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Effect of the expulsion phase of *Trichinella spiralis* on *Hymenolepis diminuta* infection in mice

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SUMMARY

The rapid elimination of the intestinal phase of *Trichinella spiralis* in NIH mice is associated with progressive inflammation of the intestinal tract. The non-specific effects of this inflammation were studied in mice concurrently infected with an unrelated parasite, *Hymenolepis diminuta*, which does not stimulate a visible inflammatory response but is also immunologically rejected by this strain of mice.

It was demonstrated that the rejection phase of *T. spiralis* infection had a marked effect upon the growth and survival of *H. diminuta*. The cestode either failed to establish or to grow; if the worms were already strobilate when inflammation developed then destrobilation occurred. There was no cross-immunity between the parasites, nor was the interaction a direct consequence of inter-specific competition.

INTRODUCTION

The immune expulsion of intestinal helminths is generally accepted as being the end-product of a series of events, involving both specific immunological mechanisms and non-specific processes. In the extensively studied nematode models of immunity, *Nippostrongylus brasiliensis* and *Trichuris muris*, worm loss is known to be the product of the sequential action of anti-worm antibody and a cell-mediated response (Ogilvie & Love, 1974; Wakelin, 1975). Although it is possible that similar components are involved in the rejection of intestinal *T. spiralis* from rats (Love, Ogilvie & McLaren, 1976) and mice (Wakelin & Lloyd, 1976*b*), the ultimate effector of worm expulsion remains controversial. Acute inflammation of the host intestine accompanies the expulsion of *T. spiralis* and it has been proposed that such an inflammation creates an adverse situation in the worms' environment, which in itself is sufficient to remove the parasites (Larsh & Race, 1975). Ogilvie & Jones (1973) suggest that the non-specific effects of such inflammation on other unrelated species should be determined and it is to this end that the present study was undertaken.

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Much of the previous work on interaction between helminths in the intestinal environment has concentrated on aspects such as parasite distribution, physiological and nutritional effects (reviewed by Schad, 1966; Crompton, 1973). Although the host's immune response against one or both species of parasites has been considered as an important factor in interactions (Larsh & Donaldson, 1944; Cox, 1952; Larsh & Campbell, 1952; Louch, 1962; Weinmann, 1964; Courtney & Forrester, 1973; Bruce & Wakelin, 1977), in many cases the work was carried out before information on the specific mechanisms of the host response became available. Its interpretation in the light of this subsequent knowledge is made difficult because, very often, controls of one or other of the concurrent infections were omitted.

In the present report we describe experiments which examine the effect of the expulsion phase of *T. spiralis* infection on a concurrent infection with *H. diminuta*. Our experiments were designed to answer four basic questions:

(1) Does the immune rejection of *T. spiralis* interfere with the survival and growth of *H. diminuta* in concurrently infected mice?

(2) Is the period of maximum effect related to the expulsion phase of *T. spiralis*?

(3) Will *H. diminuta* survive and grow normally in mice immune to *T. spiralis*?

(4) Can the two parasites survive alongside one another in the absence of a host response?

MATERIALS AND METHODS

Mice

Male NIH mice of category 4 were obtained from Anglia Laboratory Animals and used at 4–6 weeks of age, unless otherwise stated. Mice were maintained on sawdust litter in cages, not exceeding 12 mice per cage; pellet food (standard rat and mouse breeding diet, Grain Harvesters Ltd) and water were provided *ad libitum*.

Trichinella spiralis

Primary infections of *T. spiralis* are normally expelled by 9–12 days in NIH mice, but secondary infections in immune mice are rejected more rapidly (1–7 days) (Wakelin & Lloyd, 1976a). The strain of *T. spiralis* and the methods used for the infection of mice and recovery of worms have been described elsewhere (Wakelin & Lloyd, 1976a). In all experiments mice were infected with approximately 450 larvae, an infection level which was known to generate marked intestinal inflammation prior to worm expulsion.

Hymenolepis diminuta

The Rice strain of *H. diminuta* was used throughout. Mice were infected with five cysticercoids of *H. diminuta* and the worms were recovered as described by Hopkins, Subramanian & Stallard (1972). Male NIH mice usually reject a 5-cysticercoid *H. diminuta* infection between days 10 and 15 (Bland, 1976) but, as worm loss is frequently preceded by destrobilation, worms recovered at autopsy were assigned to 1 of 2 categories: destrobilated or stunted worms < 0.1 mg dry weight, or worms > 0.1 mg dry weight (Befus & Featherston, 1974).

Table 1. *Recovery of* Hymenolepis diminuta *and* Trichinella spiralis *from experimental and control mice given* T. spiralis *on day* −3, *challenged with* H. diminuta *on day 0 and killed on days 4 or 10*

	Group	No. of mice	Day killed	Mean number of *T. spiralis* recovered per mouse ± s.d.	Total *H. diminuta* recovery	*H. diminuta* mean worm length (mm ± s.d.)
A	*T. spiralis* +*H. diminuta*	10	4	250·4 ± 28·6	$\frac{0(+24)^*}{50}$	0·5 ± 0·3
B	*H. diminuta* only	10	4	—	$\frac{0(+40)}{50}$	4·3 ± 1·8
C	*T. spiralis* +*H. diminuta*	10	10	1·9 ± 2·3	$\frac{0(+3)}{50}$	N.D.†
D	*H. diminuta* only	10	10	—	$\frac{43(+0)}{50}$	N.D.
E	*T. spiralis* only	5	4	242·2 ± 15·5	—	—
F	*T. spiralis* only	5	10	1·8 ± 2·4	—	—

* $\dfrac{\text{Number of worms} > 0·1 \text{ mg } (+\text{number of worms} < 0·1 \text{ mg})}{\text{Number of cysticercoids administered}}$.

† Not done.

Cortisone

Cortisone acetate (Cortistab, Boots) was given by subcutaneous injection at 2·5 mg every second day. All the control and treated mice were given oxytetra-cycline hydrochloride (Terramycin, Pfizer Ltd) in their drinking water at a concentration of 165 mg/l.

EXPERIMENTAL DESIGN AND RESULTS

The effect of a primary Trichinella spiralis *infection on a subsequent infection with* Hymenolepis diminuta

Fifty male mice were arranged into six experimental and control groups and the *T. spiralis* infection was given to groups A, C, E and F on day −3, when the mice were 40 days old. Four groups (A–D) were infected with five cysticercoids of *Hymenolepis diminuta* on day 0 and the mice were killed either on day 4 or on day 10. The experimental design together with the results is presented in Table 1.

The establishment of *H. diminuta* in control mice (group B) was high (80% recovery on day 4), but recovery of worms was low from mice concurrently infected with *T. spiralis* (group A, 48%) and the length of *H. diminuta* in the latter group was markedly less. The establishment of *T. spiralis* was apparently unaffected by the *H. diminuta* infection (cf. groups A and E) and expulsion of *T. spiralis* was virtually complete in both groups after 13 days (groups C and F). The expulsion of *T. spiralis* in mice infected with *H. diminuta* (group C) was also accompanied by the loss of the remaining cestodes, only 6% of *H. diminuta* surviving to day 10 in this group, compared with 86% in the control group (group D).

The results of this experiment showed that some *H. diminuta* were able to

Table 2. *Survival and growth of* Hymenolepis diminuta *in control and* Trichinella spiralis-*infected mice*

(Groups of mice were infected with *T. spiralis* on day 0, challenged with five cysticercoids of *H. diminuta* on the days shown, and killed 8 days later.)

Day of infection with *H. diminuta*	Group	Percentage recovery	Worms recovered 8 days after infection	
			Percentage worms < 0·1 mg dry wt.	Mean worm biomass per mouse ± S.D. (mg dry wt.)
1	Control	80·0	10·0	2·26 ± 0·92
	T. spiralis infected	12·5	12·5	< 0·10 ± 0
6	Control	100·0	0	7·83 ± 3·49
	T. spiralis infected	8·0	8·0	< 0·10 ± 0
7	Control	94·3	0	3·06 ± 1·00
	T. spiralis infected	0	0	0 ± 0
8	Control	100·0	0	4·63 ± 3·19
	T. spiralis infected	23·0	23·0	< 0·10 ± 0
12	Control	92·5	0	2·23 ± 1·21
	T. spiralis infected	40·0	34·5	0·03 ± 0·58

establish and survive during the early phase of *T. spiralis* infection but that these worms had been lost when the expulsion of the nematode was completed. In the next two experiments an attempt was made to determine whether the detrimental effect on the cestode is related to the day on which *T. spiralis*-infected mice are challenged with *H. diminuta*.

The effect of a primary T. spiralis *infection on subsequent challenge infections with* H. diminuta *administered at different times*

Two experiments were carried out in which groups of mice were challenged with *H. diminuta* at various time intervals after infection with *T. spiralis*. All the groups were killed on day 8 of the *H. diminuta* infection. The results of these experiments are summarized in Table 2.

It is clear from the results that *H. diminuta* established and grew reasonably consistently in all the control groups, but was unable to survive as well in any of the groups previously infected with *T. spiralis* even when the interval between the infections was as long as 12 days.

The effect of cortisone on the survival and growth of Hymenolepis diminuta *in* Trichinella spiralis-*infected mice*

Thirty-two mice were arranged into four groups of 8 mice. Three groups (B–D) were infected with *T. spiralis* on day −1 and all 4 groups were challenged with *H. diminuta* on day 0. Group C was given cortisone on days 1, 3, 5 and 7 and group D on days 3, 5 and 7. All four groups were killed on day 8. The results are presented in Table 3.

Table 3. *Survival and growth of* Hymenolepis diminuta *in control,* Trichinella spiralis-*infected and cortisone-treated mice*

(The mice were infected with *T. spiralis* on day -1, challenged with five cysticercoids of *H. diminuta* on day 0 and killed on day 8.)

			Recovery of *H. diminuta*	
Group		Days of cortisone treatment	Total recovery	Mean biomass $\pm$ s.D. (mg dry wt.)
A	*H. diminuta* only	—	$\dfrac{32(+4)*}{40}$	$2 \cdot 26 \pm 0 \cdot 92$
B	*H. diminuta* + *T. spiralis*	—	$\dfrac{0(+3)}{40}$	$< 0 \cdot 1 \pm 0$
C	*H. diminuta* + *T. spiralis*	1, 3, 5, 7	$\dfrac{37(+0)}{40}$	$16 \cdot 79 \pm 9 \cdot 92$
D	*H. diminuta* + *T. spiralis*	3, 5, 7	$\dfrac{37(+0)}{40}$	$5 \cdot 64 \pm 2 \cdot 51$

$*$ $\dfrac{\text{Number of worms} > 0 \cdot 1 \text{ mg } (+ \text{number of worms} < 0 \cdot 1 \text{ mg})}{\text{Number of cysticercoids administered}}$.

In group B, which was given both parasites but was not cortisone treated, only 3 small worms were recovered at autopsy, showing that the first 9 days of *T. spiralis* infection were detrimental to the survival of *H. diminuta*. These worms must have been lost after day 3, because in group D, where cortisone was administered from day 3 onwards, $92 \cdot 5 \%$ of worms administered were recovered at autopsy and these worms were heavier than those recovered from the control group (group A versus D, $P < 0 \cdot 01$). Furthermore, the mean weight of worms per mouse recovered from group C was almost five times heavier than that of worms in group A, showing that in mice infected with *T. spiralis* and treated with cortisone, *H. diminuta* survived and grew, apparently better than in mice infected with the cestode alone.

Does cross-immunity exist between Trichinella spiralis *and* Hymenolepis diminuta?

The more rapid rejection of worms from a secondary infection with *T. spiralis* and the accelerated onset of the inflammatory response were utilized in this experiment to allow more precise timing of the inflammation in relation to the *H. diminuta* infection.

Fifty-three mice were arranged into seven groups of which three acted as controls for the primary *T. spiralis* infection (group E, 4 mice), the challenge *T. spiralis* infection (group F, 5 mice) and the secondary response in immune mice (group G, 4 mice). Of the remaining 40 mice, two groups (group C, 10 mice, group D, 10 mice) were infected with *T. spiralis* on day 0. Nineteen days later all four groups (A, B, C and D) received five cysticercoids of *H. diminuta* and then 6 days later (day 25) groups B and C were challenged with a further *T. spiralis* infection. All the mice, with the exception of group E (infectivity control for primary *T. spiralis* infection, killed on day 7) were killed on day 28.
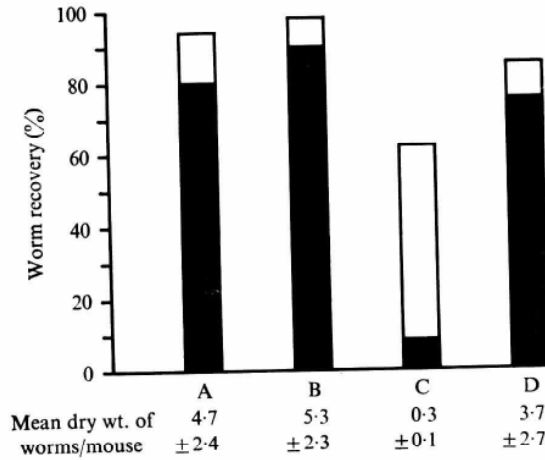
Fig. 1. Recovery (%) of 9-day-old *Hymenolepis diminuta* from male NIH mice given a five-cysticercoid infection. Solid areas of bars represent worms > 0·1 mg dry weight; open portions represent destrobilated worms (< 0·1 mg dry weight). Group A, control; group B, infected with *Trichinella spiralis* on day 6 of the *H. diminuta* infection; group C, infected with *T. spiralis* 19 days before *H. diminuta* infection and challenged with *T. spiralis* on day 6 of the *H. diminuta* infection; group D, infected with *T. spiralis* 19 days before *H. diminuta* infection.

The results of this experiment (Fig. 1) show that more than 90 % of *H. diminuta* administered to the control group (group A) were recovered on day 9. Worm recovery and growth from group B (infected with *T. spiralis* 6 days after the *H. diminuta* infection) were not significantly different from the control group, indicating that in the 3 days in which *T. spiralis* had existed alongside *H. diminuta*, there had been no adverse effect on the cestode. Worm recovery and growth in group D were also not significantly different from the control group, suggesting that no cross-immunity existed between the two species. In group C, however, which was given both primary and challenge infections of *T. spiralis* there was a marked reduction of strobilate worms by day 9. The majority of worms which were recovered from this group were considered to be destrobilated rather than stunted, because the *T. spiralis*-induced inflammation (which occurs within 24 h following a challenge infection) did not begin until day 6 of the *H. diminuta* infection, by which time worms normally possess a well-developed strobila.

The development of the effect of a secondary response to Trichinella spiralis *on* Hymenolepis diminuta

In order to investigate more precisely the onset of the effect of a secondary response to *T. spiralis* on *H. diminuta*, groups of *T. spiralis*-challenged mice and the relevant controls (10 mice per group) were killed every day for 4 days following the second *T. spiralis* infection. The mice were 32 days old when given the primary infection with *T. spiralis* and the challenge infection was given 26 days later, 5 days after the infection with *H. diminuta*.
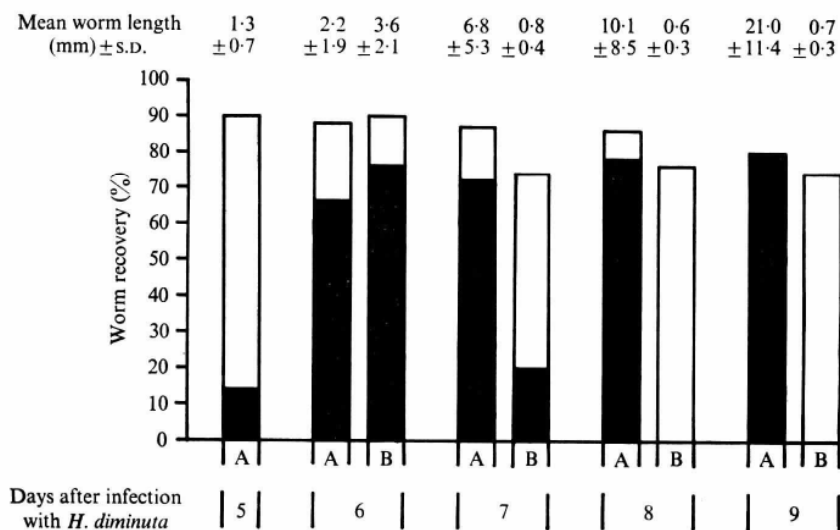
Mean worm length (mm) ± S.D.

| 1·3 ±0·7 | 2·2 ±1·9 | 3·6 ±2·1 | 6·8 ±5·3 | 0·8 ±0·4 | 10·1 ±8·5 | 0·6 ±0·3 | 21·0 ±11·4 | 0·7 ±0·3 |

Fig. 2. Recovery (%) of *Hymenolepis diminuta* from five-cysticercoid infections in male NIH mice. Solid areas of bars represent worms > 0·1 mg dry weight; open portions represent worms < 0·1 mg dry weight. Group A, infected with *Trichinella spiralis* 21 days before infection with *H. diminuta*; group B, infected with *T. spiralis* 21 days before infection with *H. diminuta* and challenged with *T. spiralis* on day 5 of the *H. diminuta* infection. Mean worm lengths are given above each bar.

Table 4. *The survival of* Trichinella spiralis *in control mice and in mice immunized by a primary infection given 26 days earlier*

	Mean recovery of *T. spiralis* ± S.D. Days after *T. spiralis* challenge infection			
Group	1	2	3	4
Control	177·3 ± 56·7	206·8 ± 26·9	227·0 ± 17·5	250·0 ± 17·2
Immune	214·3 ± 38·5	221·0 ± 38·2	230·0 ± 16·5	170·0* ± 6·6

* Significantly different from control $P < 0.025$.

The number and mean length of *H. diminuta* recovered from group A (given *T. spiralis* on day −21 and *H. diminuta* on day 0) and group B (given primary and challenge infections of *T. spiralis* on day −21 and 5 respectively and *H. diminuta* on day 0) are shown in Fig. 2. Although in group B, *H. diminuta* established at levels similar to those in group A, many worms had destrobilated 2 days after challenge with *T. spiralis* and, henceforth, only destrobilated worms were recovered. There was, however, no significant reduction in the number of *H. diminuta* recovered.

The recovery of *T. spiralis* in this experiment is shown in Table 4. *T. spiralis* established in relatively low numbers in the primary infection given on day −21 (mean worm recovery 7 days later = 123·4 ± 32·6) but the challenge infection given on day 5 showed a more usual level of infectivity. Expulsion from the immune mice began on day 4 after challenge.

DISCUSSION

Several species of nematodes induce an inflammatory response during their intestinal phase (Cox, 1952; Louch, 1962; Weinmann, 1964). The immune rejection of the intestinal phase of one such parasite, *T. spiralis*, from NIH strain mice is known to be closely associated with an inflammatory response, both in the primary infection, where worms are rejected after 8 days, and in a secondary response where expulsion occurs within a week following challenge infection (Wakelin & Lloyd, 1976a). Whether or not this inflammation is a necessary component of the rejection mechanism remains controversial.

In the present work, experiments were designed to assess the effect of the inflammation associated with the rejection phase of *T. spiralis* upon an unrelated parasite, *H. diminuta*. The results showed clearly that there was a marked effect upon the growth and survival of *H. diminuta* but only during, and for a time after, the period in which *T. spiralis* is expelled from the small intestine. This interactive effect was not mediated by a direct cross-immunity, i.e. one involving a specific immune response, directed against shared or similar antigens in the two parasites (Bruce & Wakelin, 1977). *H. diminuta* was able to establish and grow normally in mice immunized by a primary *T. spiralis* infection given 19 or 21 days earlier (Figs. 1 and 2). Equally, the interaction was not a direct consequence of inter-specific competition, since in at least two situations it was demonstrated that the parasites coexisted without *H. diminuta* being adversely affected. When mice infected with both parasites were treated with cortisone there was no detectable impairment of the growth of the cestode (Table 3) and when mice with a 6-day *H. diminuta* infection were challenged with *T. spiralis* and killed 3 days later, i.e. before the development of the inflammatory response, the cestode was again unaffected (group B, Fig. 1). These results thus confirm that the period of interaction was restricted to the time when the host was responding to and then rejecting the nematode, i.e. between days 4 and 19 in a primary infection and from 24 h onwards following a challenge infection in immune mice.

The effect of the interaction upon *H. diminuta* was reflected either in a failure to establish and/or grow in hosts responding to *T. spiralis*, or, if the worms were already strobilate before the onset of inflammation, in destrobilation and premature loss (Figs 1 and 2). It is interesting that these effects are similar to those known to occur in the immune rejection of *H. diminuta* from mice (Hopkins *et al.* 1972), although in this case there is no evidence of an inflammatory response to the cestode.

Although the present investigation shows that the inflammation induced by *T. spiralis* exerts a profound effect on *H. diminuta*, it gives no information regarding the nature of the interaction. It has been demonstrated that the acidosis associated with inflammation may have a direct effect on survival of *T. spiralis* (Castro, Cotter, Ferguson & Gordon, 1973) but it is probable that a lowering of the intestinal pH would have a less marked effect on *H. diminuta*, as it has been shown that *H. diminuta* can survive at a pH down to 3 (Podesta & Mettrick, 1974). Other factors, e.g. raised intestinal phospholipase levels, which have been demon-

strated to occur in mice infected with *T. spiralis* (Larsh, Ottolenghi & Weatherly, 1974) may exert a direct effect on a concurrent *H. diminuta* infection. On the other hand, indirect factors may be involved. The onset of inflammation undoubtedly disturbs the eating behaviour of the host (Saowakontha, 1975) and this must play a part in systems involving tapeworms which are extremely sensitive to disturbances in host diet (Read & Rothman, 1957).

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