Infection With Animal Helminths

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Brit. med. J., 1964, 1, 1001-1005

This investigation was planned to answer questions which arose out of the admission to the medical unit at the Hospital for Tropical Diseases of a child in whom *Toxocara canis* infection had been proved. Observation of this patient drew attention to the fact that some features of toxocariasis, and in particular eosinophilia, are commonly encountered not only among those who have resided in the tropics but also among others who have never been away from Europe, and that clinical features associated with toxocaral infection may present as a syndrome causing great diagnostic difficulty. In view of the high incidence of toxocaral infection which was shown by this investigation to be present among dogs and cats in Britain, and because of the known high incidence of the infection among these animals in parts of the tropics, it seems that the opportunity for man to become infected is considerable. It therefore appeared worth while to experiment with intradermal tests to determine, if possible, to what extent toxocariasis accounts for otherwise undiagnosed eosinophilia in man. The work reported here therefore falls into three parts: first, the observation of the initial patient; second, an inquiry into the incidence of *T. canis* infection among dogs and cats in Britain—that is, an inquiry into the extent of the reservoir from which man may become infected; and third, because evidence was obtained that this reservoir is considerable in size, an investigation which was carried out into the incidence of toxocariasis as revealed by an intradermal test among patients with otherwise undiagnosed eosinophilia or other allergic states. This latter investigation required further examination of the test in groups of apparently healthy controls to ensure that false-positive reactions do not occur and in other patients with non-toxocaral helminthic infections to ensure that cross-reactions do not give false results.

Life-cycle and Modes of Infection with *T. canis* and *T. cati*

Toxocara canis and *T. cati* infect dogs and cats respectively, adult *T. canis* reaching lengths of between 3 and 5 in. (7.5 and 12.5 cm.) in the intestine of dogs. The life-cycle and habits of the parasites are similar to those of *Ascaris lumbricoides* in man. When *T. canis* or *T. cati* ova (Fig. 1) are swallowed by man they develop in the intestine into larvae which penetrate the intestinal wall and, on reaching a blood-vessel, may be carried to a wide variety of organs, though it is probable that the majority are filtered out of the blood in the liver. Those, however, which pass the liver may be filtered from the blood by capillary plexuses in the lungs, eye, brain, or other organs. In these tissues they probably migrate for a period before they die. After death of a larva the helminthic protein released from it stimulates the production of a granuloma in which eosinophils are prominent. Human tissue constitutes an

environment sufficiently foreign to the larvae to be unable to support their growth to maturity and hence infection in man with adult *T. canis* or *T. cati* has not been reported.

Puppies are more commonly infected with *T. canis* than are adult dogs, the larvae having migrated from the maternal tissues to the intestines of the puppy and there matured. Young animals probably constitute the main reservoir of infection, and the greatest risk of acquiring the disease probably occurs when an infected puppy is brought into a household in which there are children; but this study shows that large numbers of older dogs and cats may be infected.

Although the parallelism between the life-cycles of these animal and human ascarids is close, it is clear that there are considerable differences in that human ascaris larvae apparently very seldom migrate through tissues other than the liver and lung. On hatching in the intestine the larvae burrow into the intestinal wall, reach blood-vessels, and are carried to the liver

FIG. 1.—Ovum of *T. canis* in stool of dog. (Courtesy of Dr. D. S. Ridley.)

or the lung. By the time they have reached these organs their size is such that they are filtered from the blood-stream by capillary plexuses and migrate to bronchioles, along which they pass to reach the trachea, epiglottis, and oesophagus, whence they are carried with food or saliva to reach the small intestine, where they mature. In contrast with this life-cycle of *A. lumbricoides* in man, only a smaller proportion of *T. canis* larvae are apparently removed from the blood by the liver or lung. This difference is almost certainly accounted for by the smallness of the larvae, which permits them to pass with relative ease through the capillary plexuses in the liver. Sprent (1955) has shown that in mice the larvae of *T. canis* one week after infection measure approximately 0.02 mm. in width and

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those of *A. lumbricoides* are nearly double that size, being 0.038 mm.

Man probably is usually infected by swallowing *T. canis* eggs which have reached the fingers as a result of fondling infected animals or, especially in the case of children, by handling soil contaminated by infected animals' excreta and putting the unwashed fingers in the mouth. An alternative method is by consuming food, more particularly vegetables such as lettuce, which has been so contaminated.

Infection with the dog hookworm, *Ancylostoma caninum*, also may give rise to eosinophilia in man. This parasite may be acquired when contact occurs between the skin and moist earth on which dogs' excreta containing *A. caninum* ova may have been passed. In such earth the ova develop into larvae which have the ability to penetrate unbroken skin. These larvae, like those of *Toxocara* species, do not mature in man but after migrating for a period in the tissues die and are absorbed.

Initially Observed Patient with Toxocariasis

This patient was a 5-year-old boy who had noted a year previously that he could not see with his left eye. The ophthalmologist to whom he had been taken found that in the macular region of this eye there was a small mass simulating a retinoblastoma. As the sight of the eye had been lost and as malignancy could not be excluded as a cause, the organ was enucleated. Section revealed that the tumour (Fig. 2) was unusual, and the specimen was sent to Professor Norman Ashton at the Institute of Ophthalmology, London, to whom we are indebted for the loan of photographs and for his interest and help. He suspected a helminthic granuloma and referred sections to Professor J. J. C. Buckley at the London School of Hygiene and Tropical Medicine. Professor Buckley identified a larva of *T. canis* in the

FIG. 2.—Section through the enucleated eye of patient showing granulomatous mass caused by larva of *T. canis*. (Courtesy of Professor N. Ashton.)

tumour (Fig. 3). This child did not complain of symptoms other than those referable to the eye. At the time at which he was first seen at the Hospital for Tropical Diseases—that is, nine months after removal of the eye—his white blood cells numbered 10,500/c.mm., the differential count being: neutrophils 61%, lymphocytes 29%, monocytes 5%, and eosinophils 4% (eosinophils 420/c.mm.). Eosinophilia in helminth infection usually occurs only for the limited period after absorption of helminthic protein such as that contained within larvae, so that in the case here considered it may well have developed shortly after the death of the larva in the eye and have

diminished by the time the patient was observed in London; but, even so, some degree of eosinophilia was present. Inquiry revealed that this child had not been away from Britain and, in fact, a dog had not been kept by his parents, but he had been in the habit of playing with one belonging to a neighbour. Observation for three years after enucleation of the eye has revealed no further disease or eosinophilia.

FIG. 3.—Section showing portion of larva of *T. canis* in the granulomatous mass found in the enucleated eye. (Courtesy of Professor N. Ashton.)

Toxocara Infection Among Dogs and Cats in Britain

The fact that the patient described above had acquired toxocariasis in Britain prompted investigation of the chance of acquiring the infection there, and the importance of this question is increased by the frequency with which patients with unexplained eosinophilia are encountered. Very little information is available on the frequency of the infection among animals in Britain. No considerable survey appears to have been carried out for 37 years since Lewis (1927) found 16.3% of 43 dogs in Aberystwyth to be so infected. Earlier, Brown and Stammers (1922) had found 3% of dogs' faeces recovered from London streets to contain *T. canis* ova. A still earlier survey by Nuttall and Strickland (1908) revealed that 17 out of 24 dogs in Cambridge were infected.

Method

The co-operation of the staff of a number of homes for dogs and cats in and around London was obtained and is gratefully acknowledged; the majority of specimens examined were received from a home to which dogs lost in the Metropolitan area were taken. Specimens were collected on the day after the dogs had been received in the home in order to ensure that the sample was, so far as was possible, representative of animals in the area and to obviate the likelihood of cross-infection occurring between animals living in close proximity with one another.

The specimens of cats' faeces examined were from animals which had not been lost but which were lodged in homes for limited periods. Specimens passed within the previous 24 hours were collected in individual cartons and examined on the day of collection after centrifugation, using the formol-ether technique of Ridley and Hawgood (1956).

From a home in which dogs and cats are maintained during the period of quarantine after arrival here from overseas faecal specimens were similarly obtained, and the results of examining them could thus be compared with those of the animals from Britain.

Results

Of 300 dogs from the Home Counties the faeces of 62 (20.7%) were found to contain ova of *T. canis*. Of these 62 animals 24 were male and 38 female. Ova of hookworms were found in 11 (3.7%), and of dog tapeworms in 2 (0.7%). Other unidentified ova, in retrospect almost certainly *Toxascaris leonina*, were seen in the stools of 6 of the 300 animals.

Ova of *T. cati* were found in the faeces of 40 (22.7%) out of 176 cats from the Home Counties.

Among 149 dogs examined while in quarantine after arrival from abroad only 5 (3.4%) were found to have ova of *T. canis* in their faeces, 35 (23.5%) had ova of dog hookworms, and 5 (3.4%) had whipworm ova indistinguishable from *Trichuris trichiura*. Of 162 similarly quarantined cats 7 (4.3%) were found to be infected with *T. cati*, 34 (21%) with hookworms, and 9 (5.6%) with a feline strongyloid worm indistinguishable from *Strongyloides stercoralis*. It is not possible to ascertain with certainty the species of dog and cat—or indeed human—hookworms and tapeworms from the appearance of their ova.

The most important result of this survey is that approximately one in five of dogs and cats from the London area were found to be infected with toxocariasis. There is no reason to doubt that they form other than a representative sample of such animals from the area so far as these infections are concerned. It might be argued that lost dogs are cared for less well than others, but the faeces from lost animals in this series were examined immediately after the dogs were brought to the home; the majority were found to have been well cared for and many were reclaimed by their owners. It is also noteworthy that among the cats lodged at the homes by their owners the proportion found to be infected was slightly greater than that among the lost dogs. A further point is that a significant proportion of the dogs from the London area were infected with hookworms. As these give rise to larvae which live in moist earth and have the power of directly penetrating the unbroken human skin, after which they may cause eosinophilia, the possibility of such infection should clearly be considered among gardeners, children, and others who have been in contact with moist earth and who have an otherwise unexplained eosinophilia. The lower incidence of helminthic parasites among quarantined dogs and cats is of interest and may perhaps be explained by these animals having had treatment in order to obtain a certificate of fitness for admission into Britain. There have been few substantial surveys of the incidence of *T. canis* infection in dogs in the tropics, but Mapstone and Bhaduri (1940) found 82 out of 100 dogs in Calcutta to be infected.

Evidence of Toxocariasis in Patients with Eosinophilia, Choroidoretinitis, or Allergic States

Adult specimens of *T. canis* were dried and aqueous solutions of antigens were prepared from them by the method of Fairley (1931). The sterile aqueous solutions were used for intradermal sensitivity tests in strengths of 1 in 1000 and 1 in 200. In carrying out the skin test 0.1 ml. of the solution was injected and a positive reaction was assessed as one in which the initial weal doubled its size within 20 minutes and became surrounded by erythema.

Skin tests were carried out in this way on 175 persons, of whom 35 were suspected of having toxocariasis by virtue of present or past asthma, urticarial skin eruptions, choroidoretinitis, or otherwise unexplained eosinophilia. These 35 patients represented all with these clinical manifestations coming consecutively under observation in the medical unit at the Hospital for Tropical Diseases during the period—approximately 18 months—in which the study here reported was carried out. The remaining 140 comprised two control groups (see below).

Toxocara Skin Test in Patients Suspected of Having Toxocariasis

Among the 35 suspected of having toxocariasis the test using antigen in 1/1000 dilution was positive in 11 and in a dilution of 1/200 in a further three (see Table). Of those in whom the test was positive using dilute antigen, two had choroidoretinitis, one asthma with eosinophilia, two eosinophilia with lymphadenopathy, two asthma, two eosinophilia, one slight unexplained hepatic enlargement, and one polyarteritis with eosinophilia. Of the three in whom the test was positive only when less dilute antigen (1/200) was used, one had asthma, one unexplained eosinophilia, and one choroidoretinitis.

Results of Skin-testing with *T. canis* Antigen

	No. Tested	Positive with Antigen at	
		1/1000 Dilution	1/200 Dilution
Apparently healthy persons without demonstrable helminthic infections and with fewer than 500 eosinophils per c.mm. blood ..	55	2	2
Patients with non-toxocaral helminthic infections ..	85	2	11
Patients with unexplained eosinophilia, choroidoretinitis, or allergic manifestations ..	35	11	3

Toxocara Skin Test in Persons Free From Recognizable Infections

The test was carried out on 55 patients at the Hospital for Tropical Diseases, none of whom gave a history of asthma or urticaria, who were free from all clinical evidence of helminthic, including filarial, infection, who had no hepatomegaly or choroidoretinitis, and whose eosinophils numbered fewer than 500/c.mm. of blood. Among these patients the antigen in a dilution of 1/1000 gave a positive reaction in only two while the stronger antigen (1/200) produced a positive reaction in a further two. One of the two whose skin test was positive with dilute antigen was found by direct questioning to have kept greyhounds some years previously, so there is a possibility that the positive skin test was a result of an old toxocara infection in this apparently healthy person. It is of course also possible that the other positive test in this group similarly resulted from an old occult toxocara infection. From this part of the study it may be therefore deduced that false-positive reactions to intradermal injection of toxocara antigen in dilutions of 1/1000 are unlikely to occur in healthy persons free from helminthic infections.

Toxocara Skin Test in Persons Known to have Helminthic Infections other than Toxocariasis

Among 85 persons with evidence of helminthic infections the test using antigen in the 1/1000 dilution was positive in two and in the 1/200 dilution in 11. In this group helminthic infections proved by demonstration of the parasite, their ova or larvae, included 37 with *T. trichiura*, 20 with hookworms, 15 with *Schistosoma mansoni*, 6 with *A. lumbricoides*, 6 with *Strongyloides stercoralis*, 6 with *Onchocerca volvulus*, 2 with *Loa loa*, and 2 with *Trichostrongylus colubiformis*—that is, a total of 94 helminthic infections proved at the Hospital for Tropical Diseases; and from this total it is apparent that some patients harboured more than one species of helminth. In addition, two patients had larva migrans, another had clinical evidence of loiasis and had seen an adult *L. loa* cross the eye beneath the conjunctiva, 12 had a positive schistosomal complement-fixation test, 20 a positive filarial complement-fixation test, and 8 from among 47 in whom it was done using the method of Fairley (1931) had a positive filarial skin test. None of these eight patients with positive filarial skin tests had a

toxocara skin test which was positive when antigen of 1/1000 dilution was used, and only one of four in whom the test was performed using antigen of 1/200 dilution reacted positively. From this it may reasonably be deduced that cross-reactions between the toxocara and filarial skin tests are unlikely to occur if the antigen for the former is used in a dilution of 1/1000.

Of the two patients in this group who had positive skin tests with antigen at 1/1000 dilution one had an infection with *T. trichiura* and one with hookworms. It is apparent that with dilute (1/1000) antigen the skin test was negative in 83 persons, among whom there were 92 proved non-toxocaral helminthic infections, serological evidence of a further 40, and indisputable clinical evidence of another three. It therefore seems that the skin test for *T. canis* does not give cross-reactions in other helminthic infections when used in this dilution.

Among the 11 patients in whom the test was positive only when strong (1/200) antigen was used were six infected with *T. trichiura*, two with hookworms, two with *A. lumbricoides*, and one with *S. mansoni*. In addition, one had a positive filarial skin test, one a positive filarial and a positive schistosomal complement-fixation test, and two had *Entamoeba histolytica* cysts in the stool. The frequencies with which these infections were encountered among those with positive and negative tests did not differ significantly, so that no worm encountered appeared to have a special tendency to provoke positive reactions. Clearly, however, stronger antigen is accompanied by an undesirable number of non-specific reactions and is unsuitable as a diagnostic agent. For this purpose dilute (1/1000) antigen only should be used, and these investigations suggest that it may be of considerable value.

Discussion

It is clear from this and other reports that *T. canis* can cause severe disease in infected persons. In an excellent review Beaver (1962) states that cases have now been reported from the U.S.A., Netherlands, Australia, the Philippines, Mexico, Hawaii, Turkey, Rumania, South Africa, and Puerto Rico as well as from Britain. To date, most cases have been reported from the U.S.A., but it seems probable that as awareness of the disease increases many more cases will be found elsewhere. The present inquiry into the incidence of the infection in dogs in Britain indicates that there is a large reservoir from which infection may be transmitted to man, and the work with the skin test indicates that possibly 20 to 30% of some series of patients with otherwise undiagnosed allergic states associated with eosinophilia may have been infected with *T. canis*.

The question arises as to what type of disease this infection most commonly causes and in particular when it should be suspected. In most previously published accounts the eye has been involved. The largest series of such cases has been reported upon from America by Wilder (1950). In that series 42 eyes removed from patients at first diagnosed on pathological grounds as suffering from pseudogliomata, Coates's disease, or endophthalmitis were re-examined; nematode larvae were found in 24 and granulomatous reaction consistent with that occurring around a nematode larva was found in a further 22. From Britain, Ashton (1960) reported a series of four patients from whom an eye was removed for suspected retinoblastoma and in which eventually nematode larvae were demonstrated in retinal sections. Much less is known about the non-ocular manifestations of the infection, but Beaver *et al.* (1952) demonstrated the larvae in an eosinophilic granuloma of the liver, and eosinophilia, fever, pneumonitis, and hepatitis have been reported as a result of the infection (Smith and Beaver, 1953).

Smith and Beaver have also drawn attention to the variability of the eosinophilia, which they consider to be proportional to the severity of the infection, being mild and sometimes absent in those who have only a very light infection, perhaps with one

or two larvae. In several of the published cases in which larvae have been shown histologically to be present there has been no eosinophilia, and Ashton (1960) reported such a case. In other cases it has been shown that the infection may give rise to marked eosinophilia continuing for several months, and such eosinophilia was demonstrated in a human volunteer infected with *T. canis* and reported upon by Chaudhuri and Saha (1959). This volunteer, before swallowing the infective dose of *T. canis* ova, had a white-cell count of 6,700/c.mm., with 5% eosinophils. On the 13th day after infection the eosinophils amounted to 26% of the total white cells present, and on the 30th day the white-cell count was 21,800/c.mm., with 62% eosinophils. Thereafter, for a further four to five months, it remained between 5,000 and 8,000/c.mm., with from 40 to 50% eosinophils.

In view of the frequency with which the eye has been involved in patients so far reported with toxocariasis it has been thought that the parasite has a particular predilection for the eye. It is, however, here suggested that this predilection may be more apparent than real. If toxocara larvae should chance to be taken to the eye, then it is likely that they will cause damage which will give rise to symptoms, and these in turn will be followed by operation and a precise histological diagnosis. It should, however, be noted that even under these circumstances the histological diagnosis may be difficult, for in one of Professor Ashton's cases 186 sections from an eye had to be examined before a larva of *T. canis* was demonstrated. If, however, larvae should be taken not to the eye but to the liver, spleen, lungs, muscles, or other organs, they would be unlikely to give rise to any specific symptoms, and on dying they would cause the development of only a small granulomatous focus measuring not more than 2 to 3 mm. in diameter and producing no clinically recognizable syndromes.

The results of investigations of a toxocara skin-testing antigen, here reported, indicate, however, that toxocara larvae may be responsible for some otherwise undiagnosed cases of eosinophilia or allergic states without ocular involvement. That the parasite may be carried to tissues other than the eye is proved by the reports of Beaver *et al.* (1952), Smith and Beaver (1953), and Beaver (1962), and by its being occasionally found accidentally in other tissues. Thus Beautyman and Woolf (1951), while carrying out a post-mortem examination on a child who had died of poliomyelitis, found an unusual granulomatous lesion in the brain. They submitted sections to Professor J. C. C. Buckley, who was able to identify in the lesion a larva of *T. canis*. In experimental *T. canis* infections in mice, Sprent (1955) found that the larvae caused many lesions in the brain and raised the possibility that they might occasionally be responsible for transmitting viruses and other micro-organisms to the brain, with resulting encephalitis. In the light of this suggestion it would be of interest to know what proportion of patients who develop poliomyelitis live in households keeping dogs or cats and what proportion of them react positively to toxocara antigen injected intradermally.

For the prevention of toxocariasis and infection with other animal helminths in man regular worming of dogs and cats and the exercise of strict hygienic precautions in handling them are clearly important.

In conclusion it is suggested that infection with larvae of *T. canis* and *T. cati* and of other related animal helminths is probably much more common than is generally realized and that, in addition to the serious ocular complications which the former may cause, they may also give rise to otherwise unexplained eosinophilia and allergic states not uncommonly encountered in Britain as well as overseas. In view of the fact that in the Home Counties of Britain there is evidence that approximately one in five dogs and cats are infected with a helminthic parasite which can give rise to serious illness in man and even blindness, it is important to recognize that these domestic dogs and cats constitute a public-health hazard.

Summary

Eggs of *T. canis* and ascarid worm of dogs hatch in man's intestine and give rise to larvae which several studies have shown may damage the sight of man; a further case of this is here reported.

A survey carried out among dogs and cats in Southern England indicated that approximately 20% are infected with either *T. canis* or the related species *T. cati*.

There is therefore a considerable possibility that infection with these parasites may occur more commonly than is generally realized among households in which a dog or cat is kept.

The seeming predilection that toxocara larvae have for invading the eye is thought to be more apparent than real. When, however, the larvae invade tissues other than the eye, diagnosis of the infection is difficult and clinically may be manifest only by a transient allergic state.

In view of this, experiments have been carried out using an intradermal test with antigen prepared from adult *T. canis*.

When antigen in a dilution of 1 in 1000 is used, cross-reactions do not seem to occur in patients infected with worms other than *T. canis* or *T. cati* and false-positive reactions rarely if ever occur in controls free from demonstrable infections.

The use of this test in a series of 35 patients with a history of past or present asthma, urticarial skin eruptions, choroido-retinitis, or otherwise unexplained eosinophilia indicated that 11 of them had been infected with *T. canis* or *T. cati* in the past.

It is suggested that more attention should be given to the danger these infections constitute to the public health.

Many members of the medical unit at the Hospital for Tropical Diseases have assisted in this work at various times and we are particularly grateful to Dr. S. Bell, Dr. Z. Farid, Dr. B. Bissu, and Dr. M. Lowenthal. To Dr. D. S. Ridley, pathologist to the Hospital for Tropical Diseases, to Dr. H. A. Dutton, to Dr. A. P. M. Page, and to Professor J. J. C. Buckley we are grateful for much help and data.

The work was supported by a grant from the Hospital for Tropical Diseases Research Fund.

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Thyrotoxicosis Treated By Surgery or Iodine-131. With Special Reference to Development of Hypothyroidism

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Brit. med. J., 1964, **1**, 1005-1010

Treatment of thyrotoxicosis with ^{131}I has been available in Britain since 1949. The attractiveness of the method lies in its simplicity from the patient's point of view and in the almost complete absence of any immediate complications. Admission to hospital is often not required. These are considerable advantages in comparison with partial thyroidectomy. However, with more experience certain disadvantages have emerged; these include delay in controlling hyperthyroidism and a high incidence of subsequent hypothyroidism (Blomfield, *et al.*, 1959). For several reasons it has not been possible to arrange an ideal comparison of these two methods of treating thyrotoxicosis.

In this country, on account of the uncertainty regarding possible late ill effects of irradiation, the use of ^{131}I is usually restricted to those over 40 years of age unless there are complicating factors which might increase the risk of surgery. These include the recurrence of thyrotoxicosis after operation, severe heart disease, and the presence of other disorders such as diabetes mellitus. In these circumstances several patients under 40 years of age have been treated with ^{131}I . On the other hand, partial thyroidectomy has been most commonly performed on otherwise fit patients under 40 years of age. There is a range of patients over this age with uncomplicated thyrotoxicosis amongst whom a scientifically designed comparison might be carried out, but it is difficult to arrange this on a large scale as the method of treatment is so commonly selected before arrival at hospital, depending on whether the patient has been referred

to a physician or surgeon. An exact comparison of the therapeutic value of the two methods has not been possible, but the progress of a large number of patients has been investigated after both forms of treatment, with particular reference to the development of subsequent hypothyroidism.

Patients Treated by Partial Thyroidectomy

A search was made of the operation registers covering the period 1 January 1949 to 31 December 1960 at the Sheffield Royal Infirmary and at an associated unit at Wharncliffe Hospital, where some of the patients were transferred for surgery. From them a list was prepared of all patients who had a partial thyroidectomy on account of established or possible thyrotoxicosis. The case records of these patients were studied to confirm the diagnosis. In the earlier years the assessment had been made largely on the clinical features, but in the later years fuller investigation, including radioactive iodine tracer tests (Wayne, 1954), protein-bound-iodine measurements (Acland, 1958), and serological tests for autoimmune reactions had been carried out. Histological study of the excised tissue had been made in all the cases, but establishment of the diagnosis on this basis alone was not possible as pre-operative treatment with iodide had invariably been given in all suspected cases of thyrotoxicosis. In many the operation had been carried out on account of nodular goitres or solitary nodules associated with anxiety symptoms and there was no well-substantiated evidence

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