Visceral and Cutaneous Larva Migrans

PAUL C. BEAVER, Ph.D.

AMONG ANIMALS in general there is a wide variety of parasitic infections in which larval stages migrate through and sometimes later reside in the tissues of the host without developing into fully mature adults. When such parasites are found in human hosts, the infection may be referred to as larva migrans although definition of this term is becoming increasingly difficult. The organisms implicated in infections of this type include certain species of arthropods, flatworms, and nematodes, but more especially the nematodes.

As generally used, the term larva migrans refers particularly to the migration of dog and cat hookworm larvae in the human skin (cutaneous larva migrans or creeping eruption) and the migration of dog and cat ascarids in the viscera (visceral larva migrans). In a still more restricted sense, the terms cutaneous larva migrans and visceral larva migrans are sometimes used to denote the formation of lesions due to a particular species of larva known or presumed to be the one most commonly involved: *Ancylostoma braziliense* in the skin, and *Toxocara canis* in the viscera. This usage of the terms is incorrect, however, since, as previously emphasized, the character and location of the lesions and the resultant symptoms are unreliable clues in the specific identification of the causative organisms (*1*).

Development of Concepts

The various groups and species of worms involved in the larva migrans type of infection, the clinical features of the diseases caused by them, and certain biological aspects of the host-parasite relationships have been discussed in a number of recent reports and reviews (*2–5*).

In the development of our concepts of larva migrans there have been four major steps. The first, of course, was the discovery by Kirby-Smith and his associates some 30 years ago of nematode larvae in the skin of patients with creeping eruption in Jacksonville, Fla. (*6*). This was followed immediately by experimental proof by numerous workers that the larvae of *A. braziliense* readily penetrate the human skin and produce severe, typical creeping eruption.

From a practical point of view these demonstrations were perhaps too conclusive in that they encouraged the impression that *A. braziliense* was the only cause of creeping eruption, and detracted from equally conclusive demonstrations that other species of nematode larvae have the ability to produce similarly the progressive linear lesions characteristic of creeping eruption. While in the initial studies by Kirby-Smith it was possible to demonstrate larvae in 10 percent of the skin biopsies from individuals with creeping eruption, no spontaneous case of cutaneous larva migrans has yet been given a specific etiological diagnosis; that is, no larvae have been identified in human skin.

For many years after it was shown that nematode larvae cause creeping eruption it was assumed that the apparently aimless migration was due to abnormal host-parasite relationships and that the larvae eventually perished and

Dr. Beaver is professor of parasitology, department of tropical medicine and public health, Tulane University School of Medicine, New Orleans, La. *This paper was presented at the Communicable Disease Center's Conference for Teachers of Veterinary Public Health and Preventive Medicine, and Public Health Workers, Atlanta, Ga., June 12–18, 1958.*

were destroyed in the skin. Two significant early observations argued against that view. Wright and Gold's finding of pulmonary infiltrations during or following the active phase of creeping eruption suggested that at least some of the larvae succeeded in making the normal migration to the lungs (*7*). It was also noted, however, that the pulmonary infiltrations could have resulted from the larvae without their having left the skin. Evidence of a more convincing nature was provided by the report of an authenticated intestinal infection of *A. braziliense* in a boy in Texas (*8*). If adults could be found in the intestine, the larvae must have migrated from the skin through the lungs enroute to the intestine. That record is no longer accepted, however, and the reports of intestinal infections of *A. braziliense* in man in other parts of the world have likewise been rendered doubtful by the observations that a morphologically very similar species, *Ancylostoma ceylonicum*, formerly regarded as a synonym of *A. braziliense*, is a valid species (*9*). An observation by Muhleisen was, therefore, of special significance (*10*). For a period of 24 days he found large numbers of larvae in the sputum of a man with severe and extensive skin lesions, leaving no doubt about migration from the skin to the lungs. Unfortunately the larvae were not identified, but it was determined without any doubt that a mature intestinal infection did not develop in this case.

Second Step

The second major event in the study of larva migrans came in 1952 with the discovery and identification of *T. canis* larvae in liver biopsies from children with a common disease which up to that time had been given a number of different names but was of unknown etiology (*11*). This was followed a year later by an experimental demonstration of the etiological role of *T. canis* (*12*) and by numerous confirmatory reports indicating that this common ascarid of dogs is responsible for much illness in children here and in other parts of the world and that it apparently is an occasional cause of death (*13*).

Biopsy and autopsy studies in children, and various types of studies in experimental animals have provided more interesting facts about *T. canis* as a cause of the visceral type of larva migrans than can be mentioned here.

Briefly, it has been established that infection is acquired by ingesting soil previously contaminated by infected dogs. Eggs passed in the feces, under favorable conditions in the soil, become infective in 2 to 3 weeks, containing second-stage larvae which, when taken into the intestine of a child, erupt from the egg, penetrate the intestinal wall, and soon reach the liver. A majority of the larvae may remain in the liver but others pass on to the lungs and to other parts of the body. Larvae have been found in nearly all organs. It is of chief interest that a high proportion of them invade the central nervous system and a considerable number have been found in the eye. The tragic consequence of invasion of the eye is the development of a lesion which by its resemblance to retinoblastoma prompts the unnecessary removal of that vital organ.

Although most of the larvae eventually come to rest in one location and stimulate fibrous encapsulation, there is a period of at least several weeks during which they move about in the tissues of the visceral organs in much the same manner as hookworm larvae migrate in the skin, leaving in their wake long trails of inflammatory and eosinophilic granulomatous reactions.

Thus in comparison with their microscopic size the wandering larvae produce large and extensive lesions that can be readily seen with the unaided eye in and on the surface of the liver and, at times, in other organs, especially the brain. This is the type of infection now called visceral larva migrans. Its most prominent clinical feature is high, stable, and persistent, eosinophilia, not uncommonly reaching levels suggestive of eosinophilic leukemia. Less outstanding and less constant features are enlargement of the liver, hyperglobulinemia, intermittent fever, infiltrations of the lungs, neurological symptoms, and deviations in behavior.

Thus far *T. canis* is the only species of larva identified in cases of visceral larva migrans. However, there is a good experimental and epidemiological basis for suspecting other species to be similarly involved. *Toxocara cati*, as common or more so in cats as *T. canis* is in

dogs, should occasionally reach the tissues of children. In one instance a larva in a child's liver has been questionably identified as *T. cati* (*14*).

Greatest anticipation of early incrimination is with *Ancylostoma caninum*. This worm is more common in dogs than *T. canis*, and occurs in cats as well as dogs. Whereas *T. canis* is relatively uncommon in older dogs and is especially uncommon in sexually mature females, *A. caninum* is found in both dogs and cats at all ages. Both parasites take full advantage of prenatal infection in maintaining a high level of endemicity and both are known to persist in the tissue of experimental animals for more than a year. There is no apparent reason why the larvae of *A. caninum* should not be found in the tissues of children along with the *Toxocara* species. However, further studies may bring to light an explanation which is presently not apparent. Larvae entering the body through the skin are less apt to be found in the liver and it is probable that *A. caninum* larvae are much less frequently ingested than the eggs of *Toxocara* and some of the other helminths.

The searching of liver biopsies for *Toxocara* larvae has in recent years uncovered three cases of *Capillaria hepatica* which formerly was found only at autopsy and was thought to be rare in man. It is hoped that when nematode larvae are encountered in the examination of human tissues it will not be assumed on circumstantial evidence that they are any particular species but rather will be identified on the basis of characteristic morphology.

Third Step

The third notable contribution to our knowledge of larva migrans came from a series of studies on the basic life cycle patterns among the ascarids. Sprent (*15*) summarized these studies and pointed out that while infections by some and perhaps most of those species adapted to carnivorous land mammals can be transferred from host to host in the same manner as *Ascaris lumbricoides*, that is, by ingestion of infective eggs in contaminated soil, the usual pattern under natural conditions includes intermediate or transport hosts.

Originally our domesticated dogs and cats may have acquired their ascarid and perhaps some of their hookworm infections not directly from the soil but indirectly by eating other mammals which by feeding on the ground had earlier picked up the infective stages, preserved or further incubated them in their tissues, and passed them on to their predators.

Experimentally, *T. canis*, *T. cati*, and *A. caninum* can be transferred to their final host by first inoculating mice or other small mammals which are then after several days, weeks, or months fed to dogs or cats. The significance of such observations is immediately apparent. They point out that our previous interpretation of larva migrans caused by these species was essentially incorrect. The migration and persistence without development in human tissues are not, as we had supposed, basically due to an abnormal host relationship. We may still regard man as an abnormal host for the adult stage, and an unnatural host for the larvae in that he provides no advantage for the parasite as a species, but the behavior of the larvae in man being the same as in natural transport hosts apparently is not abnormal. It is then to be expected that any of the larval stages of nematode parasites of wild or domesticated carnivorous animals adapted to the use of mammalian intermediate or transport hosts may grasp the opportunity to enter the tissues of human hosts and await, unsuccessfully of course, the transfer to a predator final host.

It is obvious from these remarks that detailed studies on the life cycles of all worm parasites of animals having contact with humans have great usefulness in the study of larva migrans and other zoonotic helminthiases.

Fourth Step

The fourth major advance in larva migrans research was Nichols' demonstration of the feasibility of identifying nematode larvae in microsections of tissues (*16*, *17*). These classic morphological studies, while limited to only a half dozen species considered most likely to be encountered in human tissues, left no doubt that descriptions of these and other species could be sufficiently detailed to permit reliable identification often when only fragments of the larvae are available for study. The interpretation,

prevention, and effective control of any parasitic disease are, of course, dependent upon the accurate identification of the organism which causes it. To make this possible, additional studies such as Nichols' are needed.

Research on Prevalence

Inasmuch as public health programs place strong emphasis on the reliable determination of disease prevalence and on the development of preventive measures, we should mention here two additional phases of research in which recent studies show promise of providing important, useful information.

Thus far it has not been possible to get a clear picture of either the extent or the prevalence of visceral larva migrans. Originally, diagnosis was based on liver biopsies taken by laparotomy. This procedure is too hazardous and expensive to be used routinely. Furthermore, no specific therapy is available, and usually when additional infection can be prevented, the prognosis is favorable. It is understandable, therefore, that a clinical diagnosis, unconfirmed by actual identification of the causative organism, is relied upon in the management of most cases. It is equally understandable that unconfirmed clinical diagnoses are not really satisfactory.

In view of these circumstances, it is of great interest that promising and already somewhat useful serologic techniques of diagnosis are being developed by Sadun and associates (*18*), Kagan (*19*), and Jung and Pacheco (*20*). The fault in serodiagnostic methods has been their lack of specificity due to cross-reacting antigen-antibody systems among related worms. By fractionation and purification of antigens, cross-absorption of antibodies, and application of the recently developed hemagglutination and flocculation tests apparently reliable diagnoses are now being obtained.

With the recognition that dog and cat parasites cause obscure, serious disease in humans, surveys to determine the geographic distribution and prevalence of individual species have taken on new significance. Among the first to recognize this and to carry out a thorough and meaningful survey of dog parasites were Donaldson and his associates (*21*) and Ehrenford (*22*).

Ehrenford has given at least a partial answer to one of the first and most significant questions asked about *T. canis*. Recognizing that pups are more often infected than adult dogs the question is often raised as to the actual risk with older dogs. Ehrenford's answer is that the risk depends upon the sex of the dog. Males are about as frequently infected as pups but the incidence among females is lower at all ages and is markedly lower in the mature adult. In Indiana and adjacent States less than 5 percent of mature females were found to be infected, while almost a third of the mature males were passing *Toxocara* eggs that might eventually be the cause of illness in children. These data were obtained from stray, uncared for, unwanted dogs, as has been the case in almost all published surveys.

Studies in New Orleans indicate that although the rate of infection among well cared for dogs is relatively much lower, it still is disturbingly high. Among 171 fresh dog stools collected along the sidewalks in front of houses of perhaps the most sanitation-minded, hygiene-conscious, and economically most favored families in the city, 7 percent contained *T. canis* eggs; hookworm eggs were found in 51 percent, and *Trichuris* in 25 percent. Almost all of these stools were judged to have come from adult dogs.

Also in New Orleans, among 103 immature and 222 mature dogs brought to veterinarians for various services, all relatively expensive (indicating the owners' concern for their well-being), *Toxocara* was found in approximately 15 percent of the young dogs and 3 percent of the older ones (*23*). Relatively few of the dogs of either age group were presented specifically for anthelmintic treatment. Nearly half of them harbored hookworms and one-fifth had *Trichuris* infections.

Conclusion

There is much needed information to be derived from good surveys and epidemiological studies of intestinal parasites of dogs and cats. To be of greatest usefulness such studies should be carried out with the same careful preparation and epidemiological forethought and purpose as would be acceptable in a study of hu-

man disease. In fact such studies can be regarded as being directly concerned with human disease. We are only beginning to appreciate the importance of including household pets in the total picture of the family's and the public's health.

REFERENCES

(*1*) Beaver, P.: Larva migrans. A review. Exp. Parasitol. 5: 587 (1956).

(*2*) Beaver, P.: Parasitic diseases of animals and their relation to public health. Vet. Med. 49: 199 (1954).

(*3*) Beaver, P.: Wandering nematodes as a cause of disability and diseases. Am. J. Trop. Med. & Hyg. 6: 433 (1957).

(*4*) Beaver, P.: Animal parasites and human diseases. Pediatrics 22: 380 (1958).

(*5*) Platou, R. V., and Beaver, P.: Visceral larva migrans. Acta. Paediat. 46: 64 (1957).

(*6*) Kirby-Smith, J. L., Dove, W., and White, G. F.: Creeping eruption. Arch. Dermat. & Syph. 13: 137 (1926).

(*7*) Wright, D. O., and Gold, E. M.: Löfflers syndrome associated with creeping eruption (cutaneous helminthiasis). Report of 26 cases. Arch. Int. Med. 78: 303 (1946).

(*8*) Dove, W. E.: An intestinal infection of *Ancylostoma braziliense* in a boy and skin lesions produced with larvae from this strain. J. Parasitol. 15: 136 (1928).

(*9*) Beaver, P.: The record of *Ancylostoma braziliense* as an intestinal parasite of man in North America. Am. J. Trop. Med. & Hyg. 5: 587 (1956).

(*10*) Muhleisen, J. P.: Demonstration of pulmonary migration of the causative organism of creeping eruption. Ann. Int. Med. 38: 395 (1953).

(*11*) Beaver, P., Snyder, H., Carrera, G., Dent, J., and Lafferty, J.: Chronic eosinophilia due to visceral larva migrans; report of three cases. Pediatrics 9: 7 (1952).

(*12*) Smith, M. H. D., and Beaver, P.: Persistence and distribution of *Toxocara* larvae in the tissues of children and mice. Pediatrics 12: 491 (1953).

(*13*) Dent, J., Nichols, R., Beaver, P., Carrera, G., and Staggers, R.: Visceral larva migrans: with a case report. Am. J. Path. 32: 777 (1956).

(*14*) Karpinski, F. E., Everts-Suarez, E. A., and Sawitz, W. G.: Larval granulomatosis (visceral larva migrans). Am. J. Dis. Child. 92: 34 (1956).

(*15*) Sprent, J. F. A.: The life cycles of nematodes in the family Ascarididae Blanchard 1896. J. Parasitol. 40: 608 (1954).

(*16*) Nichols, R. L.: The etiology of visceral larva migrans. I. Diagnostic morphology of infective second-stage *Toxocara* larvae. J. Parasitol. 42: 349 (1956).

(*17*) Nichols, R. L.: The etiology of visceral larva migrans. II. Comparative larval morphology of *Ascaris lumbricoides, Necator americanus, Strongyloides stercoralis* and *Ancylostoma caninum.* J. Parasitol. 42: 363 (1956).

(*18*) Sadun, E. H., Norman, L., and Allain, D.: The detection of antibodies to infection with the nematode, *Toxocara canis*, a causative agent of visceral larva migrans. Am. J. Trop. Med. & Hyg. 6: 562 (1957).

(*19*) Kagan, I. G.: Serum-agar double diffusion studies with ascaris antigen. J. Infect. Dis. 101: 11 (1957).

(*20*) Jung, R. C., and Pacheco, G.: Relationship of clinical features to immunologic reactions in visceral larva migrans (abstract). Am. J. Trop. Med. & Hyg. 7: 256 (1958).

(*21*) Donaldson, A., Steele, J., and Scatterday, J.: Creeping eruption in the Southeastern United States. Am. Vet. M. A., Proc. 87th Ann. Meet., p. 83, 1950.

(*22*) Ehrenford, F. A.: Canine ascariasis as a source of visceral larva migrans, a zoonosis. Am. J. Trop. Med. & Hyg. 6: 166 (1957).

(*23*) Vaughn, J. B.: The prevalence of *Toxocara canis* infection in dogs admitted to four veterinary hospitals in New Orleans, Louisiana. In press.

Second National Conference on World Health

The Second National Conference on World Health will be held in Washington, D.C., May 7–9, 1959, under the sponsorship of the National Citizens Committee for the World Health Organization. Conference chairman will be Dr. Milton S. Eisenhower, president of the Johns Hopkins University. Topics include prospects for the International Health Year; health and population changes; health and the American image abroad; and training and exchange programs for public health personnel.