Threadworms and IgE in allergic asthma

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Summary
A high incidence of infection with the threadworm Enterobius vermicularis has been 
demonstrated in a group of children with allergic asthma, but also in a non-allergic 
group. There was no evidence of infection with any other helminth parasites. Presence 
or absence of threadworm infection was not clearly correlated with differences in 
total serum IgE level in either allergic or non-allergic children although levels of this 
immunoglobulin were raised in the former group. Some of the allergic children gave 
positive skin reactions following intradermal injection of an antigen extracted from E. 
vermicularis. The suggestion is therefore put forward that hypersensitivity to E. vermi-
cularis allergen absorbed from the bowel might contribute to the allergic symptoms. 
The results are also discussed in relation to recently discovered experimental evidence 
that helminth infection may non-specifically potentiate unrelated IgE antibody 
responses.

Introduction
A common and striking result of infection with helminth parasites in a number of 
species including man is the production of large amounts of reaginic (IgE) antibody 
Raised levels of serum IgE are found in individuals infected with one of a variety of 
helminth parasites including Ascaris lumbricoides, Toxocara canis and ancylostomes 
(Bennich & Johansson, 1971).

Recently it has become evident that helminth infection in addition to inducing a 
reaginic (IgE) antibody response to antigens derived from the parasite, may non-speci-
fically potentiate IgE antibody responses to unrelated antigens: thus in the rat, levels 
of circulating reaginic antibody (rat IgE) to a variety of non-helminthic antigens (e.g. 
ovalbumin, haemocyanin and house dust) can be greatly elevated following experi-
mental infection of the animals with the nematode Nippostrongylus brasiliensis or the 
This raised the possibility that naturally acquired helminth infection, in performing a similar role in man, may influence the development of clinical reagin-mediated immediate hypersensitivities. The following survey of helminth infection was therefore undertaken. The results are discussed in relation to the above theory and to the finding of positive skin reactions to an antigen prepared from the threadworm *Enterobius vermicularis*.

**Materials and methods**

**Patients**
The allergic individuals in the survey were patients who had been admitted to hospital during attacks of asthma, and who gave positive skin reactions to one or more common allergens such as house dust mite or grass pollens. The group was composed of nineteen adults and twenty-four children aged from 6 to 15 years. Specimens from twenty-one control children of the same age range were also examined. These were mostly patients in a general surgical ward and were selected on the basis of age and absence of any history of allergy. Neither the allergic nor the control patients could be considered as institutionalized individuals.

**Diagnosis of helminth infection**
Three faecal specimens from each allergic patient were examined for the presence of helminth eggs by a centrifugal flotation technique using zinc sulphate (Faust & Russell, 1969). The Sellotape impression technique (Graham, 1941) was used to detect *E. vermicularis* eggs on the anal and perianal area. An early morning impression was taken on three separate days from the allergic patients and on one occasion only from the non-allergic control children.

**Assay of serum IgE**
The radioactive single-radial-diffusion method of Rowe (1969) was used to assay levels of total serum IgE. $^{125}$I was substituted for $^{131}$I in the isotopic labelling of rabbit anti-sheep globulin, but otherwise the technique was exactly as has been described. Immunoglobulin E antiseraum (69/152) and Research Standard A for human serum IgE (68/341) were supplied by the Medical Research Council, Division of Biological Standards, Mill Hill, London. The reconstituted standard contains 9346 units of IgE/ml (Rowe *et al.*, 1970) and has been estimated to contain 10,148 ng/ml, using the radioimmunosorbent technique (Rowe, 1969). In our hands the lower limit of sensitivity of the assay system lay in the region represented by a 1/64 dilution of the reference preparation, i.e. 146 units or 158 ng/ml.

**Enterobius vermicularis skin test antigen**
*E. vermicularis* adult worms were collected from appendices opened immediately after their removal for acute appendicitis. The worms were washed in sterile saline and stored at $-22^\circ$C until a sufficient number had been accumulated. Skin test antigen was prepared by homogenizing the worms in 0-15 m saline at 4$^\circ$C. The homogenate was centrifuged at 1200 g for 30 min and the supernatant used as antigen. It was made bacteriologically sterile by filtration through a Millipore membrane and could be stored in a refrigerator after the addition of 1/10,000 merthiolate. Two batches of antigen were prepared, the first being the extract of twelve worms in 3 ml
saline, and the second the extract of eight worms in a similar volume. A control solution of 1/10,000 merthiolate in saline was also prepared. Skin tests were done by injecting 0.1 ml of the antigen or control solutions intradermally.

Results
Examination of the faecal specimens revealed no evidence of infection with any helminth parasites other than *E. vermicularis*. The Sellotape impression technique was therefore instituted as it is the method of choice for detecting threadworm eggs. By its use two of the nineteen adult asthmatic patients and ten of the twenty-four allergic children were found on examination of the first specimen to be infected with *E. vermicularis*. In one of the allergic children who had three specimens examined, the third specimen was negative.

In the control sample of twenty-one children with no history of allergy, six were found to be infected with *E. vermicularis*. The difference in infection rate between the allergic and non-allergic groups of children was not found to be statistically significant ($\chi^2; 0.2 < P < 0.3$).

Serum IgE levels were determined for most of these children and are shown in Fig. 1. The IgE levels of the majority of the asthmatic children were raised. It can be seen, however, that the levels were substantially similar whether or not they were currently infected with *E. vermicularis*. The IgE levels of all but one of the non-allergic children, on the other hand, were low, irrespective of the presence or absence of infection.

Skin tests with *E. vermicularis* antigen were performed on both worm infected and uninfected groups of the allergic children. Using the first batch of antigen (see Materials and methods), five infected and two uninfected children were tested. Positive skin reactions consisting of weal and erythema appeared within 15 min in three of the infected and one of the uninfected children. The reactions ranged from weak (3 mm)
to very strong (>15 mm). Of six children tested with the second batch of antigen (three infected, three uninfected), one infected and two uninfected children showed positive reactions. Two infected children were tested with both batches of antigen. One child gave a positive and one a negative reaction to both preparations.

**Discussion**

The results indicate that there is a high incidence of infection with the threadworm *E. vermicularis* in the child population in the area of Glasgow. Examination of Sello-tape perianal impressions showed the incidence to be 41.6% in a group of children with allergic asthma and 28% in another group of children with no history of allergy. The difference in incidence between the two groups was not found to be statistically significant.

Examination of faecal specimens from the asthmatic children and from a group of allergic adults gave no evidence of infection with any other helminth parasites.

Presence or absence of threadworm infection could not be related to differences in total serum IgE levels in either the allergic or non-allergic groups of children, although as has been reported by others (Johansson, 1967; Berg & Johansson, 1969) the levels of this immunoglobulin were found to be raised in the former group. It is possible that the single non-allergic child with a high IgE level had an undiagnosed allergic condition.

Although these results give no support to the idea that helminth infections in man may non-specifically potentiate unrelated reagins, it is considered, in view of their ability to do this in experimental animals, that such a phenomenon remains a distinct possibility. *E. vermicularis* does not appear to have a potent IgE stimulating effect, but it is likely that those helminths which do (e.g. *Ascaris*) will be found to have an IgE antibody potentiating effect in man.

Scotland is evidently not the most appropriate place to pursue this idea since clinical cases of helminthiasis are rare and all the more likely helminthic candidates for potentiation in man such as the hookworm or ascarid parasites are either not endemic or otherwise rarely seen because of the standards of hygiene. Further evidence for such a phenomenon will require to be sought in countries in which the incidence of infection with such parasites is higher than in the U.K.

Tullis (1970) reported that 198 of 201 patients with bronchial asthma in Ontario, Canada, were infected with one of three intestinal parasites: *Ascaris lumbricoides*, *Strongyloides stercoralis* or *Necator americanus*. There has been controversy about these rather startling results, including a refutation by van Dellen & Thompson (1971) who, in a survey of 123 asthmatic patients in Minnesota, U.S.A., were unable to find the parasites reported by Tullis. Certainly none of these parasites was found in the patients described here.

An incidental finding of more immediate interest is the presence of dermal sensitivity to *E. vermicularis* antigen which has been demonstrated here in some allergic children. A proportion of both infected and uninfected groups of the asthmatic children gave positive skin test reactions. The reactions in the uninfected children presumably give evidence of previous infection with this parasite. In view of the well-known allergenicity of helminth antigens under the condition of helminth infection this result is not surprising. However, as threadworm infection is so common, the possibility must be considered that hypersensitivity to *E. vermicularis* antigen, absorbed from the bowel, might contribute *per se* to the state of allergic asthma. This possibility has not been investigated here. Although the infected children were treated
with anthelminthic, any possibly beneficial action on asthma could not be discriminated from the effects of other measures which were also taken.

Acknowledgments
Dr Ellen Jarrett is in receipt of a research fellowship from the Wellcome Trust. The work was supported by grants from the Medical Research Council and Fisons Ltd, Pharmaceuticals Division.

We are grateful to Mr Dan Young of the Royal Hospital for Sick Children, Glasgow, for allowing us to study patients under his care, and to Dr Jane Fordyce, Mr W. Miller, of the Royal Hospital for Sick Children, Glasgow, Dr K. Patel and the nursing staff of the respiratory unit for their help with the collection of specimens.

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