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Immune Responses to Intestinal Nematode Infections
The Influence of Host and Parasite Variables

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Abstract

Intestinal nematodes are among the commonest parasites of humans and animals, and are of major clinical and economic importance. The intestinal location determines many features of their host-parasite relationships, particularly the ways in which they elicit and are affected by host immunity. An understanding of the factors that determine whether hosts can develop effective immunity is of considerable theoretical and practical importance. Laboratory studies with experimental models have clarified many aspects of immunity to these parasites. In particular it has shown that the outcome of infection is heavily influenced by the genetically-determined ability of the host to mount immune and inflammatory responses and by the genetically-determined capacity of the parasite to generate such responses. This review describes and discusses recent research with three murine systems, involving *Heligmosomoides polygyrus*, *Trichuris muris* and *Trichinella* species, that has given particular insights into the control and expression of immune responses to intestinal nematode infection and illustrated the variability in immunogenicity that can occur between different isolates of the same species of parasite.

Key words: Immunity, Genetics, Host and Parasite Variation, Mouse, *Heligmosomoides polygyrus*, *Trichuris muris*, *Trichinella* species.

Introduction

Intestinal nematodes are among the commonest of all parasites, the distribution, prevalence and intensity of such infections being strongly influenced by environmental factors. In humans high prevalence is associated with warm climates and poor socio-economic conditions, whereas in domestic animals levels of infection are primarily influenced by husbandry conditions, in particular by population density. The factors influencing prevalence and intensity of intestinal nematodes in wild populations are much less well defined, but must include those related to local environment and population density. It is characteristic of these infections that they are aggregated in the host population, i.e. the majority of worms is found in a small number of individuals (Bundy and Medley, 1991). The causes of this aggregation have been the subject of considerable debate and both environmental and host-related factors have been implicated.

Heavy infections with intestinal parasites are known to cause considerable host pathology. Even relatively light infections can incur a significant metabolic cost to the host because of disturbed digestive and absorptive functions. It seems obvious, therefore, that there ought to be strong and effective immune responses to these parasites and that hosts should acquire significant levels of resistance to protect themselves against infection. However, it is clear that the immunological outcome of infections in host populations is extraordinarily variable (Maizels *et al*, 1993; Windon, 1991). At one extreme, there may be a strong and effective immunity that provides the host with complete or near-complete resistance. At the other extreme, hosts appear unable to develop such resistance, sustaining long-term (chronic) infections and being susceptible to repeated reinfection. It is clear

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therefore that, although environmental and behavioural variables undoubtedly are involved in generating aggregated parasite distributions in host populations, the observed degree of variation in the immunological component of the host-parasite relationship must also play an important role.

The fact that there is significant host-host variation in response to infection is itself not surprising. Natural host-parasite relationships involve interactions between populations of parasites that are genetically heterogenous, and therefore certain to vary antigenically, and equally heterogeneous populations of hosts that have variable and genetically-determined differences in their capacity for immune responsiveness (Wakelin and Blackwell, 1993). What is largely undetermined is the relative importance of each source of variation and this can only be measured accurately in experimental systems where all other variables can be held constant.

Experimental Systems

Three systems, involving infections of laboratory mice with *Heligmosomoides polygyrus*, *Trichinella* species and *Trichuris muris* have been particularly valuable in determining the contributions of host and parasite variables to the immunological outcome of host-parasite relationships involving intestinal nematodes. All have been established as laboratory cultures for many years, in each case having been isolated from naturally infected hosts. A wide diversity of *Trichinella* isolates is available, and this has facilitated analysis of parasite variability as a determinant of host response; the use of three isolates of *T. muris* has similarly been valuable in this regard. Use of the mouse as an experimental host has allowed precise studies to be made of the contributions of host variables, particularly those involving genetic and immunological components. Genetic factors can be identified through infections established in strains that are random-bred (genetically heterogeneous), inbred (genetically homogeneous) or MHC-congenic (homogeneous except for defined MHC genes) and immunological factors identified by experimental manipulations involving the use of the extensive range of immunobiological and immunochemical reagents now available.

Heligmosomoides polygyrus

H. polygyrus (formerly *Nematospiroides dubius*) is a natural parasite of small rodents and has a typical trichostrongyle life cycle. Infection occurs by ingestion of infective L3 larvae, which invade the intestinal mucosa where they undergo development to the L4 and juvenile stages. Adult worms re-emerge into the intestinal lumen after about 8 days and egg laying commences 2 days later. The adult worms live in close contact with the mucosa, but do not penetrate into the tissues. In a majority of mouse strains, infections with *H. polygyrus* are long-lasting, and this parasite therefore provides a useful model for analysis of chronic gastrointestinal parasitism (Monroy and Enriquez, 1992). Immunogenetic studies using this parasite have been carried out by a number of groups in Australia, the UK and the USA. Each group has used rather different protocols and because of this their data are not always strictly comparable. This review will focus largely on the work of Behnke and colleagues in Nottingham, who have studied host variability in the context of single-pulse primary infections.

When mice are given a single inoculum of infective larvae the duration of infection, as determined by faecal egg output or by adult worm recovery, is dependent upon the strain of mouse involved. Low-responder strains support adult worm burdens for several months, the worms eventually succumbing to senility, whereas high-responders may expel the infection within 6 to 8 weeks (Fig. 1A). The outcome of infection - expulsion or persistence - is determined by both background (non-MHC) and MHC-linked genes (Behnke and Wahid, 1991; Wahid and Behnke, 1993a) and depends upon a genetically-determined balance between responsiveness to the immunogenic, mucosal L4 larvae and susceptibility to down-regulation of immunity by immunomodulatory factors released from the adult worms.

The immunogenicity of the L4 stage is clearly shown by experiments in which infections are limited to this stage by chemotherapy or by irradiation of the infective L3 (Behnke and Robinson, 1985). Under these conditions high levels of immunity to subsequent challenge can be generated even in strains of mice that have little ability to expel the

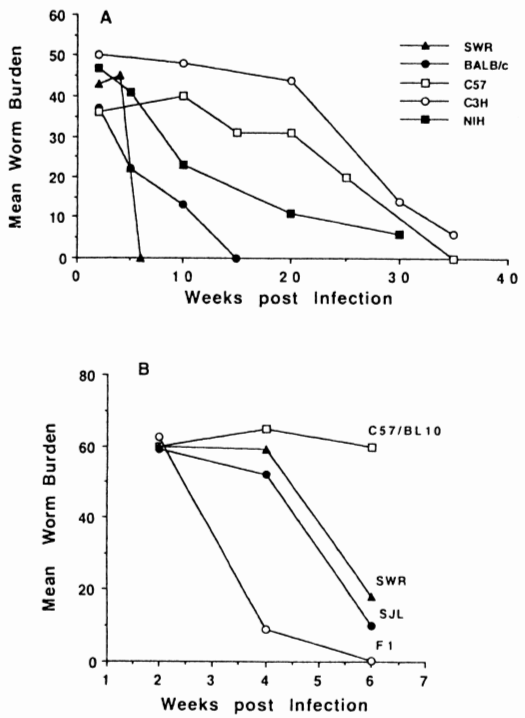

Fig. 1 1A. Time course of infection with *Heligmosomoides polygyrus* in 5 inbred strains of mice infected with 50–60 larvae and killed at intervals to determine the numbers of worms present. [Data from Wahid and Behnke, 1993b].

1B. Time course of infection with *Heligmosomoides polygyrus* in low-responder C57 BL/10 mice, high-responder SWR and SJL mice and (SWR×SJL) F1 hybrids. Mice were infected with 70 larvae and killed at intervals to determine the numbers of worms present. [Data from Wahid and Behnke, 1993a].

adult worms of a primary infection. Some low-responders, however, fail to respond to abbreviated immunizing infections showing that there is clear genetic control of the ability to develop and express immunity.

Immunomodulation by the adult worms downregulates responses to both homologous and heterologous antigens. Depression of responses to the immunogenic L4 larvae was elegantly demonstrated in experiments involving the direct implantation of adults into mice immunized by exposure to irradiated larvae (Behnke, Hannah and Pritchard, 1983). Whereas mice immunized by irradiated larvae showed complete immunity to challenge, there was almost no immunity if adult worms were implanted before immunization and signigicantly less immunity to challenge if adults were implanted after immunization. This down-regulation by the adult stage is dose-dependent and reflects the release by the worms of immunomodulatory factors (IMF). These have now been identified with low molecular weight components present in excretory/secretory (ES) material (Monroy, Dobson and Adams, 1989; Pritchard *et al.*, 1994). Although their mode of action is unclear it is suggested that they may operate against T cell-mediated components of host resistance, possibly interfering with release of T cell cytokines. A key objective is to identify the means by which high-responder mice resist the influence of IMF so that they can express effective immune responses and limit the duration of infection with the adult worms. It is clear that the mechanisms involved are under genetic control but their nature is not understood. One speculation is that high responders produce antibodies that inactivate IMF thus allowing the normal expression of immunity.

As mentioned above, there are major, genetically-determined differences between strains of mice in ability to express immunity to a primary infection. Among those strains that do express immunity there are at least two distinct genetically-controlled means of controlling adult worm infections. Thus, both SJL and SWR mice are high responders capable of expelling worm within a relatively short period, but the response of their F1 hybrid is even faster (Fig. 1B) implying some form of gene complementation and a synergy between the different parental resistance mechanisms (Wahid and Behnke, 1993a). SWR respond to infection with a mucosal mast cell response and develop specific anti-parasite IgE but have a delayed IgG1 response. SJL mice, on the other hand, show little mucosal mastocytosis and have negligible IgE, but do have a rapid and high level IgG1 respond. The F1 hybrids respond with all of these components.

It is known that immunity to *H. polygyrus* is dependent upon the activity of $CD4^+$ T cells (Urban, Katona and Finkelman, 1991) and that infection intitiates a rapid response characterized by cytokine release from cells of the T helper 2 (TH2) subset (Svetic *et al.*, 1993). Recent studies have

shown that response phenotype is correlated with particular patterns of T helper (TH) cell and cytokine response (Wahid *et al.*, 1994). When cells from the draining mesenteric lymph nodes of infected high-responder mice are stimulated *in vitro* they release large amounts of the cytokines IL-3, IL-4, IL-9 and IL-10, implying that the response predominantly involves cells of the TH2 subset. Cells of low-responder mice produce only moderate amounts of IL-3, IL-4 and IL-9 in the first two weeks after infection and little or no IL-10. It seems, then, that the genetic influences on resistance and susceptibility in this particular system are mediated through complex effects upon T cell responses to parasite antigens. This is supported by an analysis of the suppressive effects of concurrent *H. polygyrus* infection upon the immune and inflammatory responses elicited by *Trichinella spiralis*. When both parasites are present in NIH strain mice (high-responder for *T. spiralis*; low to intermediate responder for *H. polygyrus*) the expulsion of *T. spiralis* is delayed and mucosal mast cell responses markedly depressed (Dehlawi, Wakelin and Behnke, 1987). Mesenteric node lymphocytes taken from singly and concurrently infected mice show quite different patterns of cytokine release (Table 1), notably a significant reduction in IL-9 and IL-10 (Behnke *et al.*, 1993).

Trichuris muris

T. muris is also a natural parasite of mice. It has a direct cycle, the infective stage being an embryonated egg containing the L1 stage. Infection occurs by oral ingestion, the eggs hatch in the small intestine and larvae invade the epithelial layer of the large intestine. As the worms grow they maintain their anterior regions in this intra-epithelial position, but the large posterior regions lie free in the intestinal lumen. In the majority of laboratory mouse strains, infection elicits a strong protective immune response that results in expulsion of the worms before they reach sexual maturity (at day 35) although there is considerable variation in the time at which this occurs i.e. there are high- and low-responders (Else and Wakelin, 1988). Some strains, however, are non-responders and fail to mount a protective response, the worms then surviving for several weeks (Fig 2). Resistance is inherited as a dominant characteristic, the F1 progeny of high- X low-responder parents behaving like the more resistance strain (Wakelin, 1975).

Much of the literature on *T. muris* refers to experiments carried out with the Edinburgh isolate, which was derived from mice trapped in Edinburgh in 1954. A derivative of this isolate has been maintained by Professor Y. Ito, Kitasato, Japan since about 1970 and this shows a quite distinct host-

Table 1 Immunomodulation by *Heligmosomoides polygyrus* of responder NIH mice, measured by effects upon infection with *Trichinella spiralis*. (Data from Dehlawi *et al.*, 1987 and Behnke *et al.*, 1993)

Group of mice	No. of *T. spiralis*		Mucosal mast	Cytokine levels day 8†	
	Day 6	Day 9	cells day 9*	IL-9	IL-10
No infection	–	–	n.d.	4.8	0.5
T. spiralis	206	94	404	>1000	7.9
H. polygyrus	–	–	<5	144.8	1.5
H.p. + *T. sp*	158	165	110	530.6	3.5

Dehlawi *et al.* – 300 *H. polygyrus* larvae and 300 *T. spiralis* given day 0
Behnke *et al.* – 250 *H. polygyrus* given day -14 and 300 *T. spiralis* day 0

*=Mucosal mast cells expressed as numbers per 200 villus crypt units
†=Cytokine levels expressed as Units/ml of supernatant from Con A-stimulated mesenteric lymph node cells.

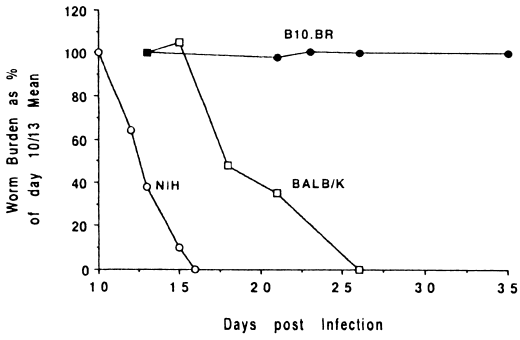

Fig. 2 Schematic time course of infection with *Trichuris muris* (Edinburgh isolate) in high-(NIH), low-(BALB/K) and non-responder (B10.BR) mice. Mice infected with 400 eggs and killed at intervals to determine the numbers of worms present. BALB/K and B10.BR are MHC-compatible (*H-2*^{k}). [Data from Else and Wakelin, 1988].

parasite relationship, as do worms of a more recent isolate derived from mice trapped in Sobreda, Portugal. The description that follows refers initially only to the Edinburgh isolate.

The genetic control of response phenotype involves both MHC-linked and background genes, with the latter exerting the major influence. This is seen very clearly when the kinetics of infection are followed in MHC-congenic mice of the BALB and B10 backgrounds (Else and Wakelin, 1988). All BALB background mice are responders, different MHC (H-2)-haplotypes being associated with relatively small variations in time of worm expulsion (H-2^d – day 21; H-2^b and H-2^k – day 26). In B10 background mice expulsion occurs much later, and haplotype differences are more pronounced, expulsion beginning after day 22 in H-2^b, after day 26 in H-2^d and failing to occur to any degree in H-2^k. A significant finding is that, in certain B10 background strains where the onset of expulsion is delayed, e.g. in B10.D2/n, some individual mice behave as non-responders and fail to eliminate the infection (Else, Entwistle and Grencis, 1993). This also occurs in other inbred strains, notably the DBA/2 strain, and in certain random-bred strains, (see Wakelin, 1988). Non-responder mice appear to become permanently unresponsive to *T. muris*. Once an adult worm population has been established, mice are unable to develop a protective immunity to subsequent infection, even if the initial worm burden is removed.

Resistance to *T. muris* is dependent upon responses mediated by CD4$^+$T helper cells (Tamauchi, Koyama and Ito, 1995) and specifically by cells of the TH2 subset (Else and Grencis, 1991). Although the precise mechanisms involved in worm expulsion are not defined, there is good evidence that IgA antibodies can transfer protection (Roach *et al.*, 1991) and there appears to be an additional reqirement for some form of more direct T cell activity. A critical factor in the development of effective resistance appears to be the ability to remove the bulk of worm population before about day 25. If this is not achieved, as in certain low-responders and in non-responders, the TH response is switched to the TH1 subset, with down-regulation of TH2 cytokine release (Table 2). The response phenotype of a given strain of mouse can be reversed by enhancing or by blocking the activity of TH1 or TH2 cytokines. Blocking IL-4 (TH2) activity in responder mice makes them non-responsive, whereas administration of IL-4 to non-responders allows them to expel worms; depletion of IFN-γ (TH1) activity in non-responders also restores the ability to expel worms (Else *et al.*, 1994).

Genetic factors appear to determine response phenotype through effects upon the speed of response. In mice that begin to expel worms early, i.e.

Table 2 Levels of TH1 and TH2 cytokines released from mesenteric lymph node cells of responser BALB/K and non-responder B10.BR mice infected with *T. muris*. Cells were stimulated *in vitro* with the mitogen Con A and the levels of IFN-γ (TH1) and IL-5 (TH2) in the supernatant measured in Units/ml. Data from Else and Grencis (1991)

Mice	Cytokine	Days after infection with 400 eggs			
		Day 0	Day 13	Day 20	Day 34/5
B10.BR	IFN-γ	39.0	40.4	269.0	140.0
	IL-5	9.5	0.0	3.4	16.8
BALB/K	IFN-γ	18.0	5.6	70.0	14.0
	IL-5	24.1	22.8	54.0	65.0

before the moult to the L3 stage (about day 17), the development of the required TH2 response is unaffected. However if, because of a slower response, the bulk of the infection persists beyond day 25, it seems that immunomodulatory factors released from the maturing worms bring about a switch in TH phenotype, effectively preventing the further development and expression of immunity. Once this switch has been made, the mouse retains a susceptible phenotype unless exogenous cytokines are administered. Genetically-determined non-responsiveness is associated with a delayed onset of T cell responsiveness to parasite antigen and then a relative anergy, in which cells fail to respond to *in vitro* stimulation.

The work described above has defined the importance of host genotype in determining the outcome of infection with *T. muris*, but it is clear from other experimental studies that parasite genotype is also important (Fig. 3A). The isolate maintained by Professor Ito is expelled quite rapidly from B10 BR mice (Ito – personal communication) a strain of mouse that was defined as non-responsive to the original Edinburgh isolate (Else and Wakelin, 1988). Recent experiments with this isolate in B10.BR mice, however, have shown a late loss of worms. With the Sobreda isolate of *T. muris*, there is scarcely any loss of worms from B10.BR mice over a 5 week period. Analysis of specific anti-worm antibody responses to each isolate in this strain have revealed an interesting correlation between the degree of expulsion and the levels of lgG1 and lgG2a antibodies (Fig. 3B). Mice infected with the Sobreda isolate show the least protective immunity and make a good lgG2a antibody response, whereas mice infected with the Japanese isolate respond primarily with an lgG1 response. It is well established that lgG1 antibody is controlled by cytokines associated with TH2 cells, whilst lgG2a is under TH1 control, thus it appears (as would be predicted) that the non-responsiveness of B10.BR to the Sobreda isolate reflects TH1 - mediated influences and the responsiveness to the Japanese isolate reflects TH2 activity. Given the identical life cycle and host location of the two isolates, this difference in host T cell response must be induced by antigenic differences between the worms.

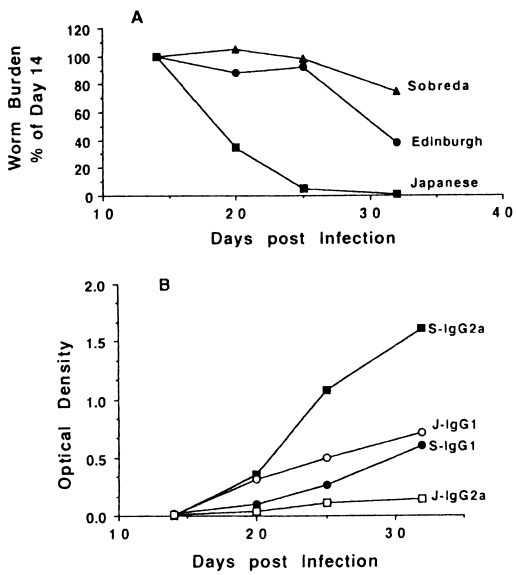

Fig. 3 3A. Time course of infection with the Edinburgh, Japanese and Sobreda isolates of *Trichuris muris* in B10.BR mice. Mice were infected with 400 eggs and killed at intervals to determine the numbers of worms present. [Data from Bellaby, Robinson and Wakelin, unpublished]

3B. Time course of anti-*Trichuris muris* IgG isotype responses in B10.BR mice infected with 400 eggs of the Japanese and Sobreda isolates of *T. muris*. Isotypes were determined in ELISA against excretory/secretory antigens prepared from the homologous isolate [Data from Bellaby, Robinson and Wakelin, unpublished].

Trichinella

In taxonomic terms the genus is complex, containing eight separate gene pools (designated T1 to T8) five of which are independent species (Pozio *et al.*, 1992). Host specificity is extremely low and almost all mammals can be infected, in consequence isolates of *Trichinella* spp have been obtained from a variety of hosts in many countries of the world and passaged into laboratory rodents. The most widely used species in laboratory research, and the species of the greatest clinical significance, is *T. spiralis* (T1). Like all members of the genus, *T. spiralis* has a unique life cycle, in which the parasite completes an entire generation within the body of a single host. Infection occurs when the host ingests infective L1 larvae encysted in the muscles of another animal. The larvae invade the

epithelial cells of the small intestine and complete their development to the adult stage extremely rapidly, fertilized female worms releasing newborn larvae into the mucosa from about day 5 after infection. These larvae move through the lymphatics and blood vessels and eventually penetrate into host muscle cells where they develop into the infective L1.

Much of the research into the immunology of *T. spiralis* infections has focused on the responses initiated by and relevant to the intestinal stages. In different strains of mice the duration of infection with these stages is much less variable than that seen with *H. polygyrus* or *T. muris* (Wakelin, 1980) ranging from about 10–12 days in high-responder strains to about 25 days in low-responders (Fig. 4). Response phenotype is heritable, high-responsiveness being inherited as a dominant characteristic. Again, both background and MHC-linked genes regulate the speed of response but, unlike the situation with *T. muris*, there does not seem to be any major polarization of TH subset responses associated with resistance or susceptibility, although this has been disputed (Pond, Wassom and Hayes, 1989). Comparison of two strains of mice with differing degrees of responsiveness showed that both generate TH2 responses, but the former do so more quickly and are able to translate these more rapidly into the intestinal inflammatory changes needed to expel the adult worms (Grencis, Hultner and Else, 1991; Crook and Wakelin, 1993). There is clear-cut genetic control of the ability of mice to develop inflammatory responses involving a number of the cell types that are prominent in the mucosal and systemic changes that are induced by infection, most notably eosinophils and mucosal mast cells (Wakelin and Grencis, 1992).

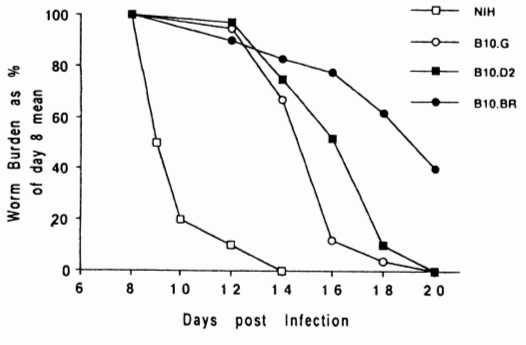

Fig. 4 Time course of infection with *Trichinella spiralis* (T1) in 4 strains of inbred mice. Mice were infected with 300 larvae and killed at intervals to determine the numbers of worms present. NIH and B10.G are MHC-compatible ($H\text{-}2^q$), B10.G, B10.D2 and B10.BR are MHC congenic strains ($H\text{-}2^q$, $H\text{-}2^d$ and $H\text{-}2^k$ respectively). [Data from Wakelin, 1980].

Recent studies using a number of isolates, both of *T. spiralis* sensu stricto and other *Trichinella* species, have provided some interesting comparative data concerning the role of parasite variables in determining the host-parasite relationship with a particular strain of mouse. Overall, the response phenotype of a given mouse strain will be expressed against infection with any *Trichinella* isolate. Thus, mice that are high-responders to *T. spiralis* (T1) are high responders also to *T. nativa* (T2), *T. britovi* (T5), *Trichinella* T6 and *T. pseudospiralis* (T4) (Palmas, Wakelin and Cabaj, 1985; Bolas-Fernandez and Wakelin, 1989; 1990). However, each parasite isolate generates distinct infection characteristics that must reflect differences in parasite immunogenicity or behaviour. This was seen very clearly in mice infected with two isolates of *T. spiralis* (T1) designated Spanish (S) and London (L) (Bolas-Fernandez and Wakelin, 1989). The former elicited much less immunity in the high-responder NIH strain of mouse, the worms surviving for more than 12 days, than did the L isolate, which was expelled completely within that time (Fig. 5A). Similar data, showing a more striking difference in infection kinetics, were obtained with two isolates belonging to *T. spiralis* (T1) and *T. nativa* (T2) (Fig. 5B) and it was concluded, by following the time course of worm loss after immune suppression of the host, that differential parasite immunogenicity was an important factor in determining the outcome of infection (Bolas-Fernandez and Wakelin, 1989).

Different geographical isolates of *T. spiralis* (T1) also generate host responses that differ quantitatively and qualitatively. When high- and low-responder mice were infected with three isolates of *T. spiralis* originating from England, Poland and Spain there were distinct differences in the level and isotype of antibody response and level of eosinophilia and mucosal mastocytosis in each case (Goyal and Wakelin, 1993). Analysis of cytokine

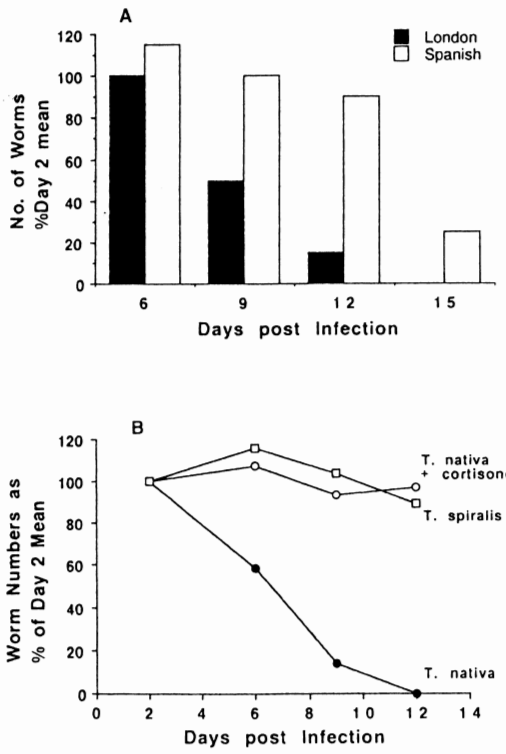

Fig. 5 5A. Time course of infection with two isolates (London and Spanish) of *Trichinella spiralis* (T1) in inbred NIH mice. Mice were infected with 300 larvae and killed at intervals to determine the numbers of worms present. [Data from Bolas-Fernandez and Wakelin, 1989].

5B. Time course of infection with *Trichinella spiralis* (T1) in 3 groups of inbred NIH mice, one of which was immune suppressed by injection of cortisone acetate on days -4, -2 and 0 before infection with 300 larvae. Mice were then killed at intervals to determine the numbers of worms present. [Data from Bolas-Fernandez and Wakelin, 1989].

responses during these infections (Goyal, Hermanek and Wakelin, 1994) showed significant differences in the time at which the host underwent a change from a TH1-dominated to a TH2-dominated response profile (Table 3). Isotype and cytokine differences in host response have also been recorded during infection with *T. spiralis* and *T. pseudospiralis* (T4) (Wakelin *et al.*, 1994).

Table 3 Production of the cytokines Interferon-gamma (IFN-γ) and Interleukin-5 (IL-5) by mesenteric lymph node cells taken from NIH mice after infection with 300 larvae of the London (L), Polish (P) and Spanish (S) isolates of *Trichinella spiralis*. Cytokine values are given in units/ml. Maximum value for IFN-γ assay was 307u/ml, for IL-5 was 500u/ml. (Data from Goyal *et al.*, 1994)

Cytokine assayed	Day after infection	Isolate of *T. spiralis* L	P	S
	2	307	307	307
IFN-γ	4	30	188*	51
	6	11	188*	3
	4	71	55	69
IL-5	6	151	113	500*
	8	480	500	391*

*=value significantly different ($P<0.05$) from other two isolates.

Conclusions

The various isolates of *Trichuris* and of *Trichinella* used in the experiments described above are all morphologically very similar and occupy similar niches in the host, i.e. all are intracellular in the epithelial cells of the mucosae of the large and small intestines respectively. It can be concluded from this that isolates of each species will share a similar relationship with the immune system of the host in terms of antigen exposure and processing. This being so, it is clear that the quite different patterns of host responses elicited by infection with different isolates must arise from genetically-regulated molecular (antigenic) differences between them. At the present time, the nature of these differences is not known, but the importance of the observations is that genetic differences between populations of parasites can exert significant influences upon the outcome of infection in the host. However, this outcome is simultaneously influenced by the genetically-controlled response capacity of the host. There is, therefore, a complex interaction between host and parasite variability, mediated through the immune and inflammatory systems which will determine the intensity and duration of infection and the nature and degree of immune responsiveness (Fig. 6)

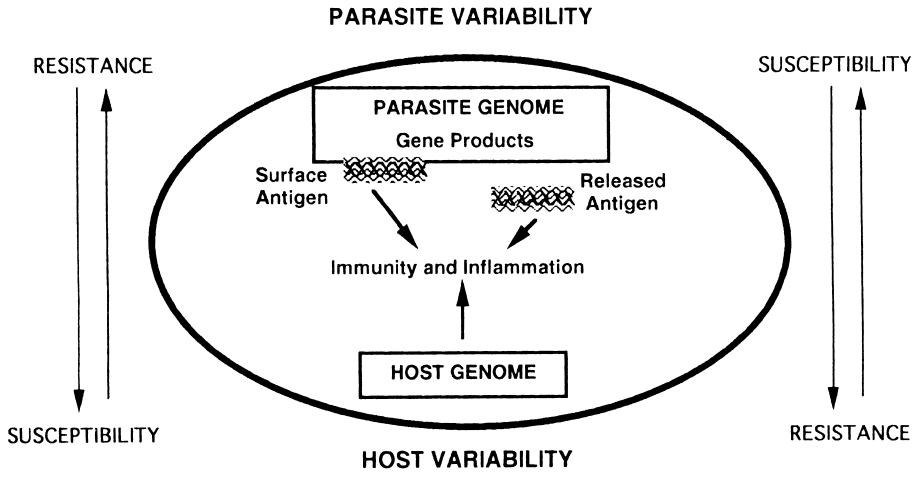

Fig. 6 Scheme of the interactions between the genetically-controlled variables of host and parasite origin that determine the balance of resistance and susceptibility in the host-parasite relationship.

This conclusion has important consequences for aspects of parasitology as diverse as the effectiveness of immunoprophylaxis, the clinical and economic consequences of immunopathological responses, and the long-term evolution of host-parasite relationships (Wakelin, 1993) and it cautions against simple extrapolation from observations on particular host-parasite systems to broader conclusions about the behaviour of a given species of parasite in a given species of host:

Immunoprophylaxis: The fact that isolates of parasites differ in antigens that play important roles in generating immune responses which regulate the host-parasite interaction has important consequences for the design of vaccines that will be used against geographically widely dispersed parasite species. Similarly, the fact that not all hosts are equally able to respond protectively to the same degree must be allowed for in designing vaccine strategies for use in particular host populations.

Immunopathology: The facts that isolates of parasites differ in their capacity to elicit inflammatory responses, and that hosts vary in their response capacity, mean that there can be considerable variation in the degree of immunopathology associated with infections of a given species of parasite in a given host. Identification of parasite variability within endemic areas may therefore be an important component of the data necessary for a full understanding of the pathological potential of the host-parasite relationship concerned.

Evolution: Parasitism always has a cost to the host in terms of the resources diverted into parasite growth and reproduction. There is also a cost in terms of the immune and inflammatory responses made to infection. The more immunogenic a parasite isolate, and the more responsive a host, the greater this latter cost becomes. It may be desirable for hosts to reduce their responsiveness to limit the cost of infection, but there is then the risk of overinfection by the parasite and a correspondingly greater loss of resource. For the parasite, host immune and inflammatory responses may be harmful directly, they may reduce the suitability of the host environment for the parasite, and at the extreme may kill the host. It may therefore be desirable for the parasites to reduce their immunogenicity, unless this prevents the host from regulating the absolute size of the parasite population; if there are too many parasites present, parasite survival and reproduction may again be threatened. It is almost impossible to predict the optimum balance for the two species involved in any given relationship because this will always be dynamic, changes in one partner being counterbalanced by changes in the other. Such a dynamic situation implies a pool of very considerable variation in both host and parasite, and this is precisely what the experimental data recorded here

have shown.

Knowledge of host and parasite variation is therefore crucial to many facets of parasitology, both theoretical and applied. Much of our present information about the detailed processes involved in host-parasite relationships has necessarily come from well-controlled laboratory studies in which only restricted variants of host and parasite have been employed. Now that we have this background of experimental data it is necessary to define the extent and the consequences of variation in each component, so that we can gain a much more realistic picture of the possible outcomes of infections, devise appropriate strategies for control and more fully understand the dynamic processes by which host-parasite interactions evolve.

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