Immunological relationships during primary infection with *Heligmosomoides polygyrus* (*Nematospiroides dubius*): expulsion of adult worms from fast responder syngeneic and hybrid strains of mice

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SUMMARY

The time-course of low and high intensity primary infections with *Heligmosomoides polygyrus* was monitored in SJL and SWR mice, both of which usually expel worms within 7 weeks of larval administration. Worm expulsion in these strains was not dependent on the intensity of infection, with low and high intensity worm burdens being lost within the same period of time. The ability to expel worms rapidly was inherited in a dominant manner in F_1 offspring of SJL or SWR mice mated with $C_{57}Bl_{10}$ mice; the latter being a strain in which no loss of worms was evident within 10 weeks of infection. However, neither (SJL × $C_{57}Bl_{10}$)F_1 nor (SWR × $C_{57}Bl_{10}$)F_1 mice expelled worms as rapidly as the parental SJL and SWR strains. (SWR × B10G)F_1 [H-2^q] mice eliminated worms faster than (SWR × $C_{57}Bl_{10}$)F_1 [H-2^{bq}], suggesting that the b haplotype had a moderating influence on the expulsion process. In fact (SWR × B10G)F_1 mice showed a significant reduction in worm burdens by week 4 but by weeks 6–8 the rate of worm loss had slowed considerably. In contrast, SJL and SWR mice, whilst initiating rejection slightly later, (after week 4) expelled all worms within the following 2 weeks. Thus two distinct patterns of response were observed among the fast responder strains as exemplified by SWR and SJL mice on the one hand and (SWR × B10G)F_1 on the other. Our results support the hypothesis that the course of a primary infection with *H. polygyrus* is influenced by multiple host gene loci, some of which are encoded within the MHC. SJL and SWR mice probably have similar if not identical gene combinations at loci which determine a fast responder phenotype, distinguishing them from the other mouse strains which have been studied.

Key words: *Heligmosomoides polygyrus*, worm expulsion, fast responder mice, immune response.

INTRODUCTION

The mechanisms which enable parasitic nematodes to evade host immunity and hence to cause chronic infections are still poorly understood. The duration of an infection in a particular host–parasite combination may be the outcome of interactions between a variety of factors including genes encoding for resistance or susceptibility, parasite-mediated immunodepression and/or other evasive strategies and the parasite's intrinsic life-span (see review by Behnke, 1987). *Heligmosomoides polygyrus* is a parasitic nematode which has been widely studied because of the prolonged duration of primary infections in a variety of laboratory mouse strains (Liu, 1966; Day *et al.* 1979; Behnke & Robinson, 1985; Keymer & Hiorns, 1986; Behnke *et al.* 1987). In $C_{57}Bl_{10}$ mice, for example, the infection may last over 30 weeks and it is likely that this reflects the maximum natural life-span of *H. polygyrus* (Robinson *et al.* 1989).

However, in other mouse strains, infections are curtailed in a shorter period of time (Prowse *et al.* 1979), suggesting that adult worms are not totally successful in avoiding host immunity and that the parasite's evasive strategies can be overcome by mice of an appropriate genotype. In BALB/c and Q strain mice, primary infections are dose dependent and, under low intensity exposure, adult worm survival is significantly shorter (e.g. BALB/c, 10–15 weeks) than when heavy larval inocula are used (e.g. BALB/c, 21–32 weeks) (Robinson *et al.* 1989; Dobson, Sitepu & Brindley, 1985); observations which are consistent with the view that adult parasites exert a dose-dependent, immunomodulatory influence on events in the intestinal environment.

The literature also contains references to mouse strains which have the capacity to expel adult worms in a still shorter period of time. Surprisingly, these strains have received relatively little attention and yet an understanding of the mechanisms used by such strains to limit parasite survival may point to the lesion in other strains, which the worms exploit to facilitate their own survival. If adult worm survival is dependent on an immunomodulatory strategy, then strains of mice which clear worm

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burdens prematurely may be insusceptible to or may overcome parasite immunomodulatory factors. The earliest report of a fast response to *H. polygyrus* was by Cypess *et al.* (1977), who reported that LAF_1 mice $(A/He \times C_{57}L)F_1$ lost 50% of their adult worm population 14–20 days after a primary infection. In both parental strains, worm burdens were stable over this period. However, in a subsequent paper, Jacobson, Brooks & Cypess (1982) concluded that primary worm burdens were stable in LAF1/J mice for 6 weeks following infection. Several reports have singled out SJL/J mice as particularly fast responders; for example Mitchell *et al.* (1982) found that worm loss was complete by week 11, although earlier work from the same laboratory had suggested a more rapid response, with worm burdens declining significantly by day 19 (Prowse *et al.* 1979).

In the course of our studies on the immunology of chronic infections with *H. polygyrus*, we have screened a variety of mouse strains for the stability and duration of primary infections (Robinson *et al.* 1988). Our experiments have confirmed that SJL mice are able to mount a rapid response to *H. polygyrus* but, in addition, we have identified SWR mice as showing comparable resistance. In this paper we present evidence that expulsion of *H. polygyrus* from SJL and SWR mice is dose independent and that the responder phenotype is inherited in a dominant manner in F_1 hybrids resulting from crosses with the susceptible $C_{57}Bl_{10}$ strain.

MATERIALS AND METHODS

Animals

Syngeneic NIH, SWR, SJL, $C_{57}Bl_{10}$ and $DBA/_2$ mice originally purchased from Harlan Olac Ltd and together with the hybrid strains were bred in the departmental animal house. The MHC haplotypes of the various mouse strains employed in the present study are shown in Table 1. The animals were housed under conventional animal house conditions with access to food and water *ad libitum*.

Parasite

The methods used to maintain *H. polygyrus*, infect mice and recover worms at autopsy have all been described previously (Jenkins & Behnke, 1977). Faecal egg counts were carried out as described by Behnke & Parish (1979).

Statistical analysis of results

The results are presented as the mean number of worms recovered (MWR) ± S.E.M. Where appropriate differences between groups were analysed by the Mann-Whitney U-test (Sokal & Rohlf, 1969). Additionally, strain mean values at set time points were compared by a one-way analysis of variance (ANOVA), followed by calculation of the least significant difference (Festing, 1989).

Table 1. MHC haplotypes of the mouse strains which were studied

Strain	H_2 haplotypes
NIH	q
SWR	q
B10G	q
$(SWR \times B10G)F_1$	q
SJL	s
DBA/2	d
$(NIH \times C_{57}Bl_{10})F_1$	qb
$(SWR \times C_{57}Bl_{10})F_1$	qb
$(SJL \times C_{57}Bl_{10})F_1$	sb

RESULTS

The time-course of infection in SJL, NIH and $C_{57}BL_{10}$ mice

The course of primary infections with *H. polygyrus* was studied in SJL mice and compared to that in NIH and $C_{57}Bl_{10}$ mice. The results of Exp. 1 are shown in Table 2. The infection was relatively stable in $C_{57}Bl_{10}$ mice over the course of 7 weeks but NIH mice lost 11·9% and SJL mice rejected 99·2% of their initial worm burden.

In a second experiment (Exp. 2), 10 NIH (Group A) and 9 SJL (Group B) mice were given 500 L_3 and 10 NIH (Group C) and 8 SJL (Group D) were infected with 50 larvae. All the mice were male and the course of infection was followed by regular faecal egg counts (Fig. 1). The results show that faecal egg counts were similar in both strains for the first 4 weeks post-infection and continued thereafter in NIH mice but declined sharply in SJL mice exposed to both low and high intensity infections. The animals were killed for worm counts in week 7 and the following worm burdens were recorded; NIH mice, 398·1 ± 7·5 (Group A) and 42·1 ± 4·1 (Group C); SJL mice, 2·2 ± 1·5 (group B) and 0 (Group D). The higher level of infection proved excessive for SJL mice and 7 mice were culled before day 49. Two killed on day 39 had 4 and 32 worms respectively.

Low and high intensity primary infections in various syngeneic mouse strains

The pattern of worm expulsion was studied in a series of 4 experiments (Exps 3–6) in each of which a different combination of mouse strains was examined. Three of these experiments included SJL mice, two SWR mice and one DBA/2 mice. When available NIH and $C_{57}Bl_{10}$ mice were incorporated as

Table 2. Exp. 1. Comparison of the time-course of primary infection with *Heligmosomoides polygyrus* in SJL, NIH and $C_{57}Bl_{10}$ mice
(Statistical analysis of results. Groups with the same superscript were compared and have the following values for P: [2], $P < 0{\cdot}001$; [3], $P = 0{\cdot}05$.)

	Mean worm recovery ± S.E.M. (% reduction)			
Mouse strain*	Week 2	Week 4	Week 5	Week 7
SJL	$72{\cdot}0^{2} \pm 5{\cdot}6$	$71{\cdot}2 \pm 4{\cdot}8$	$70{\cdot}8 \pm 4{\cdot}1$	$0{\cdot}6 \pm {}^{2}0{\cdot}2$ (99·2)
NIH	$77{\cdot}5^{3} \pm 3{\cdot}8$	N.D.	N.D.	$68{\cdot}3^{3} \pm 1{\cdot}9$ (11·9)
C57Bl10	$74{\cdot}3 \pm 4{\cdot}1$	N.D.	N.D.	$85{\cdot}0 \pm 5{\cdot}3$ (0)

* All the mice were infected with 100 L_3 on day 0 and each group comprised 6 female mice.
N.D., Not determined.

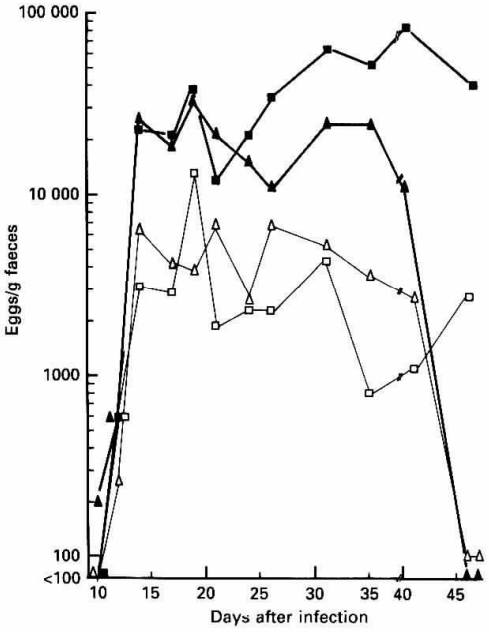

Fig. 1. Faecal egg counts in groups of male NIH (□, ■) and SJL (△, ▲) mice given 50 L_3 (□, △) or 500 L_3 (■, ▲) *Heligmosomoides polygyrus*.

the reference strains. The results are summarized in Table 3.

It was again obvious during these experiments that SJL mice did not tolerate heavy infections very well and in Exp. 5B, some mice were culled earlier than originally intended. It is nevertheless apparent from Table 3 that worm burdens were stable in this strain until after week 4 of infection, but worm expulsion occurred soon afterwards. Faecal egg counts during Exp. 4 (Fig. 2) suggest that worm loss occurred after day 35 and was virtually complete by the end of week 6 irrespective of the worm burden.

SWR mice behaved much like SJL, but were more tolerant of heavier infections. In Exp. 4D a slight delay in worm expulsion was observed in the mice given the heavier inoculum and this was confirmed in the faecal egg counts (Fig. 2B). However, such a delay was not apparent in Exp. 6 in which SWR mice had an initially heavier infection. Worm expulsion in mice with low and high intensity infections was almost completed by day 35 and this was reflected in the faecal egg counts.

$DBA/_2$ mice showed no significant change in worm burdens over a 6-week period of infection. No significant change was observed in $C_{57}Bl_{10}$ or NIH mice over the same period although in Exp. 4G (NIH), 47·2% of the mean worm recovery in week 2 was lost by week 10.

The time-course of infection in various combinations of F_1 hybrid strains

Two experiments were completed comparing the survival of *H. polygyrus* among hybrid mouse strains and, when possible, the parental and/or reference strains were included as controls. However, it was not always possible to examine the full range of strain combinations nor to include the parental and reference strains in each experiment. Some mouse strains did not breed as well as others and logistical considerations entailed a limit to the number of animals which could be processed.

In Exps 7 and 8, mice were infected with 50 L_3 and were killed for worm counts in week 2 or 8. The mean worm recoveries in week 8 were expressed as the mean percentage worm recoveries of the worm burdens in week 2 and these data are presented in Fig. 3. In some cases insufficient numbers of mice were available to include groups killed in both weeks. In these cases the worm burden in week 8 was expressed as a percentage of one of the other groups. Although initial parasite establishment in week 2

Table 3. The time course of infection with *Heligmosomoides polygyrus* at low and high intensities in various syngeneic mouse strains

Experiment and group	Strain and sex*	Infection intensity†	Mean worm recovery ± S.E.M. (no. of mice) in weeks after infection						
			2	3	4	5	6	7	10
3 A	SJL F	Low		62·5 ± 10·0 (6)				2·3 ± 1·7 (6)	
3 B	SJL F	Intermediate		103·2 ± 19·0 (6)				0 (6)	
3 C	SJL F	High		166·3 ± 69·9 (6)				0·4 ± 0·4 (6)	
4 A	SJL F	Low	43·2 ± 2·7 (4)		44·8 ± 2·6 (4)		0·1 ± 0·1 (9)		0 (6)
4 B	SJL F	High	187·0 ± 3·3 (4)		183·5 ± 6·5 (4)		0·6 ± 0·6 (9)		0 (8)
4 C	SWR F	Low	41·5 ± 4·0 (4)	37·0 ± 2·4 (4)	39·6 ± 3·8 (5)		0·6 ± 0·4 (7)		
4 D	SWR F	High	153·0 ± 7·5 (4)	177·5 ± 4·9 (4)	166·4 ± 35·5 (5)		50·5 ± 30·8 (6)		2·0 ± 1·1 (5)
4 E	$C_{57}Bl_{10}$ M	Low	50·2 ± 3·4 (5)		47·4 ± 2·4 (5)		44·0 ± 4·3 (6)		41·7 ± 2·4 (7)
4 F	$C_{57}Bl_{10}$ M	High	191·4 ± 15·8 (5)		198·0 ± 7·8 (4)		171·1 ± 6·9 (6)		177·8 ± 3·5 (7)
4 G	NIH F	Low	46·0 ± 2·7 (4)						24·3 ± 6·6 (6)
5 A	SJL M	Low	37·8 ± 2·7 (4)					3·9 ± 3·7 (8)	
5 B	SJL M	High	269·0 ± 4·4 (4)					155·7 ± 76·3 (9)‡	
5 C	NIH M	Low	38·0 ± 1·8 (5)					37·5 ± 1·9 (11)	
5 D	NIH M	High	266·4 ± 12·4 (5)					264·5 ± 5·7 (11)	
6 A	SWR F	Low	47·3 ± 2·3 (8)	53·0 ± 4·1 (7)		14·0 ± 8·3 (6)	4·6 ± 2·9 (9)		
6 B	SWR F	High	237·4 ± 7·5 (8)	240·3 ± 8·9 (8)		18·6 ± 6·9 (5)	1·9 ± 0·7 (7)		
6 C	DBA/2 F	Low	43·1 ± 4·0 (8)				56·4 ± 4·2 (5)		
6 D	DBA/2 F	High	250·9 ± 10·8 (7)				250·4 ± 9·6 (5)		
6 E	NIH F	Low	48·7 ± 2·6 (9)				49·4 ± 3·3 (9)		

* F, female; M, male.

† Low = 50–100 L_3; intermediate = 170 L_3; high = 250–500 L_3.

‡ 6 of the 9 mice in this group were killed earlier *in extremis*. The MWR of 155·7 is based on worm burdens in the surviving 3 mice which were 3, 232 and 232 respectively.

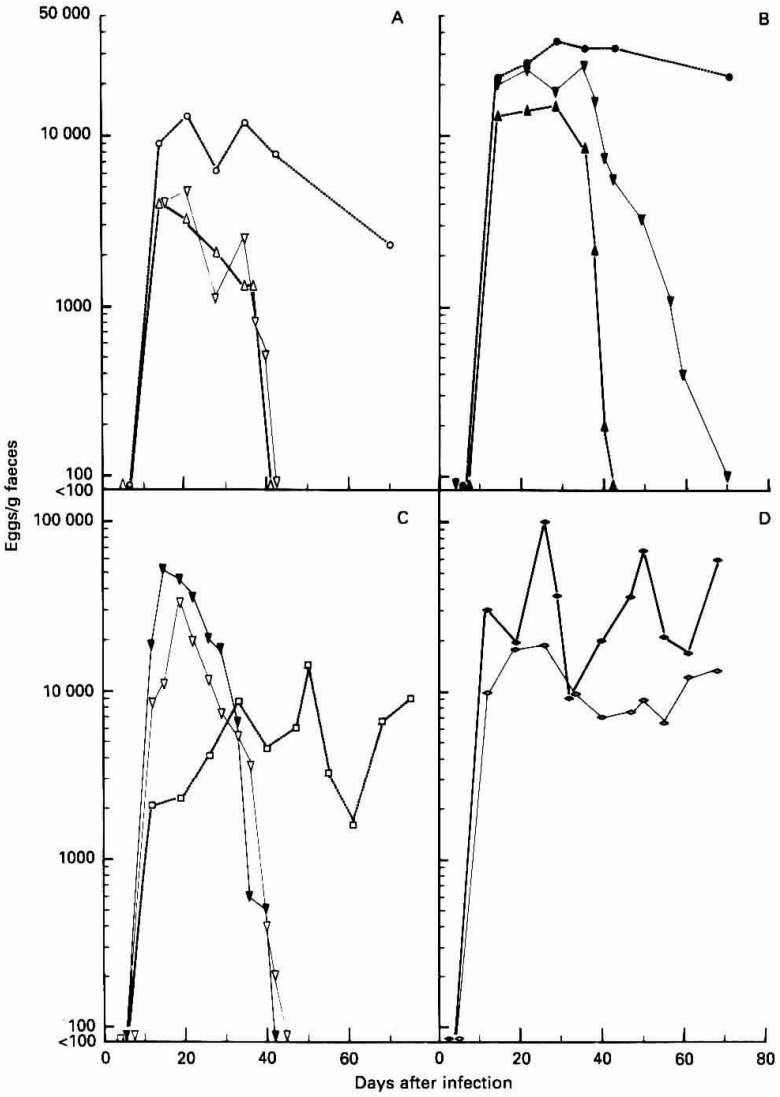

Fig. 2. Faecal egg counts in various mouse strains during a primary infection with *Heligmosomoides polygyrus*. (A) [Exp. 4], low intensity infections in SJL (△), SWR (▽) and $C_{57}Bl_{10}$ (○) mice, (B) [Exp. 4], high intensity infections in SJL (▲), SWR (▼) and $C_{57}Bl_{10}$ (●) mice, (C) [Exp. 6], low intensity infection in SWR (▽) and NIH (□) mice and high intensity infection in SWR mice (▼), (D) [Exp. 6], low (◇) and high (◆) intensity infections in DBA/2 mice.

varied between strains, no significant differences were observed. Faecal egg counts were also carried out on most strains and these data are presented in Fig. 4.

Several points emerge from the data presented in these figures. (a) (NIH × $C_{57}Bl_{10}$)F_1 mice expelled significantly more worms than either of their parental strains. (b) However, (SJL × $C_{57}Bl_{10}$)F_1 hybrids did not show an advantage over the parental SJL strain and indeed in the case of this combination a highly variable data set was obtained, but in all cases worm expulsion appears to have been delayed in comparison to SJL mice. (c) Although no SWR mice were available for inclusion in Exps 7 and 8, the two previous experiments (Exps 4 and 6, Table 2) indicated that worm expulsion would be complete in these mice by week 8. Fig. 3 shows that this was not the case in (SWR × $C_{57}Bl_{10}$)F_1 hybrids, again implying that the $C_{57}Bl_{10}$ contribution to this hybrid resulted in a retarded host response. (d) In contrast (SWR × B10G)F_1 mice, although still harbouring worms in week 8, showed the best response among

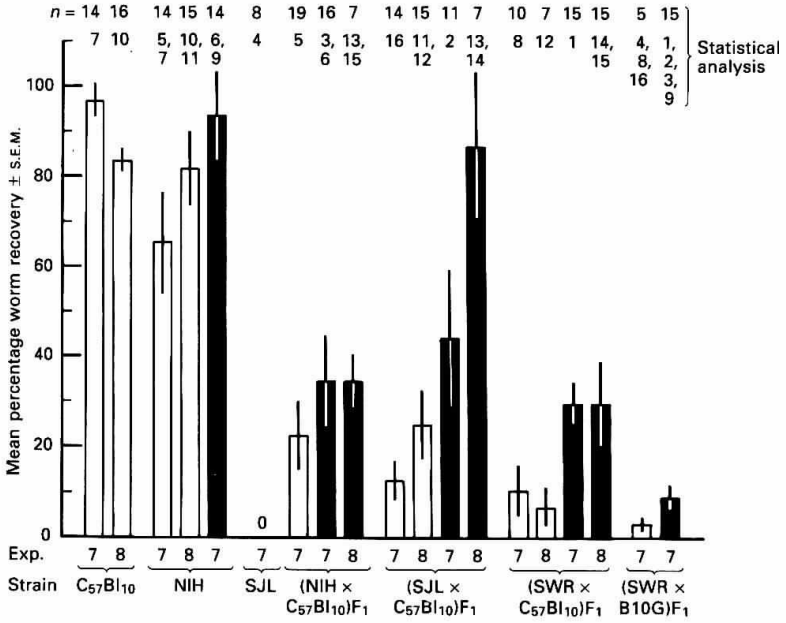

Fig. 3. Experiments 7 and 8. Comparison of worm burdens in various parental and hybrid strains 8 weeks after infection with 50 L_3. The results are expressed in terms of the mean percentage recovery ± S.E.M. calculated after transformation of individual mouse worm burdens into the percentage of the mean worm recovery in week 2. □, Female mice; ■, male mice. Columns with the same superscript were compared and have the following P values: 3, 8; 10, 15 and 16, P = not significant; 4, $P = 0{\cdot}05$; 12, $P < 0{\cdot}05$; 13 and 14, $P < 0{\cdot}025$; 2, $P < 0{\cdot}01$; 5, $P < 0{\cdot}005$; 1, 6, 7, 9 and 11, $P < 0{\cdot}001$.

the hybrid strains tested. Few female mice were available for inclusion in Exp. 7 but the male group was sufficiently large to enable comparisons to be made. No B10G mice were available during the course of this study other than those used in breeding, but from published work it is known that worm burdens remain stable in these mice for at least 5 weeks post-primary infection (Behnke & Robinson, 1985). On the basis of these results (SWR × B10G)F_1 mice were therefore almost as resistant as their parental SWR strain but this point was explored further in Exp. 9.

The faecal egg count data presented in Fig. 4 shows that parasites established in all the mouse strains used and that expulsion, as reflected in declining egg counts, commenced only after 4 weeks of infection. It can also be seen that faecal egg counts dropped over a period of 2 to 3 weeks in those strains which expelled the worms. In general there was good agreement between the onset and subsequent course of declining faecal egg counts and worm burdens in week 8. Thus SJL mice showed a dramatic drop in faecal egg counts from week 4 and their entire worm burden had been eliminated by week 8. Similarly, marked changes were observed in female (B10 × SWR)F_1 and (SJL × $C_{57}Bl_{10}$)F_1 mice which also lost over 90 % of their worm burden by week 8. However, this was not always the case and, for example, male (SWR × $C_{57}Bl_{10}$)F_1 mice had fewer than 100 epg in week 8 and yet approximately 30 % of their original worm burden was still present.

The final experiment (Exp. 9) was carried out to follow up our observations on (SWR × B10G)F_1 in Exp. 7. As neither SWR nor B10G mice were available in sufficient numbers to enable their inclusion in this experiment, a group of 51 female $C_{57}Bl_{10}$ mice were included as a reference strain. The results are presented in Figs 5 and 6. The hybrid mice lost 57·6 % (females) and 38·9 % (males) of their initial worm burden by week 4 of infection. Neither SWR nor SJL mice in our earlier experiments showed any reduction in parasite burdens as early as this (Exp. 4, Table 3). However, the rate of worm loss in the hybrid strain subsequently slowed down, when compared to observations on SWR and SJL mice in Exp. 4. The latter strains lost almost their entire worm burden by week 6 once expulsion had been initiated. In week 8, female hybrid mice had only 2·3 % ± 0·8 of their starting worm burden, a figure which is consistent with the data from Exp. 7. Male mice, however, had 34·4 % ± 9·5 which is more than in Exp. 7 but comparable to that in other hybrid strains in week 8 (Fig. 3).

It is apparent from Exp. 7 and also from the data in Fig. 3 that the expulsion of adult worms was slower in male mice compared to female mice in all

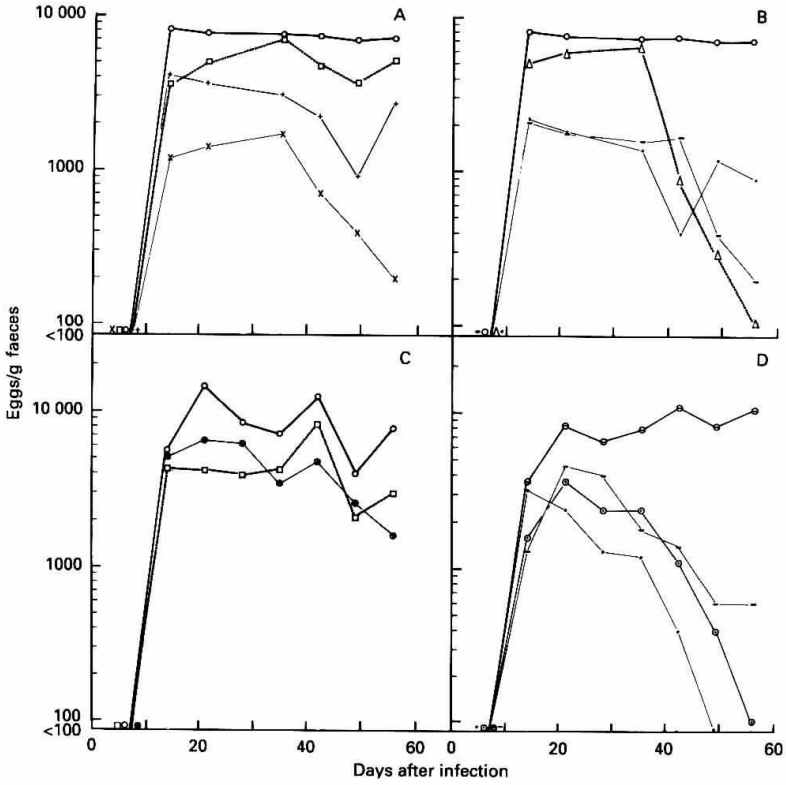

Fig. 4. Faecal egg counts in groups of hybrid and parental mouse strains given low intensity infections with *Heligmosomoides polygyrus*. (A) [Exp. 7], female $C_{57}Bl_{10}$ (○), NIH (□), $(NIH \times C_{57}Bl_{10})F_1$ (+), and $(SWR \times B10G)F_1$ (×), (B) [Exp. 7], female $C_{57}Bl_{10}$ (○), SJL (△), $(SJL \times C_{57}Bl_{10})F_1$ (−), and $(SWR \times C_{57}Bl_{10})F_1$ (·), (C) [Exp. 8], female $C_{57}Bl_{10}$ (○), female NIH (□) and male $(NIH \times C_{57}Bl_{10})F_1$ (⊕), (D) [Exp. 8], female $(SJL \times C_{57}Bl_{10})F_1$ (−) and $(SWR \times C_{57}Bl_{10})F_1$ (·). Male $(SJL \times C_{57}Bl_{10})F_1$ (⊖) and $(SWR \times C_{57}Bl_{10})F_1$ (⊙).

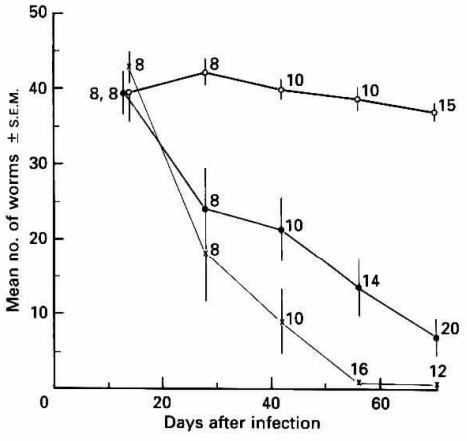

Fig. 5. [Exp. 9]. Worm burdens following a low intensity infection with *Heligmosomoides polygyrus* in female $C_{57}Bl_{10}$ (○), female $(SWR \times B10G)F_1$ (×) and male $(SWR \times B10G)F_1$ (⊗). The number beside each mean worm recovery = *n*.

the strains tested. This conclusion is consistent with previous findings (Robinson *et al.* 1988) and, as discussed in our earlier paper, supports an immunological explanation for parasite loss in these strains.

DISCUSSION

Like many economically and medically important gastrointestinal nematode parasites, *H. polygyrus* generally causes chronic primary infections in its host the mouse. Most of the strains used in medical research cannot expel worms within 7 weeks of the administration of infective larvae and in many the parasites live for 25–40 weeks. SJL and SWR mice therefore appear to be unique among the inbred strains in having the capacity to reject adult worms within 7 weeks of a primary infection. Furthermore neither of these two strains was affected by the intensity of infection, as both rejected low and high intensity infections in the same period of time. There is a striking parallel here to similar studies with *T. spiralis*: NIH mice which showed the fastest ex-

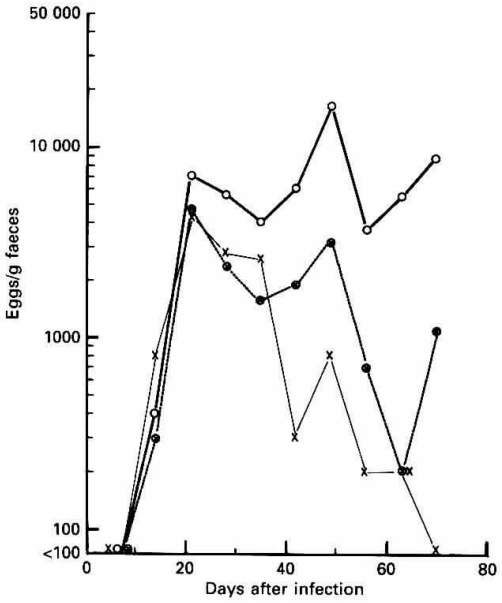

Fig. 6. [Exp. 9]. Faecal egg counts during the course of a low intensity infection with *Heligmosomoides polygyrus* in female $C_{57}Bl_{10}$ (○), female (SWR × B10G)F_1 (×) and male (SWR × B10G)F_1 (⊗) mice.

pulsion, were not affected by the infection intensity whereas B10 mice which showed slower responses were severely compromised during high dose infections, expelling the parasites 6 or so days later than normal (Wassom *et al.* 1984; Wakelin, Donachie & Grencis, 1985). These latter observations suggested that a poor host response was related to parasite-produced immunomodulatory factors and hence to the number of parasites present.

As yet, no immunological correlates have been identified to support the contention that expulsion of *H. polygyrus* from SJl and SWR mice was mediated immunologically. Indeed, it is known that the loss of worms from SJL mice is not accompanied by mastocytosis, a characteristic feature of the immunologically controlled inflammatory response, associated with the rejection of *T. spiralis* from mice (Dehlawi *et al.* 1987; Dehlawi & Wakelin, 1988). Thus the possibility remains that inter-strain variation in the properties of the intestinal habitat may have determined the duration of parasite survival in SJL and SWR mice. However, we feel that an immunological explanation is more likely because the initial establishment of *H. polygyrus* in SJL and SWR mice, as reflected in worm burdens in week 2, was as good as in susceptible strains and there followed another 2-week period during which parasite numbers remained stable and during which faecal egg counts were similar to those in other mouse strains. Had the intestinal environment in SJL and SWR mice been inappropriate for the development and survival of *H. polygyrus* through non-immunological characteristics, a reduction in initial worm establishment and/or fecundity might have been expected. In fact, worm expulsion was preceded by a reduction in faecal egg counts and this was followed by a complete loss of worms over the course of the subsequent 3 weeks, although on occasion expulsion occurred later (Table 3). In most respects this sequence of events was identical to that observed in *T. spiralis* and *Nippostrongylus brasiliensis*, where the immunological basis of worm rejection is well documented, except that *H. polygyrus* showed a more protracted expulsion phase in comparison to the former species which are expelled within a few days once the intestinal response has been initiated.

It is believed that the chronic infections with *H. polygyrus* are maintained in the host by immunodepression of local immunological activity in the intestine (Behnke, 1987) and therefore to minimize the effects of parasite immunomodulation we employed low level infections to compare strains and their various hybrid combinations. However, even at the intensities which were used, NIH and $C_{57}Bl_{10}$ mice did not expel significant proportions of their parasite burden during the first 8 weeks of infection. In contrast both SJL and SWR mice rapidly expelled the worms.

The unusually rapid response of SJL and SWR mice to infection with *H. polygyrus* prompted us to review the available literature on parasitic infections and immune responses in these two strains, in an effort to identify common features which distinguish them from other mouse strains particularly those which normally sustain chronic infections. Neither SJL nor SWR mice can be regarded as outstanding in their ability to respond to other parasites including *T. spiralis*. SJL mice were considered by Tanner (1978) to be weak responders, whilst SWR were reported by Wakelin (1980) to be relatively fast responders but not as rapid as NIH mice. These studies were confirmed by Wassom *et al.* (1983). The two strains also differed in respect of their ability to control *M. corti*; SJL mice were resistant whereas SWR were susceptible (A. Lammas, unpublished observations).

SJL and to a lesser degree SWR mice have been used in several immunological studies but few such studies have compared the strains in respect of a particular set of characteristics. It seems that SJL mice do not acquire the competence to mount DTH responses until 10 weeks after birth because of the slow maturation of antigen-presenting macrophages (Stohlman *et al.* 1985), are highly susceptible to the development of experimental allergic encephalomyelitis (Lublin *et al.* 1986), are sensitive to histamine and produce low-key IgE responses (Watanabe *et al.* 1977; Mitchell *et al.* 1982). SJL

mice develop intense eosinophilic responses to *Toxocara canis* (Sugane & Oshima, 1985) and *M. corti* (A. Lammas, unpublished information), characteristics which may be related to a defect in their ability to generate antigen-specific suppressor T cell responses (Amagai & Cinader, 1981; Cooke & Hutchings, 1984; Hutchings, Varey & Cooke 1986) and a functional B-cell defect (Hutchings *et al.* 1986). It is conceivable that these lesions in immunoregulation cause exaggerated responses in SJL mice and enable *H. polygyrus* to be overcome faster than in other strains. *H. polygyrus* is known to generate antigen-specific suppression, which may be important in its evasion strategy (Pritchard, Ali & Behnke, 1984) and clearly if this is so, then SJL mice would not be affected as long as their immunological defects encompassed the suppressor cell compartment associated with the intestine. A further consequence of the defective suppressor system manifested by SJL mice is their resistance to tolerance induction to rabbit gammaglobulin (Fujiwara & Cinader; 1974). However, SWR mice are not resistant and develop tolerance, suggesting that their suppressor systems function normally. It is unfortunate that so little comparable information is available for SWR. Nevertheless, the two strains (SWR and SJL) behaved so similarly to each other in our system and yet so differently from other strains that we feel it is likely that they possess gene combinations which are similar, if not identical, at loci which determine responsiveness to infection with *H. polygyrus*.

SJL and SWR mice both have their origins in the mouse stock imported to the USA by Lynch from Lausanne, Switzerland and are therefore distantly related but were derived at different times (1926 and 1947 for SWR/J and 1955 for SJL/J) and in different laboratories (Rice & O'Brien, 1980). Several studies have compared these and other mouse strains at polymorphic gene loci. In an analysis of allozyme compositions, Rice & O'Brien (1980) found only 3 differences between SJL and SWR mice at the 46 loci which were examined. Other differences have been described by Taylor (1972) and Festing & Roderick (1989). Overall SJL and SWR mice have 72·2% of their genes in common, based on 108 different loci selected for polymorphic qualities (Festing & Roderick, 1989). When they were compared to $C_{57}Bl_{10}$ and CBA mice, (strains which harbour chronic infections with *H. polygyrus*) the percentage of shared genes was considerably lower (SWR versus $C_{57}Bl_{10}$ = 43·2%; SWR versus CBA = 51·4%; SJL versus $C_{57}Bl_{10}$ = 40·7%; SJL versus CBA = 52%). SJL and SWR mice do not share MHC haplotype; SJL express H-2^s whereas SWR H-2^q. The H-2^q haplotype is frequently encountered among strains which show good responsiveness to *T. spiralis* (Wassom *et al.* 1983, 1984) but in our case the better response of SWR mice is not purely an H-2 effect because NIH mice which also express H-2^q do not reject *H. polygyrus* within 7 weeks of infection.

Another possibility is that, unlike other strains, SJL and SWR mice have the capacity to resist parasite-mediated immunodepressive effects during a primary infection with *H. polygyrus*. SJL mice are capable of generating an intestinal mast cell response during infection with *T. spiralis*, but as has already been pointed out, they fail to show mastocytosis during a primary infection with *H. polygyrus*. Even at the height of the intestinal response, when worms are being rejected, there are few mast cells in the intestine (Dehlawi, Wakelin & Behnke, 1987). This may reflect partial success of the immunomodulatory strategy of the parasite, the mast cell response being suppressed, but expulsion is clearly not hindered and hence other effector mechanisms must remain intact. It has been proposed that the immunomodulatory products of *H. polygyrus* affect a T helper population of lymphocytes which influence the maturation of mast cell precursors from the bone marrow (Dehlawi & Wakelin, 1988). If this is the case another population of T cells must remain insusceptible to these effects and these cells help to mobilize the response which eventually results in worm expulsion in SJL mice. Comparable experiments have not yet been carried out in SWR mice but we are currently investigating SWR and the hybrid strains to determine whether their responses show similar characteristics.

The response phenotype of the resistant SJL and SWR mice was inherited in a dominant manner in F_1 offsprings from crosses with the totally susceptible $C_{57}Bl_{10}$ strain. The hybrid strains without exception showed response characteristics more closely allied to the resistant parent than to the slow responder, a finding which is consistent with the results of Prowse & Mitchell (1980). However, none, with the possible exception of (SWR × B10G)F_1, were totally comparable to SWR or SJL mice, their responses being marginally slower when assessed through parasite burdens in week 8. The (SWR × B10G)F_1 hybrids express the H-2^q haplotype of both parental strains but in most other respects these mice would be identical to the (SWR × $C_{57}Bl_{10}$)F_1 hybrids. It is therefore conceivable that genes within the H-2^{bq} haplotype, presumably the H-2^b element, exerted a moderating influence on the rate of worm expulsion.

It is also apparent from our results that the (NIH × $C_{57}Bl_{10}$)F_1 hybrids showed a significant advantage over both parental strains in being able to clear most of their worms by week 8. We have reported this example of gene complementation previously (Robinson *et al.* 1989). NIH mice are known to have the capacity to express cell-mediated and inflammatory responses to intestinal infections with a rapidity and intensity unsurpassed by other strains. However, NIH mice produce relatively weak

host protective antibody responses to *H. polygyrus* even after repeated exposure to infective larvae. In contrast, $C_{57}Bl_{10}$ mice generate protective antibody (Williams & Behnke, 1983), but lack the capacity to express rapid inflammatory responses in the gut (Wakelin & Donachie, 1981; Wakelin *et al.* 1985). The F_1 hybrids may therefore benefit through being able to express both types of response, but this possibility has not yet been tested experimentally. The fast response of the (NIH × $C_{57}Bl_{10}$)F_1 hybrids strain was very similar to that shown by the other hybrid combinations in this study and it may be that all of these strains have common characteristics which enable them to mount such responses. One possibility may be that mouse strains which can express both antibody and cell mediated responses to *H. polygyrus* also require the gene products of loci encoded within the H-2^s and H-2^q haplotypes to guarantee full responder status on par with SJL and SWR mice. In mouse strains expressing H-2^{qb} or H-2^{sb} the response may be slower than in H-2^q mice (SWR × B10G) because of the retarding influence of H-2^b gene products. This hypothesis could be further explored by studying primary infections with *H. polygyrus* in (SJL × B10S)F_1 [H-2^s] and (NIH × B10G)F_1 [H-2^q] hybrids. In fact the latter strain was studied in our earlier paper and was shown to respond at least as quickly as (NIH × $C_{57}Bl_{10}$)F_1 but the two strains were not compared directly and it is not possible to be certain about whether the former responded more quickly.

It is evident from this and other studies that the sets of genes located in the MHC and outside the MHC interact closely to bring about the response phenotype of a particular animal. It is not yet clear how the possession of relevant genes affects the mouse's capacity to resist parasite-mediated immunodepression but it is apparent that SJL and SWR mice probably have this property and that it is a dominant response phenotype expressed in all the F_1 hybrids examined. Such a strong response can also arise in hybrid strains derived from parental stock not capable of expelling worms as in the (NIH × $C_{57}Bl_{10}$)F_1 strain. How relevant genes control intestinal host protective antibody and cellular responses to *H. polygyrus* is still debatable and because multiple gene combinations encoding for products which influence the various aspects of the overall response, are probably involved, it will not be easy to isolate the factors involved. For this reason the congenic strains on B10 and BALB backgrounds probably offer the best possibilities for dissecting the role of MHC genes in resistance to primary infection with *H. polygyrus*. Fortunately B10 mice are susceptible and BALB/C resistant, although considerably slower than SJL or SWR mice.

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