Papers and Originals

Toxocariasis*

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Sydney Watson Smith, whose memory this lecture commemorates, had probably never heard of toxocariasis, and there are many of the profession today to whom the same observation would apply. It is proposed, therefore, to describe the toxocara parasite, to review the current knowledge concerning it, and to draw together and summarize some of the contributions my colleagues and I have been able to make to that knowledge. Of the relevance of the parasite to modern medicine there is little information, and an attempt will also be made to answer the question, What is its relevance to medicine today?

As this lecture commemorates Sydney Watson Smith it is appropriate that it should be said that the subject would, it is thought, have interested him. His interests as judged by his writings could be classed into diseases of the skin, selective infective disorders, and the effect of climate on health. He wrote on actinomycosis (Smith, 1938), rheumatism (Smith, 1925), wound diphtheria (Smith, 1931), and particularly about the outbreak of typhoid fever in Bournemouth in 1936 (Smith, 1936, 1942a). He was a keen observer, and his experience with typhoid stimulated his interest in the importance of fluid balance in febrile states. He made observations on food and fluid in typhoid fever (Smith, 1937) and on hydration and dehydration in health and disease (Smith, 1942b). He was an outward-looking man and led the British Medical Association on its first world tour—to Australia in 1935. His interest in infections, particularly unusual ones, which came his way at home and overseas and the influence of climate on health could well have come together in toxocariasis had he been aware of it, for it is an infection which so far as man is concerned may be regarded as unusual or "new," having been recognized in man for only some 18 years. During this time, however, it has become clear that it is a not uncommon human infection, and, further, part of our work has shown that it is more common in certain warm climates than it is in Britain.

The Parasite

Why should we have become interested in *Toxocara canis* and its near relative *Toxocara cati*? The answer is that a patient was admitted to the medical unit at the Hospital for Tropical Diseases with proved *T. canis* infection, and this raised a number of questions which led to a series of planned investigations. This patient was reported (Woodruff, Ashton, and Stott, 1961; Woodruff and Thacker, 1964). In brief he was aged 5 and had had an eye removed for a suspected retinoblastoma. The tumour turned out to be a granuloma, and after considerable difficulty and after cutting some 100 sections a larva was found and identified as *T. canis* by Professor J. C. C. Buckley. The boy had never been away from Britain, and the question was therefore asked how he had become infected. What is the risk of acquiring such an infection

in Britain and overseas, particularly in tropical regions? These questions when answered led on to a number of others.

The Parasites T. canis and T. cati

The original identification of the parasite now known as *T. canis* is attributed to Werner in 1782, but until recently there has been great confusion between it and related species, particularly *Toxascaris leonina*, which was not clearly differentiated from *T. canis* until described by Lieper (1907). The full development of these worms was not studied until done so by Sprent (1958). Adult toxocaral worms measure 3 to 5 in. (7·5 to 12·5 cm.) and live in the intestine of dogs and cats. They produce eggs which after maturing are infective to other dogs and cats and to man. When dogs, cats, or man swallow infective eggs the larvae are liberated in the intestine and burrow into the intestinal wall. When this occurs in puppies under the age of 5 weeks the larvae can go on to mature into adult *T. canis*, probably pursuing a cycle of development similar to that of *Ascaris lumbricoides* in man. That is, being taken to the liver or lung in the blood and there leaving the blood vessels to migrate up the bronchial tree and re-enter the intestine. The most usual method of infection of dogs, however, is prenatally; when older dogs swallow *T. canis* eggs the larvae resulting migrate in the tissues and persist in the second stage for long periods. From these tissues, particularly the retroperitoneal tissues, larvae from the pregnant bitch probably enter the fetus by a route the details of which are not known. The result is that puppies are very commonly infected with *T. canis*, the older dogs less commonly so.

In cats prenatal infection does not often occur, and probably the commonest mode of infection in them is for older cats to swallow eggs or larvae contained in the tissues of mice which then pursue a full cycle of development leading to the presence of *T. cati* in the animals' intestinal tracts. Eggs of *T. canis* and *T. cati* are swallowed by mice, rats, monkeys, and a wide variety of animals and develop into second-stage larvae just as they do in cats and dogs, but in these animals they do not go beyond the second stage. If, however, dogs or cats should eat meat of rats or mice containing second-stage *T. canis* or *T. cati* larvae respectively these larvae will then develop into adults. When ingested in this way larvae of *T. cati* develop into adults in cats more readily than do those of *T. canis* in dogs (Sprent, 1958).

When infective *T. canis* or *T. cati* eggs are swallowed by man larvae emerge from the eggs in the human intestine, penetrate the bowel wall, and are taken in portal blood to the liver and the lungs and usually beyond them to other tissues throughout the body. Sprent (1955a) deduced that it is the size and shape of the body of the larva which determines the kind of vessel it enters and hence how it proceeds along its migratory pathway. Once in a vessel the larva appears to leave it at a point at which its body approaches the diameter of the vessel. This is indicated by the occurrence of haemorrhages at specific sites, such as those on the surface of the brain in mice experimentally infected with *T. canis* (Sprent, 1955b). This is also likely to explain the somewhat uniform position

of granulomata caused by larvae of *T. canis* emerging from retinal blood vessels (Duguid, 1961a, 1961b). It explains, too, why ascaris larvae are filtered out of the circulation in man in the liver or lung and do not pass, in the blood, beyond these organs to other parts of the body. A week after infection *A. lumbricoides* larvae reach a diameter of 0·038 mm., whereas at the same stage *T. canis* larvae are only 0·02 mm. in diameter.

The appearance of the second-stage larva which infects man is shown in Figs. 1-3. These are the first known to have been taken of *T. canis* larvae with the scanning electron microscope, and they demonstrate well the chitinous mouth parts and the alae, or wings, with which the larva is equipped. It is this larva which penetrates the alimentary wall of the host and is carried in portal blood first to the liver, where some, both in man and in experimental animals, are filtered out and form granulomata. They have been demonstrated in the liver by Beaver (1952) and in one case in Dr. Avery Jones's unit in London.

Reservoir from which Man may be Infected

The boy who was our first toxocaral patient had not been out of Britain, and this therefore posed the question of how common the infection is among dogs and cats in this country and what are the chances of man becoming infected from

FIG. 1.—*T. canis* larva photographed (x 420) with Cambridge Instrument Company's scanning electron microscope.
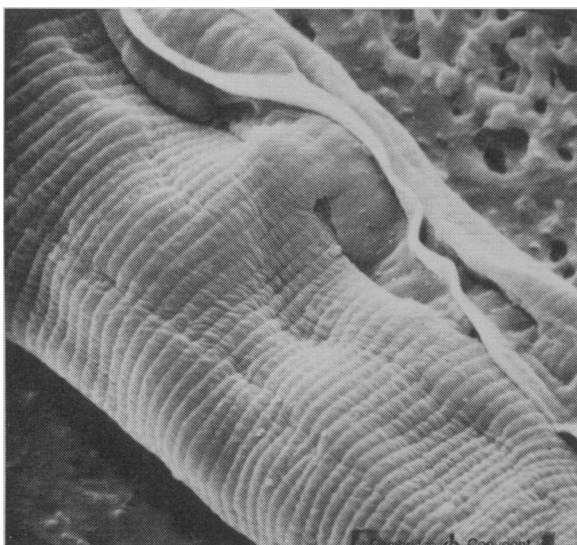

FIG. 2.—Body of *T. canis* larva (x 4,700). The ala (or wing) is clearly visible (scanning electron micrograph).
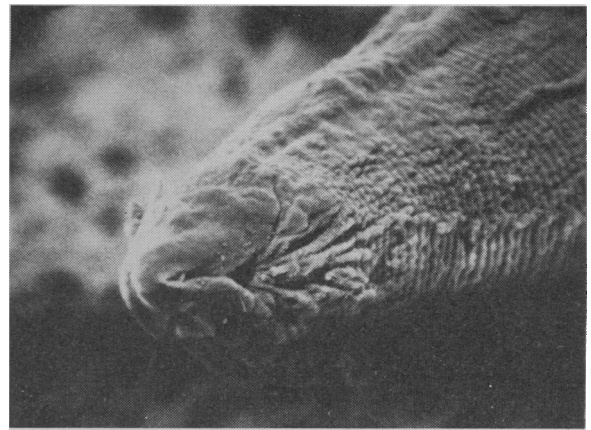

FIG. 3.—Anterior extremity of *T. canis* larva (x 5,250). The cuticular mouth parts are visible (scanning electron micrograph).

these animals. Very little information on this could be found, and one had to go back to 1927 for any recorded survey of *T. canis* incidence in dogs in Britain. Lewis (1927) then found 16·3% of 43 dogs in Aberystwyth to be infected. Brown and Stammers (1922) had found that 3% of dog faeces recovered from London streets contained *T. canis* ova.

From homes for dogs and cats specimens of faeces have therefore been collected and examined for *T. canis* eggs by the method of Ridley and Hawgood (1956). A considerable proportion of the dogs have been found to be infected; over 1,100 have been examined from these homes, the overall prevalence rate being 12·8% (Table I). In recent years there has been a tendency for the prevalence rate to fall and it is believed that this is related to worming carried out because of the publicity which this work has had. Among dogs and cats in quarantine the rates have been low since these observations began, and in such stations it is certainly related to the worming on admission.

The earliest of these results was published in 1964 (Woodruff and Thacker, 1964), and since then there has been a renewal of interest in the prevalence of the infection among animals in this country. Oldham (1965) carried out necropsies on 250 dogs and 100 cats and found *T. canis* in 6·4% of the dogs and *T. cati* in 8% of the cats. Oldham published a personal communication from Dr. J. E. Sloan, who from 1950 to 1963 had examined 9,000 faecal specimens from dogs and found a fall in incidence of *T. canis* from 17·5 to 7·5%. Dubey (1966) performed necropsies on 110 cats obtained from an animal dealer in London and found *T. cati* in 45·4%. This is of particular interest in that Oldham (1965) had given it as his opinion that the prevalence rates we had reported in dogs and cats were too high and were not representative of those in the country as a whole; but our figures are much lower than those reported by Dubey (1966). Moreover, Dubey remarks that faecal examination indicates a lower infection rate than does examination for adult worms at necropsy, for only 21 out of 39 infected cats had gravid worms. It is probable, therefore, that our figures do not reflect the total numbers of infected animals; these are likely to be rather higher than those found by us.

TABLE I.—*Results of Examining for T. canis Ova the Stools of Dogs from London and the Home Counties*

Year	No. Examined	% Whose Stools Contained *T. canis* Ova
1962–3	300	20·7
1964	60	21·7
1965	130	21·5
1967	96	16·7
1968	360	5·3
1969	161	2·5
Total	1,107	12·8

Our figures do, however, show the proportion of animals which by passing ova in their faeces are to be regarded as a public health menace. If Dubey's estimate of the proportion of infected animals to those actually passing ova or containing gravid worms is correct then our figures should be multiplied by a factor of 1·8 in order to obtain the absolute incidence of infection.

From these studies it seems clear that there is a large reservoir of infection with toxocariasis in dogs and cats in Britain. This posed a further problem. Bearing in mind the close contact between man and domestic animals, transmission of infection to man would be expected to be common, yet only some 200 proved cases of toxocariasis have been reported, almost certainly because the means of recognizing it have not been available. How often then does man become infected from this large reservoir of toxocaral parasites in domestic animals?

Detection of Toxocaral Infection in Man

When our studies were started there had been very few reported cases of toxocaral infection in man. In Britain they were limited to seven reported by Ashton (1960), who had found the larvae in granulomata in the choroid and retina of eyes that had been enucleated for suspected retinoblastoma but in which the mass had proved on section to be a granuloma. Beaver (1952) found *T. canis* larvae in one of three children with eosinophilia, but the prevalence of such infection in man was completely unknown.

The prime difficulty is that infection gives rise to larvae which migrate in the tissues but do not develop beyond the second stage in man. Unlike ascaris they do not mature, enter the gut, and reveal their presence by passing ova. In tissues they are extremly difficult to find, and even in the relatively small granulomata which they produce in the eye more than 100 serial sections may be needed to locate one. The parasite is difficult enough to locate in a granuloma in the eye even though this is only a few millimetres in diameter; it would be much more difficult to find in large organs such as the liver, spleen, or brain. When demonstrated in the liver during life in man it has been by open operation and removal of a granuloma visible on the surface. Yet it seemed worth while to look for evidence of infection, for in this work it had been found that many dogs and cats are infected and it is known that domestic contact with these animals is close. In experimental animals the parasites become widely disseminated, and it appeared probable that this occurred in man. Moreover, as the eye is a small organ and yet most identified *T. canis* larvae have been found there, it would appear probable that for every case in which it was involved there would be several in which other tissues were invaded, but that invasion occurs with fewer symptoms than when the eye is affected. If sight is damaged a patient soon seeks medical help, but if larvae invade the liver, lung, or even the brain they are likely to give rise to symptoms the significance of which is difficult to assess.

Serological or immunological tests therefore appear to offer the best opportunity for determining the prevalence of toxocaral infection among apparently healthy persons, and also to provide diagnostic evidence among those in whom the infection is suspected. When this work was started some preliminary studies had been carried out by Duguid (1961c) in observing delayed skin responses in patients with ocular lesions suspected of being toxocaral in origin. A haemagglutination test had been used by Kagan, Norman, and Allain (1959) but cross-reactions with sera from patients with *A. lumbricoides* had been obtained. Dr. D. S. Ridley (personal communication) carried out complement fixation tests on serum from patients with toxocariasis but found that the specificity of the complement fixation test in this infection was poor. We had very extensive experience with skin tests which have been in use in the Hospital for Tropical Diseases for 30 years for the diagnosis of filarial and schistosomal infections. A skin-testing antigen was therefore prepared with the well-tried method of Fairley (1931), and it was decided to explore the diagnostic possibilities of the skin test along with a fluorescent antibody test adapted for toxocaral infection.

Diagnostic Methods

Skin Test

It is clearly of prime importance to standardize any skin test which it is proposed to use, and from the outset care has been taken to see that this has been done. Initially antigen was used at two dilutions, 1/1,000 and 1/200, the object being to determine whether false-positive or cross-positive reactions were obtained with the stronger antigen. These early results (Woodruff and Thacker, 1964) showed that when dilute antigen was used there were only about 2% of positive reactions among those who were apparently healthy and also among those who had had helminthic infections. No significant number of false-positive or cross-positive reactions was occurring. When, however, stronger antigen (1/200) was used some additional positive reactions were obtained among those who had known non-toxocaral helminthic infections. In view of this all diagnostic and survey work has been carried out with dilute antigen (1/1,000) only. To date 485 apparently healthy persons have been tested and 1·86% have given positive reactions; 207 with non-toxocaral helminthic infections have been tested and 2·4% have given positive reactions. The difference between these two proportions is not statistically significant as assessed by the χ^2 test ($\chi^2=0·229$, $N=1$, $0·7>P>0·6$).

Experiments with Skin Test in Laboratory Animals

Further evidence of the value and specificity of the skin test has been sought from experiments with mice and with rhesus monkeys (Wiseman and Woodruff, 1967; Wiseman, Woodruff, and Pettitt, 1969). Six mice were infected with 200, 400, or 600 *T. canis* eggs and the skin test in them was observed to become positive from the ninth day of infection. No reaction occurred in control non-infected animals; the injection of several amounts of the antigen did not of itself therefore cause the test to become positive. Nor was there any reaction in animals injected with saline as a control measure.

In the experiments with monkeys, initially two were infected with large numbers of eggs—500 and 1,000 respectively. Before the experiment one was found to be infected with *Enterobius vermicularis* and hookworms and the other with *E. vermicularis* and *Trichuris*. Before infection with toxocara eggs both showed negative toxocaral skin tests; but these converted to positive five weeks after infection—that is, one to two weeks after they had shown their peak eosinophilia.

The experiment was later continued with four monkeys infected with much smaller doses of eggs. One object of this experiment was to determine how small an infecting dose could be and yet give rise to conversion of the skin test and to eosinophilia. The four monkeys were infected with from 200 to as few as 20 eggs. The skin test in all four converted from negative before the experiment and during the early post-infective period to positive four to six weeks after infection. It seemed that even quite a small infecting dose of eggs (20) was sufficient to give rise to conversion of the skin test and that this conversion took little longer but was less permanent in the lightly infected than in the moderately and heavily infected animals. In the most lightly infected animals the eosinophilia also was delayed in its appearance and less pronounced than in those moderately and heavily infected.

Conclusions from These Experiments.—The last experiment indicates that small numbers of larvae may be involved in infections and that in such cases the chance of demonstrating the larvae definitively is small. Further conclusions are that conversion from a negative to a positive toxocaral skin test is clearly related to toxocaral infection but that within the limits of the infecting doses used the time required for conversion appears to be unrelated to the intensity of the infection. It thus has the appearance of an allergic reaction dependent on small amounts of antibody being adsorbed on skin cells. Before the experiment all of these four animals were found to be infected with *Enterobius* species and two of them with *Trichuris* species. Thus a further valuable conclusion from the experiment is that there is a high degree of specificity in the skin test in that negative reactions were obtained before infection with *T. canis* even though there were pre-existing infections with *Enterobius* in all animals and with *Trichuris* and hookworm infections in some.

Fluorescent Antibody Test in Toxocariasis

When these experiments on the fluorescent antibody test in toxocariasis were started no work on the test as applied to this infection had been published. Voller and Taffs (1962) and Taffs and Voller (1963) had shown that ova and larvae of *A. lumbricoides* could be used as antigen in performing the fluorescent antibody test in ascariasis, and experiments were therefore carried out using the ova and the larvae of *T. canis* as antigen for the fluorescent antibody test in toxocariasis. Details, of the technique and of results have been published (Bisseru and Woodruff, 1968). When ova were used as antigen a good deal of trouble with autofluorescence was encountered, and though ova are much easier to obtain than larvae their use was ultimately abandoned because of this trouble.

Larvae have to be obtained by infecting mice with embryonated eggs of *T. canis*, killing the animals 60 to 72 hours later, and recovering the larvae from their liver and brain by the Baermann funnel technique. Much better results were obtained with them, but cross-reactions occurred with the sera of patients who had *A. lumbricoides* infection. In these cases, however, it was possible to adsorb the serum, and good differentiation was then obtained between the results in patients with toxocaral infection and those with only infection with *A. lumbricoides*. The *A. lumbricoides* suspension used for adsorption was one in which 2 mg. of dried powdered *A. lumbricoides* worm was suspended in 1 ml. of saline and incubated for 12 hours before filtration. Best results were obtained when one volume of serum from a patient with toxocariasis was adsorbed with two volumes of *A. lumbricoides* extract (Table II).

Cross-reactions were obtained in one out of two patients with *Wuchereria bancrofti* infection but not in other patients who had known helminthic infections of non-toxocaral type. Good correlation was obtained between the results of the fluorescent antibody test and the skin test, but it has been possible to show that a positive fluorescent antibody test persists for less time than does a positive skin test. A result of

this is that not all of those who have a positive skin test also have a positive fluorescent antibody test. This was shown in a later series of nine patients in each of whom a *T. canis* larva had been found in a retinal granuloma, in each the toxocaral skin test was positive, but in four the fluorescent antibody test for toxocariasis was negative. It was noted that the shortest time which had elapsed since the demonstration of the infection was three years and that in no patient was there a really significant eosinophilia.

One of the difficulties encountered in performing this test was that the larvae after being harvested had to be used within four to five weeks, otherwise autofluorescence developed when they came to be employed. Dr. I. G. Kagan suggested that this difficulty might be overcome by digesting the larvae with a pepsin-hydrochloride acid solution and later fixing with a solution of bovine serum albumin in normal saline, the method being that used by Sulzer (1965), for *T. spiralis* fluorescent antibody tests. This procedure resulted in considerably improved specificity of the test, which was negative in 12 patients who were known to have had *A. lumbricoides* infection. It was also negative in a further 44 patients with other assorted non-toxocaral helminthic infections. In addition sera from 16 healthy controls have been tested with negative results. The test has been used in about 300 cases in which toxocariasis had been suspected on various grounds.

In mice infected with 200 eggs the test has been shown to become positive 24 days after infection, and in mice infected with 500 eggs 12 days after infection.

With these partially digested and fixed larvae the test is reliable and of very good specificity.

This test and the skin test are the main tools which, taken together with the clinical features of the patient and the presence or absence of eosinophilia, have been used to seek evidence of toxocaral infection in given situations.

Clinical Syndromes Presented in Toxocariasis

What then are the clinical syndromes which toxocariasis is known to cause or in which it might be suspected of playing a part? Beaver, Snyder, Carrera, Dent, and Lafferty (1952) were the first to recognize a larva of *T. canis* in human tissues. They did so in the liver of a child aged 2½ years who had pyoderma, frequent upper respiratory tract infections, and eosinophilia. Repeated examination of stools had failed to reveal parasites. Laparotomy showed an enlarged liver studded with white plaques, one of which was removed and in it a larva was found. There was marked necrosis and eosinophilic infiltration round the worm and its track. In view of this report hepatomegaly associated with eosinophilia is clearly one of the conditions in which toxocariasis should be suspected.

The development of eosinophilia and also of hepatomegaly in children infected with *T. canis* was confirmed experimentally by Smith and Beaver (1953) in work following up the last-mentioned study by means of an experiment which cannot be commended. They infected mentally defective children aged 2 and 3 years old respectively with 200 embryonated eggs of *T. canis*. Both developed very significant eosinophilia and some degree of hepatomegaly. In both cases significant eosinophilia persisted for 13 months after infection.

Nichols (1956) successfully demonstrated *T. canis* larvae as a cause of granulomatous reaction in the choroid and retina of the eye, and Ashton (1960) was the first to describe the parasite as a cause of enophthalmitis and retinitis in Britain. The patient who originally started us thinking about the problem of toxocariasis in Britain and overseas was among the earliest of these ophthalmic toxocaral cases to be reported in this country (Woodruff *et al.*, 1961). Clearly in our studies choroidoretinitis of otherwise undetermined origin was one of

TABLE II.—*Comparison of Fluorescent Antibody Titres by Indirect Technique Using T. canis Larvae as Antigen with Sera from Patients with Toxocara and Ascaris Infections (From Bisseru and Woodruff, 1968)*

	Dilutions			
	1/10	1/160	1/640	1/2, 560
1 vol. serum from a patient with toxocariasis adsorbed with 2 vol. A. lumbricoides extract				
Toxocara serum	2+	2+	2+	+
Toxocara serum adsorbed	+	+	+	+
Ascaris serum	2+	2+	+	+
Ascaris serum adsorbed	+	−	−	−

the conditions which should be looked at with the possibility in mind of toxocariasis being its cause.

As the *T. canis* larvae enter the lungs of experimental animals the toxocaral skin test has been performed in patients with asthma and in others with pneumonitis and eosinophilia. The results of the preliminary studies of patients in these categories are shown in Table III.

With Dr. C. M. P. Bradstreet's co-operation antigen has been distributed to doctors requesting supplies for specific patients through the Public Health Laboratory Service. To date 91 patients in various hospitals throughout the country have in this way had a toxocaral skin test carried out for choroidoretinitis and 8·8% have given positive reactions. Nearly 30% of patients with hepatomegaly, most of whom also had eosinophilia, have given positive reactions and 17% of 76 patients with asthma, bronchitis, or cough, again mostly in association with eosinophilia, have given similarly positive reactions (Table III). These percentages compare with 2% of positive reactors among apparently healthy persons. The 8·8% of positive reactors among this series with choroidoretinitis agrees well with the 10% of children with uveitis attributed to toxocariasis by Perkins (1966). It should be noted that work in publication from this unit has shown that the toxocaral skin test in man once positive tends to remain so for many years. Thus in a given population the proportion of persons over 10 years of age showing a positive skin test is a good indication of the amount of toxocaral infection that has taken place in that population.

Eosinophilia, has, as is to be expected, been very common among those who have had a positive skin test. It has been found that about 90% of positive skin reactors have a significant eosinophilia—that is, more than 500 eosinophils/cu. mm. (Wiseman and Woodruff, 1968).

These studies show that in patients with choroidoretinitis, hepatomegaly, asthma or pneumonitis and eosinophilia of undetermined origin toxocariasis should be suspected, and then investigations using the skin test and fluorescent antibody test may enable conditions of this kind to be removed from the category of idiopathic or of unknown aetiology.

Wider Implications of Knowledge of Toxocariasis

Transmission of and Predisposition to Infection

Early in this work Professor J. J. C. Buckley drew attention to a report of a larva having been found in the brain (Beautyman and Woolf, 1951). The suspicion that this larva was of *T. canis* has subsequently been proved (Beautyman, Beaver, Buckley, and Woolf, 1966). The child in whom this larva had been found had died of poliomyelitis. This fact and the fact that *T. canis* larvae leave the lumen of the bowel to migrate widely in the tissues suggested that they may carry with them bacteria or viruses or cause damage in the central nervous system and other tissues which could afford foci for the growth of viruses or bacteria circulating at the time at which the damage was done. Sprent (1955a) demonstrated experimentally in mice infected with *T. canis* that the larvae migrate to the brain, especially the cortical regions, and he suggested that they may occasionally carry with them viruses and other micro-organisms. Mochizuki, Tomimura, and Oka, (1954) demonstrated experimentally in mice that *T. canis* lar-

vae in migrating to the brain are able to carry with them the virus of Japanese B encephalitis. The way in which infection is transmitted or acquired commonly presents considerable epidemiological questions. This together with the demonstration that about 2% of apparently healthy persons become infected with toxocariasis, usually without it being known, suggested that it might be worth while to explore the possibility that the larvae could convey poliomyelitis. The fact that it was after death from poliomyelitis that a *T. canis* larva had been found in the brain in the case reported by Beautyman and Woolf (1951) further strengthened the view that this was worth investigating.

With help from various clinics it was possible to test 191 persons who had had poliomyelitis and who had some residual paralysis. Of these, 26 (14·6%) gave a positive skin reaction as compared with 2% of positive reactions among healthy controls, a difference which is clearly highly significant ($\chi^2=26·7$, P<0·001).

While doing this work Brain and Allan (1964) reported the development of encephalitis in a child in whom the diagnosis of toxocaral infection was highly probable.

There may well be other infections which are transmitted by or predisposed to by toxocaral infection, and Hutchison (1965, 1967) produced evidence that *T. cati* ova and larvae may be concerned in the transmission of toxoplasmosis. In conjunction with Dr. D. Fleck it has been possible to arrange for Dr. Wiseman to test 65 patients whose sera had been referred to Dr. Fleck for a toxoplasmal dye test and in many others because of uveitis. Among five who had a positive toxocaral skin test, however, none had a positive toxoplasmal dye test titre. This work is published elsewhere (Wiseman, Fleck, and Woodruff, 1970). Through the co-operation of Dr. Bradstreet, of the Public Health Laboratory Service, the skin test has been carried out on 14 patients who had positive toxoplasmal dye test titres, and in 2 (14·3%) of them a toxocaral skin test was positive. The figures are small, but the first study gives no support to the view that toxocaral larvae and toxocaral infection are involved in the transmission of toxoplasma; the latter figure is, however, not inconsistent with such a view.

Tissue Damage Caused by Toxocaral Larvae

Both in experimental animals and in man the second-stage larvae of *T. canis* and *T. cati* are known to wander widely in the tissues and to reach many organs, including the brain. As they burrow through the tissues they produce tracks in which there are haemorrhage, necrosis, and inflammatory cells. When they die and disintegrate they give rise to granulomatous foci. Knowing that the brain had been involved in man on at least one proved occasion the question was asked whether there were any diseases resulting from brain damage in which toxocaral invasion might play a part and in which therefore it would be worth while to look for evidence of the infection.

Epilepsy appeared to be a possibility in this category, and the skin test was therefore carried out in a series of 349 patients with epilepsy, 297 of whom were resident at Lingfield Hospital School for Epileptics. Of these, 7·5% reacted positively—in other words, the proportion of positive reactors was about three and a half times as great as among the apparently healthy population, a difference which is highly significant ($\chi^2=10·6$, P<0·002). Among those with a positive skin test and epilepsy 77% had had a dog or cat in their household for at least three months before the development of their epilepsy, and there was therefore a known opportunity for them to have become infected. It should here be emphasized that infection can be acquired without known contact with dogs and cats; in some of our patients with proved infections the contact has been casual.

TABLE III.—*Results of Skin Testing with Toxocaral Antigen Prepared in the Unit and Distributed Through the Public Health Laboratory Service to Doctors Throughout Britain*

	No. Tested	No. Positive
Choroidoretinitis	91	8 (8·8%)
Hepatomegaly	41	12 (29·3%)
Asthma, bronchitis/cough..	76	13 (17·1%)

Myocarditis

A toxocaral larva was found in the myocardium of a patient by Dent, Nichols, Beaver, Carrera, and Staggers (1956), and Friedman and Hevada (1960) reported a case in which the circumstantial evidence for toxocaral myocarditis was strong. Their patient had had several attacks of fever, bronchitis, and pneumonitis and had been in contact with a dog in whose faeces ova of *T. canis* were found. This patient also had lymphadenopathy and cardiomegaly which improved in unison with the eosinophilia. Woodruff (1965) suggested that involvement of the myocardium in this way may play a part in the production of the puzzling endomyocardial fibrosis which has been reported from Africa in recent years.

An illustration of the kind of problem in which this infection may be playing a part is given by a block which Professor M. S. R. Hutt kindly sent me from Makerere, East Africa (Fig. 4). This specimen was taken at necropsy from a 25-year-old sweeper who had had a history of vague substernal discomfort lasting about a month; but this had not been incapacitating, and he had carried on with his work until he had suddenly developed pain in the chest, become short of breath, produced copious sputum, and been admitted to hospital. Pulmonary oedema was present on admission and he died within a few hours. At necropsy his lungs were grossly oedematous but no parasites of any kind were detectable in the bowel; the heart showed extensive myocardial degeneration with gross eosinophilic cell infiltration. Professor Hutt remarks that the eosinophils "in some areas appeared to be arranged around a central region of necrosis reminiscent of worm tracks" (Fig. 4). Unfortunately by the time the necropsy had been done some serum from this patient was no longer available for a fluorescent antibody test, and of course a toxocaral skin test was not done before death. Nevertheless, Professor Hutt remarks: "The changes appear to be those of parasitic infiltration. The patient did not have any evidence of *Ascaris* infection and I have no evidence of any other parasitic infection."

We have evidence that toxocariasis is not uncommon among dogs in the Kampala area. As part of our series of investigations Dr. Wiseman examined the faeces from 116 dogs in Kampala and found 12·5% to be infected. The skin test was carried out on 161 in the Baganda there, and an extraordinarily high incidence of positive reactors was found— 40 (25%) from among 161. In view of this evidence of the prevalence of infection in the locality there seems to be every reason for suspecting that this eosinophilic myocarditis was of toxocaral origin. Damage so severe as this could well be followed by a fibrotic reaction. The causation of endomyocardial fibrosis is at present unknown, but here we have a lead which should be followed up.
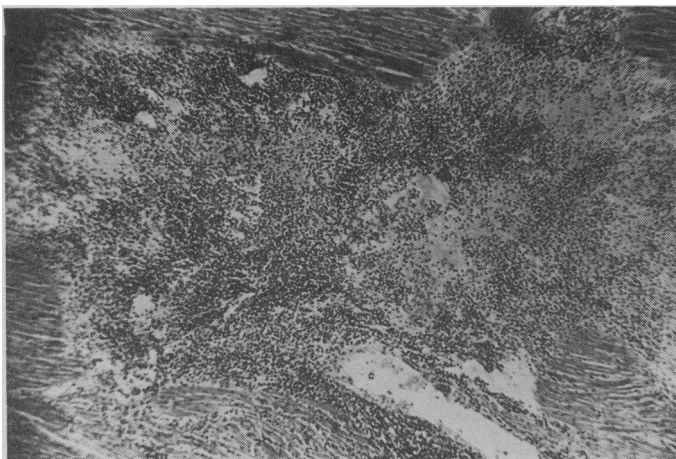
Toxocaral Endophthalmitis

In the past five years there have been among the patients referred to the medical unit at the Hospital for Tropical Diseases with choroidoretinitis, eight in whom a lesion has been present in association with a strongly positive skin test and in four cases a strongly positive fluorescent antibody test. In five of these cases there was a pronounced eosinophilia. Most of these patients were referred through the kindness of Professor E. S. Perkins, Professor N. Ashton, or Mr. Lorimer Fison, to all of whom I am most grateful.

What are the features by which these cases may be recognized? An excellent description has been given by Ashton (1969), and observations will here be limited to those which might help physicians and other non-ophthalmic specialists on the track of the diagnosis.

Patients in this series have invariably had a unilateral lesion, and this is what one might expect, for the chance of larvae entering both eyes must be small even in quite heavy infections. The presence, therefore, of bilateral lesions suggests a diagnosis other than toxocariasis.

The lesions have mostly been near the macular region, the larva having apparently entered by the retinal artery; but one earlier patient, not in this series, who had had his eye removed, was found to have the parasite not far behind the iris, a situation to which it had been conveyed almost certainly by the ciliary vessels. Toxocaral anterior uveitis has been described by Ashton (1969); it is less common than lesions in the macular region.

Early lesions are almost invariably raised as a result of the development of granulomatous tissues.

These features then should suggest toxocariasis, a unilateral raised lesion, the presence of eosinophilia, a positive toxocaral skin test, and usually a positive toxocaral fluorescent antibody test.

Treatment in these cases has been with a standard course of diethylcarbamazine—that is 3 mg./kg. body weight thrice daily for 21 days. In one child considerable extension of the lesion occurred during the course of treatment, but after this it remained static. In several cases there was a rise in the eosinophil count during treatment, suggestive of death and disintegration of the infecting larvae. The longest period of follow up now extends to just under five years, and in all patients there has been nothing suggestive of a retinoblastoma, which formerly was indistinguishable clinically from toxocaral choroidoretinitis. In all cases the eye has remained quiet after the initial active period in which some of them presented. It is therefore now possible to provide good grounds for recognizing and distinguishing toxocaral eye lesions from retinoblastomata, and in this way at least these eight eyes have been saved.

Significance of Toxocariasis Overseas

The question was asked how common is toxocaral infection among animals and man overseas. A study was therefore planned and Dr. Wiseman proceeded overseas to gather information on these matters in selected areas. The results are shown in Table IV. It is clear that there is a great deal of this infection in certain areas abroad. Apart from this study there is little information concerning its incidence overseas; Maplestone and Bhaduri (1940), however, found 82 out of 100 dogs in Calcutta to be infected, and Ehrenford (1956) found 21%

FIG. 4.—Section through myocardium of patient in Uganda who died of possible toxocaral myocarditis.

TABLE IV.—*Proportion of Dogs in Whose Stools T. canis Ova were Present in Different Regions*

	No. Examined	% Infected
Malta—dogs	52	28·8
Nigeria (Ibadan)—dogs	72	37·5
Uganda (Kampala)—dogs	116	12·5
Kenya (Nairobi)—dogs	35	5·7
(Masai villages)—dogs	25	12·0
Tanzania (Dar-es-Salaam)—dogs	50	28·0

of 1,465 dogs in Indiana to be infected, an incidence very similar to our own in Britain. In a recent study in Mexico City Styles (1967) showed that 93% of 120 stray dogs aged under 6 months were infected with *T. canis* in that city.

Bearing in mind the close contact that there is between dogs and man, not only at home but overseas, it is clear that the possibility of human infection is very considerable. In this connexion a point of note is that salad vegetables are not uncommonly contaminated with soil-transmitted helminthic eggs and that in a recent study in Rome, Mastrandrea and Micarelli (1968) found that one out of four groups of vegetables sampled in Rome markets was infected with ova of *Ascaris* species which could, of course, include *Toxocara*. There can be little doubt that transmission of eggs of this species could readily occur under domestic circumstances.

Conclusions

What then are the conclusions from these studies? Firstly, the answer to our question of how big is the reservoir of toxocaral infection in domestic dogs and cats is that it is very considerable, not only in Britain but also overseas, and perhaps more particularly overseas where the kind of problem it causes clinically, especially eosinophilia, is so much more common than in temperate regions.

This raised a further question, How often is man infected from this reservoir? The answer to this is that he is infected much more commonly than is suggested by the small number of ocular cases reported. Work carried out in this unit indicates an incidence of about 2% in adults in Britain.

In addition to the eye, organs which may be the seat of infection include the liver and lungs. Toxocara larvae also occasionally invade the heart and the brain and are a common cause of eosinophilia.

The next question is, What are the wider implications of the knowledge which has accrued of the natural history and of the considerable prevalence of toxocariasis in man? The first is that it seems probable that larvae in their migrations from the gut may occasionally either be a vehicle of infection or facilitate infection by the damage they cause. There is some evidence of this process in poliomyelitis.

There is also evidence that some cases of epilepsy almost certainly result from toxocaral invasion of the brain. This knowledge has therefore helped to recover from the many labelled as idiopathic some cases of epilepsy and some of hepatomegaly, asthma, and eosinophilia.

The diagnostic features which may help in the saving of an eye are unilateral choroidoretinitis, particularly if it occurs near the macular region, but also, in a minority of cases, anterior lesions. Visible early lesions are raised and are usually associated with an eosinophilia and almost invariably with a positive toxocaral skin test.

Because the larvae are small and because as few as 20 may cause significant illness or lesions it is certain that in most infected patients it will never be possible to diagnose the infection by recovering larvae. Even when the larvae are present in quite small lesions many serial sections may be necessary to locate one. Immunological tests at the present time afford the most valuable diagnostic means available, and of these the standardized skin test and fluorescent antibody test are the most reliable and practicable.

The evidence which has accrued through the use of these tests combined with clinical methods indicates that this infection in man is widespread, often silent, but not uncommonly serious.

The evidence indicates that there is now enough knowledge to act, firstly, to control the infection in dogs and cats and thus prevent many developing the disease, and, secondly, to increase awareness of and use of diagnostic and therapeutic facilities to deal with the infection in man. Possibly the most important conclusion from this work is that though hardly known as a human infection till 10 years ago toxocariasis is

widespread and an important cause of morbidity. The clinical and public health problems the infection presents are serious and need urgent attention.

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