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Genetic control of immunity to *Trichinella spiralis*: influence of H-2-linked genes on immunity to the intestinal phase of infection

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Summary. The time course of expulsion of adult *Trichinella spiralis* from the intestine was determined in B10 background, H-2 congenic and recombinant mice. Non-H-2 genes exerted the major influence on worm expulsion (i.e. determined rapid or slow response phenotype) but marked time course differences were seen among the slow responder B10 background strains, implying that H-2-linked genes also influence this parameter of immunity. Independent H-2^q haplotype mice showed the most rapid expulsion, H-2^k and H-2^b the slowest. Data from H-2 recombinant mice carrying the *q* allele suggested that alleles at H-2K loci have a strong influence in immunity, but showed also that H-2D alleles exert a significant modulating effect. The *q* allele in otherwise susceptible *k* haplotype mice (B10.AKM) gave increased resistance; the *d* allele at H-2D in mice carrying the *q* resistance allele elsewhere [B10.T(6R)] gave decreased resistance. Adoptive transfers using immune mesenteric node lymphocytes (IMLNC) from a series of donors were used to identify how the modulating influence of H-$2D^d$ was expressed in B10.T(6R) mice. IMLNC from this strain transferred immunity to recipients of other (histocompatible) strains, but IMLNC from such strains failed to accelerate expulsion in B10.T(6R) recipients as did homologous B10.T(6R) cells. Two alternative models are proposed to explain these results: either that H-$2D^d$ influences the response of myeloid precursors to lymphocyte-derived factors, and thus the generation of intestinal inflammatory changes necessary for expulsion, or, on the assumption that the generation of intestinal inflammation requires initial cooperation between helper and effector lymphocytes, that H-$2D^d$ is associated with a restricted ability of effector cells to respond to the helpers present in IMLNC.

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INTRODUCTION

It has been shown in many species that genes located within the major histocompatibility complex (MHC) play an important part in the control and regulation of immune responses, including those which contribute to resistance against viral and bacterial infections (Krco & David, 1981). However, although it is firmly established that protective immune responses to protozoan and metazoan parasitic organisms may show well-defined, genetically determined variation, MHC-linked control has been identified relatively infrequently, variation being more often associated with genes located elsewhere, in the genetic background of the host (reviewed in Wakelin, 1978). The characteristics of parasitic infections may well militate against the identification of MHC-linked influences upon protective immunity, in that parasites are complex organisms, presenting the host with complex antigens (which may modulate throughout infection)

and thus evoking multiple responses. In addition, the resistance induced in the host is measurable only by rather crude parameters, such as the numbers of parasites, their reproductive performance and their survival.

Despite these limitations, examples of MHC linkage have been described. The best studied of these concern infections in mice with species of the protozoan *Leishmania* (Blackwell, Freeman & Bradley, 1980; De Tolla, Semprevivo, Palczuk & Passmore, 1980) and with the nematode *Trichinella spiralis* (Wassom, David & Gleich, 1979). In each case, resistance is influenced by both background and MHC (H2) linked genes. In the former, background genetic influence is expressed through the activities of macrophages, and H-2-linked genes control the subsequent manifestations of acquired immunity. With *T. spiralis*, it has been shown that background genes determine the major characteristics of the T-cell-mediated inflammatory expulsion of intestinal adult stages, i.e. determine whether mice behave as rapid or slow responders in this respect (Wakelin, 1980), but both background and MHC-linked genes appear to influence overall resistance to infection, as measured by the total number of muscle larvae recovered (Wassom *et al.*, 1979). Analysis of the H-2 loci involved has shown that alleles at I-A and/or I-B determine the degree of resistance expressed on a particular genetic background, but that the influence of resistance alleles at these loci can be modulated by alleles present at H-2D (Wassom, David & Gleich, 1980).

In order to analyse the expression of genetic control during *T. spiralis* infections it is important to know where H-2-determined differences in resistance may be generated. Accordingly, a study has been made of the effects of H-2-linked genes upon immunity acting in the intestine against adult worms. The experiments were carried out in B10 background congenic and recombinant inbred strains, all of which express the overall characteristic of a slow response to *T. spiralis*, i.e. expulsion of adult worms takes place after day 12 of infection.

MATERIALS AND METHODS

Animals

Inbred NIH mice (H-2^q) were purchased from Hacking and Churchill Ltd (Huntingdon). The congenic and recombinant strains B10 (C57 BL/10 ScSn-H-2^b), B10.G (H-2^q), B10.D2/n (H-2^d), B10.BR (H-2^k), B10.S (H-2^s), B10.T(6R) (H-2^{y2}), B10.AKM (H-2^m) and B10.AQR (H-2^{y1}) were purchased from Olac 1976 Ltd (Bicester) as were inbred SJL (H-2^s) mice. The haplotypes of the B10 background mice are given in Table 1. Male mice were used throughout, in groups of five or six, at approximately 8 weeks of age.

Table 1. Haplotypes of B10 background mice used

		I					
Strain	K	A	B	J	E	C	D
B10	b	b	b	b	b	b	b
B10.G	q	q	q	q	q	q	q
B10.D2/n	d	d	d	d	d	d	d
B10.BR	k	k	k	k	k	k	k
B10.S	s	s	s	s	s	s	s
B10.T(6R)	q	q	q	q	q	q	d
B10.AKM	k	k	k	k	k	k	q
B10.AQR	q	k	k	k	k	k	d

Parasite

The strain of *T. spiralis*, and the methods used for infection of mice and recovery of worms have been described previously (Wakelin & Lloyd, 1976; Wakelin & Wilson, 1977). In all experiments mice were infected with approximately 300 larvae.

Cell transfers

Donor mice were immunized by infection with 300 larvae and immune mesenteric lymph node cell (IMLNC) suspensions prepared as described previously (Wakelin & Wilson, 1977). Cells were transferred by injection into the lateral tail vein of recipient mice.

Statistics

The significance of differences in mean worm recoveries between groups was determined using the non-parametric Wilcoxon test (Sokal & Rohlf, 1969). A probability value of $P > 0{\cdot}05$ was considered non-significant.

RESULTS

Major influence of non-H-2 genes on response phenotype

Previous data showing that H-2-linked genes do not exert the major influence upon the status of mouse

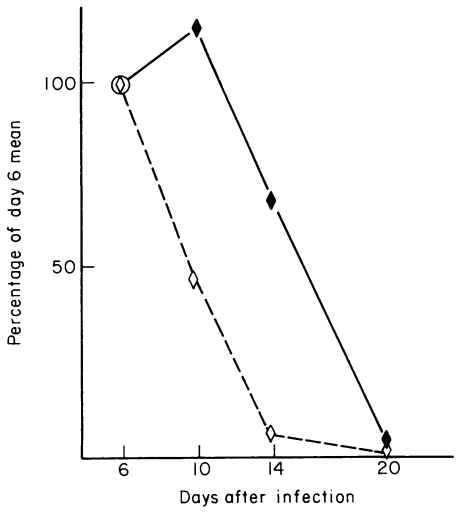

Figure 1. Time course of expulsion of *T. spiralis* from B10.S (♦——♦) and SJL (◇- - -◇) mice infected with 300 larvae. Mean worm recoveries are expressed as percentages of the day 6 mean value for each strain. Means for SJL mice significantly lower than B10.S on days 10, 14 and 20.

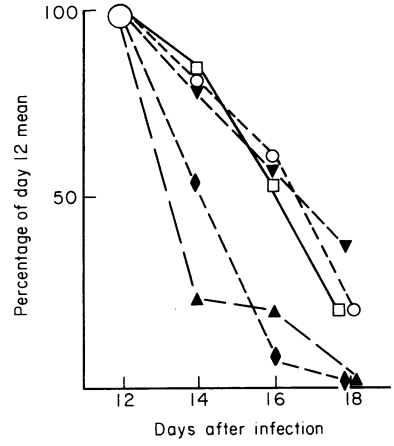

Figure 2. Time course of expulsion of *T. spiralis* from B10 background, congenic and recombinant mice. Mean worm recoveries are expressed as percentages of the day 12 mean value for each strain. B10.G (♦- - -♦), B10.AKM (▲- - -▲), B10.AQR (□——□), B10.BR (○- - -○), B10 (▼- - -▼). Mean for B10.AKM significantly lower than all other strains day 14; mean for B10.G significantly lower than B10, B10.BR, B10.AQR day 14; means for B10.AKM and B10.G significantly lower than all other strains days 16 and 18.

strains as rapid or slow responders were limited, in that all rapid responder strains identified at that time (Wakelin, 1980) shared the H-2^q haplotype. That H-2^q itself did not determine this phenotype was evident from the slow response seen in B10.G mice, which also carry this haplotype. These data have now been supported by examination of the response patterns of the strains SJL and B10.S, which share the H-2^s haplotype. As is shown in Fig. 1, the former are rapid responders, with significant worm loss by day 10, whereas the latter behave as slow responders.

H-2-linked influence on worm expulsion pattern in slow responder, B10 congenic mice

All B10 congenic mice so far tested (Wakelin, 1980 and above) have behaved as slow responders, but it is clear from a more detailed examination of the course of infection that, although in each case worm loss occurs after day 12 of infection, marked differences in kinetics of worm expulsion can occur between strains. Figure 2 shows the course of infection in strains with the independent haplotypes H-2^b (B10), H-2^q (B10.G), H-2^k (B10.BR) and the recombinant haplotypes H-2^m (B10.AQR) and H-2^{y1} (B10.AKM). The results imply that genes linked with, or located near to, the H-2 complex, can influence the process of worm expulsion in mice carrying the B10 background-determined slow response phenotype.

Modulating influence of the H-2D^d allele

Wassom *et al.* (1980), using the parameter of total muscle larval recovery, have shown that the relatively greater resistance to *T. spiralis* associated with certain haplotypes on the B10 background can be modulated by the presence of the H-2D^d allele. Three appropriate strains of B10 congenic mice were therefore examined to see whether similar modulation of resistance was detectable at the level of adult worm expulsion. The strains used were B10.G, B10.D2/n and B10.T(6R). Their haplotypes are given in Table 1 and the course of worm expulsion shown in Fig. 3a. B10.G (H-2^q) mice showed the most rapid expulsion, B10.D2/n (H-2^d) mice the slowest, and the recombinant B10.T(6R), which carry the *d* allele at H-2D, were intermediate. In a repeat experiment, involving B10.G and B10.T(6R), similar expulsion patterns were again recorded (Fig. 3b).

Adoptive transfer between H-2^q mice and H2^q recombinant mice carrying H-2D^d

Previous work (Wakelin & Donachie, 1980; 1981) with

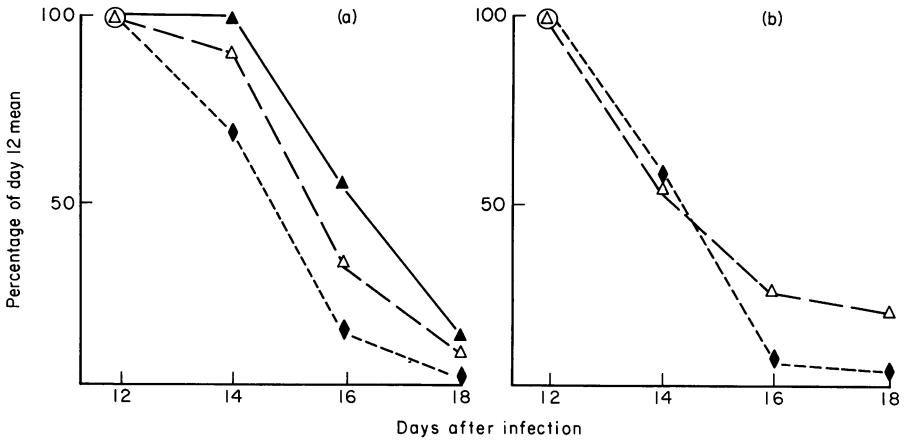

Figure 3. Time course of expulsion of *T. spiralis* from B10.G (♦– – –♦), B10.T(6R) (△– – –△) and B10.D2/n (▲——▲) mice infected with 300 larvae. Mean worm recoveries are expressed as percentages of the day 12 mean value for each strain. (a) Experiment 1, means for B10.G significantly lower than B10.T(6R) and B10.D2/n on days 14, 16 and 18; mean for B10.T(6R) significantly lower than B10.D2/n on day 16 only. (b) Experiment 2, means for B10.G significantly lower than B10.T(6R) on days 16 and 18.

the $H2^q$ compatible strains NIH and B10.G has shown that reciprocal adoptive transfer of their IMLNC does not alter the major, non-H-2 determined differences in worm expulsion phenotype. From this it can be concluded that the influence of non-H-2 genes upon expulsion is expressed through some cell population other than IMLNC. In order to identify how the influence of H2D alleles is expressed in expulsion, reciprocal adoptive transfers were carried out between $H\text{-}2^q$ mice (NIH or B10.G) and the recombinant B10.T(6R) strain. Additional transfers, essentially for control purposes, were carried out using B10.BR and B10.AKM mice. The haplotypes of these mice are shown in Table 1.

The protocols for all the experiments were similar. Donors of IMLNC were infected 8 days before cell transfer and recipients were killed 8 (NIH strain) or 12 (B10 background strains) days after transfer and challenge. These times were based on previous experience with the adoptive transfer system and were chosen to optimize differences in worm numbers between recipient and control animals. NIH mice were used in the initial experiments for reasons of economy and because the rapid response of this strain is more easily monitored.

When NIH mice were used as recipients for IMLNC (Table 2) successful transfer of immunity was achieved with cells from homologous NIH donors, from H-2 compatible B10.G and also from H-2 recombinant B10.T(6R). Cells from B10.BR (H-2 incompatible) and B10.AKM (H2 compatibility only at H-2D) did not transfer immunity. The ability of B10.G and B10.T(6R) cells to transfer immunity to NIH recipients was confirmed in several replicate experiments and it was also shown that substantial immunity was transferred by B10.T(6R) cells to B10.G recipients.

In the reciprocal experiment, i.e. when MLNC from NIH donors were transferred into NIH and B10 background recipients, successful transfer was

Table 2. Ability of IMLNC from B10 background, congenic and recombinant donors to transfer immunity to *T. spiralis* in NIH recipients

Donor† strain	Donor haplotype K	I	D	No. of worms recovered 8 days after challenge Mean	SD	Result of transfer
1. No cells control	—	—	—	161·8	10·0	
2. NIH	q	q	q	43·3*	13·4	+
3. B10.G	q	q	q	46·5*	25·0	+
4. B10.T(6R)	q	q	d	47·2*	32·5	+
5. B10.AKM	k	k	q	153·4	25·7	–
6. B10.BR	k	k	k	142·4	36·0	–

* Mean significantly lower than no-cells control.

† Donor mice infected with 300 *T. spiralis* 8 days before immune mesenteric lymph node cells (IMLNC) were collected. Recipients given 2×10^7 cells and infected with 300 *T. spiralis*.

Table 3. Ability of B10 background, congenic and recombinant recipients to express immunity to *T. spiralis* after transfer of IMLNC from NIH mice

Recipient strain†	Recipient haplotype K	I	D	NIH cells transferred	Day killed after challenge	No. of worms recovered Mean	SD	Result of transfer
NIH	q	q	q	–	8	183·4	34·0	+
				+	8	123·8*	19·6	
B10.G	q	q	q	–	12	184·0	16·8	+
				+	12	126·6*	20·5	
B10.T(6R)	q	q	d	–	12	180·2	47·6	–
				+	12	165·6	35·4	
B10.AKM	k	k	q	–	12	172·8	25·9	–
				+	12	194·2	31·9	

* Mean significantly lower than corresponding no-cells control.

† Donor mice infected with 300 *T. spiralis* 8 days before immune mesenteric lymph node cells (IMLNC) were collected. Recipients given 3×10^7 cells and infected with 300 *T. spiralis*.

achieved only in homologous NIH and H-2 compatible B10.G (Table 3). No immunity was transferred to B10.T(6R) or to B10.AKM mice. This result was confirmed in a replicate experiment in which greater percentage reductions were seen in NIH and B10.G recipients.

It was considered desirable to repeat the experiment using B10.G mice as the donor strain in order to rule out any effects arising from non-H2 identity in the donor-recipient combinations. B10.G cells were transferred into B10.G, B10.T(6R) and B10.AKM recipients (Table 4). The results confirmed the previous experiments in that immunity was transferred successfully in B10.G mice with homologous cells, but not with B10.G cells in B10.T(6R) mice, which differ from B10.G at H2D, nor in B10.AKM.

Table 4. Ability of B10-background, congenic and recombinant recipients to express immunity to *T. spiralis* after transfer of IMLNC from B10.G mice

Recipient strain†	Recipient haplotype K	I	D	B10.G cells transferred	No. of worms recovered 12 days after challenge Mean	SD	Result of transfer
B10.G	q	q	q	–	161·3	17·6	+
				+	111·0*	24·6	
B10.T(6R)	q	q	d	–	161·4	10·3	–
				+	152·0	39·6	
B10.AKM	k	k	q	–	160·1	31·9	–
				+	157·3	20·0	

* Mean significantly lower than corresponding no-cells control.

† Donor mice infected with 300 *T. spiralis* 8 days before immune mesenteric lymph node cells (IMLNC) were collected. Recipients given $2{\cdot}5 \times 10^7$ cells and infected with 300 *T. spiralis*.

A further experiment tested the ability of cells from B10.T(6R) to transfer immunity to homologous recipients, activity of the cells being controlled by their effects in NIH recipients (Table 5). Whereas the IMLNC accelerated expulsion in NIH recipients by day 8, no such effect was seen in B10.T(6R) recipients by day 12. This result was confirmed in a replicate experiment.

DISCUSSION

The results described strengthen previous observations that non-H-2 genes exert the major influence on the ability of mice to expel *T. spiralis* from the intestine but show for the first time that this response can also be regulated by genes linked with the MHC. When a number of B10 background, congenic strains were infected, distinct differences in worm expulsion patterns were observed, the haplotypes H-2^k, H-2^b being associated with relatively slow expulsion and H-2^q with relatively rapid expulsion. It is striking that similar haplotype-dependent differences have been

Table 5. Ability of IMLNC from B10.T(6R) donors to transfer immunity to *T. spiralis* in syngeneic and in NIH recipients

Recipient strain†	B10.T(6R) cells transferred	Day killed after challenge	No. of worms recovered		Result of transfer
			Mean	SD	
NIH	–	8	116·4	31·9	+
	+	8	24·5*	23·4	
B10.T(6R)	–	12	115·8	22·9	–
	+	12	100·3	17·2	

* Mean significantly lower than no-cells control.

† Donor mice infected with 300 *T. spiralis* 8 days before immune mesenteric lymph node cells (IMLNC) were collected. Recipients given $2{\cdot}5 \times 10^7$ cells and infected with 300 *T. spiralis*.

demonstrated using the numbers of muscle larvae established from a uniform primary infection as a parameter of resistance (Wassom *et al.*, 1979). Comparison of the independent haplotypes H-2^q (B10.G) and H-2^k (B10.BR) with the recombinant haplotypes H-2^m (B10.AKM) and H-2^{yl} (B10.AQR) suggests that the presence of the *q* allele at H-2D (Fig. 2: B10.AKM cf B10.BR) exerts a strong influence over the pattern of expulsion, whereas the presence of this allele at H-2K is not significant (Fig. 2: B10.AQR cf B10.BR). The results do not confirm the conclusions of Wassom *et al.* (1980) that alleles at I loci exert the greatest influence on resistance, as B10.AKM and B10.G showed similar response patterns. However, Wassom's data were based on a strain in which resistance alleles at H-2K could have been overriden by the *d* allele at H-2D.

The resistance associated with the H-2^q haplotype was modulated in recombinant mice carrying the *d* allele at H-2D, B10.T(6R) mice showing a markedly slower worm expulsion pattern than B10.G (Fig. 3). Again, this supports the data of Wassom *et al.* (1980). It is not possible, however, to conclude from this observation that the *d* allele is the genetic factor directly responsible for this modulation. The H-2D locus is closely associated with H-2L, and it has recently been demonstrated (Hansen, Ozato, Melino, Coligan, Kindt, Jandinski & Sachs, 1981) in H-2^d and H-2^q haplotype mice that a further locus, designated H-2R, may also exist in this region. In addition, further loci located between H-2D and Tla may well have to be considered (Klein, 1975).

The results of the adoptive transfer experiments suggest that the genetic influence associated with the presence of the *d* allele at H-2D is not expressed through the population of lymphocytes transferred with donor IMLNC. Thus, when NIH or B10.G were used as recipients, worm expulsion was accelerated after the transfer of either B10.G or B10.T(6R) cells, implying that mice of the latter strain do make an adequate lymphocyte response. However, when B10.T(6R) mice were used as recipients, adoptive transfer was not achieved with either homologous cells or cells from B10.G donors, although in each case, the population of IMLNC used was shown to be effective in other recipients. The results obtained with transfers into B10.BR and B10.AKM mice (Tables 2, 3 and 4) suggest that compatibility in the I region between donor and recipient is necessary for effective transfer of immunity and thus the failure of B10.T(6R) mice to respond to NIH or B10.G IMLNC is unlikely to arise from any H-2 restriction on activity of cells in the recipient. This is confirmed by (i) the fact that the reciprocal transfers were effective, and (ii) the fact that B10.T(6R) mice failed to respond to their own cells.

Two hypotheses can be proposed to explain the origin of the poor response seen in mice carrying H-$2D^d$. These are not mutually exclusive and at present only circumstantial evidence can be provided to support them. The first hypothesis is that the products of the allele are expressed in non-lymphoid cells of bone marrow origin and this may have one of two consequences. Either macrophage populations may function less well in antigen presentation, or stem cell precursors of the myeloid cells associated with intestinal inflammation may be relatively slow in their ability to respond to factors from sensitized lymphocytes.

In many of the cases where genetic variation of non-lymphoid cell responses to infectious agents has been described (Skamene, Kongshavn & Landy, 1980), control has been associated primarily with non-H-2 genes. However, in at least one case, in the early response of mice to infection with murine cytomegalovirus, not only is H-2-linked control also involved, but the *d* allele at H-2D appears to exert a marked modulatory effect, resulting in increased susceptibility (Chalmers, 1980). In this system, as with *T. spiralis*, the phenotype of a mouse strain reflects a balance determined by both non-H-2 and H-2-linked influences, the latter modifying susceptibility within limits imposed by the non-H2 background. H-2-linked regulation of macrophage-expressed acquired immunity against intracellular organisms has also been described, for example with *Leishmania* and with *Listeria* (Blackwell *et al.*, 1980; De Tolla *et al.*, 1980; Zinkernagel, 1974).

The second hypothesis is that genetic control is expressed in a population of lymphocytes, not transferred with IMLNC, but which requires to interact with helpers present in IMLNC in order to generate the inflammatory response. Support for this idea comes from the results of transfers involving B10.BR and B10.AKM recipients, which showed that I region compatibility (characteristic of helper cell interactions) was necessary for successful transfer of immunity. In H-2D^d mice these cells would appear to be poor either in responding to help from IMLNC, hence response phenotype is not altered by adoptive transfer, or in generating the factors which influence myeloid stem cells.

Strassmann, Eshhar & Mozes (1980) have shown that the genetic defect in certain strains of mice that are non-responders to the synthetic terpolymer (T,G)-A--L is expressed not at the level of helper T lymphocytes, but in collaborating T cells that mediate the efferent phase of the response. Thus non-responder H-2^k and H-2^q mice can generate helper cells which will generate responses in appropriate (responder × non-responder) F_1 recipients but fail to do so in syngeneic recipients. Similarly, H-2D-linked influences on immunological responses involving cooperative interactions between helper and effector lymphocyte populations have been well documented for cytolytic responses to infected or hapten-modified syngeneic cells. One partial analogy with the present situation is found in the H-2 regulation of the generation of cytolytic T lymphocytes (CTL) by peptides of Sendai virus protein (Miskimen, Guertin, Fan & David, 1982). Mice carrying particular H-2K or H-2D alleles, including H-2D^d, show poor CTL responses, despite normal helper cell proliferation. These data have been interpreted as showing that there are *Ir* genes, mapping to these loci, which regulate CTL responses, although the mechanism of this regulation is not clear. Differential responsiveness associated with the alleles H-2D^q and H-2D^d has also been demonstrated in mice infected with the radiation murine leukaemia virus (Meruelo, Lieberman, Ginzton, Deak & McDevitt, 1977). In this case susceptibility was H-2^q-linked and resistance H-2^d-linked. B10.G mice survived poorly after inoculation, none surviving for more that 30 weeks, whereas B10.T(6R) mice survived well, only 40% having died at this time.

An additional relevant example concerns H-2D-associated variation in the ability of mice to respond to murine thyroglobulin and to generate the inflammatory changes that lead to thyroiditis (Krco & David, 1981; Kong, David, Giraldo, Elrehewy & Rose, 1979). It is interesting that, in this system, the relative ranking of the *q*, y^2 and *d* haplotypes for these responses (high, medium and low respectively) corresponds with that reported here for infections with *T. spiralis*.

Analysis of the mechanisms through which H-2-linked control of intestinal immunity to *T. spiralis* is expressed is hindered by the inability to model worm expulsion *in vitro*. Useful data may be gained, however, from detailed studies of myeloid (eosinophil and mast cell) responses in appropriately manipulated mice (Alizadeh & Wakelin, 1982), from experiments designed to elucidate the precise role of IMLNC in adoptive transfer and from *in vitro*, antigen-induced lymphocyte transformation studies of the type initiated by Krco, David & Wassom (1982).

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