willis, C. J. and Mullins, J. F.: Effect of thiabendazole on Ancylostoma caninum. Arch Derm., *92:* 59–62 (July) 1965.
5. Bever, P. C.: Parasitological Reviews—Larva Migrans. Exp. Parasit., *5:* 587–621, 1956.
6. Muhleisen, J. P.: Demonstration of pulmonary migration of the causative organism of creeping eruption. Ann. Intern. Med., *38:* 595–600, 1953.
7. Chandler, A. C.: *Hookworm Disease*, New York, The MacMillan Company, 1929.
8. Stone, O. J. and Mullins, J. F.: Creeping Eruption—Host–Parasite Relationship. Clin. Med., *72:* 465–472 (Mar) 1965.
9. Chandler, A. C. and Read, C. P.: *Introduction to Parasitology*, New York, John Wiley and Sons, Inc., 1961.