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The susceptibility of BALB/C and other inbred mouse strains to *Brugia pahangi*

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Summary

The susceptibility of several strains of inbred mice to infection with the filarial worm *Brugia pahangi* has been examined. BALB/C, C57BL/10, C3H/He, 101, CBA/Ca mice, congenitally asplenic (DH/+) mice and their normal litter-mates (+/+) were each challenged by the intraperitoneal inoculation of 50 infective larvae. During the first four weeks of infection high (19–42%) larval recoveries were obtained from the CBA/Ca, BALB/C and Dh/+ mice but fewer than 10% of inoculated larvae were recovered from C3H/He, 101; C57BL/10 and +/+ mice. Larval growth rates in all mice were similar. BALB/C and Dh/+ mice only were examined later than four weeks after infection. The yield of adult worms from BALB/C was 7.5% at 16 weeks and from Dh/+ 4.2% at 21 weeks. Microfilariae were present in the peritoneal fluids but not the blood of some mice harbouring both adult male and female worms.

Key words: *Filaria*; nematode; *Brugia pahangi*; inbred mouse; susceptibility; BALB/C; congenitally asplenic mice.

Introduction

In early and unsuccessful attempts to infect mice with *Brugia* species infective larvae were inoculated subcutaneously into 'white' mice which were bled and filmed at intervals and post-mortem over six months later (Laing et al., 1961; Ahmed, 1967); Ahmed (1967) further attempted to infect splenectomised mice. The first successful infection of mice (two unnamed strains) with *B. pahangi* was described by Chong and Wong (1967). Mature adult parasites were recovered from those mice but no microfilariae were observed in tail blood. Attempts to infect rats with *B. pahangi* and *B. malayi* have been more successful (reviewed

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by Denham and McGreevy, 1977) and an 'improved' rodent model for *B. malayi* and *B. pahangi* was provided by the successful infection of the Mongolian jird, *Meriones unguiculatus* (Ash and Riley, 1970a, b). The limitations of jirds and rats as experimental animals (WHO, 1979) have led to further attempts to infect inbred strains of immune competent and immune-deficient mice with *B. pahangi* (Suswillo et al., 1980, 1981; Vincent et al., 1980). Suswillo et al. (1980) demonstrated that AKR, BALB/C, CBA/Ca and TO mice were resistant to infection with third stage larvae of *B. pahangi* although third, fourth and fifth stage parasites transplanted from the peritoneal cavity of jirds into the peritoneal cavity of mice continued to develop. A more detailed study by Wong et al. (1982) of the susceptibility of seven inbred mouse strains demonstrated a degree of susceptibility in the CSW/CWB, CBA/CAJ, DBA/IJ and C3H/HEJ strains. Congenitally athymic (nude) and thymectomised mice were susceptible to infection with third stage larvae (Suswillo et al., 1980, 1981). Vincent et al. (1980) recovered subcutaneously inoculated larvae of *B. pahangi* from normal C3H/HeN nu/+ and +/+ mice at eight days post infection (pi) but not at 50 or at 72 days pi. These workers also found nude mice C3H/HeN nu/nu highly susceptible to infection.

In this paper we present observations on the innate susceptibility to *B. pahangi* of several inbred mouse strains, including a congenitally spleenless mouse strain.

Material and Methods

The strains of mice employed in this study were: BALB/C, CBA/Ca, C57BL/10, 101, C3H/He, asplenic mice (Dh/+) and their normal homozygote litter-mates (+/+). Male mice six to ten weeks of age were used throughout except where stated otherwise. Mice were employed in groups with a minimum of five mice. In the case of Dh/+ mice, a proportion of animals identified as asplenic because of evident acromegaly were found at autopsy to possess spleens. Because of the depleted numbers of asplenic mice recoveries from male and female Dh/+ mice were pooled (see Table 1).

During the period of this investigation the strain of *B. pahangi* employed has been continuously maintained within the laboratory in Mongolian jirds, *Meriones unguiculatus*. Mosquitoes (*Aedes aegypti*, SS) were infected by feeding on a suspension of jird microfilariae in stock dog blood. Thirteen days post infection infective larvae were isolated from mosquitoes following the method of Ash (1974). All mice were infected by the intraperitoneal (ip) injection of 50 third stage larvae of *B. pahangi*. Infected animals were examined at various times post infection, as described in the section of Results. Larval recoveries on day 28/29 have been employed as the basic interval at which strain susceptibility was determined, since in a susceptible host such as the cat or the jird, larvae at day 28 may be assumed to have completed both the third and fourth larval moults (Schacher, 1962; Howells and Blainey, in press). Larvae were recovered by lavage of the peritoneal cavity with sterile Hanks' balanced salt solution and the pooled washings from individual mice were examined for larvae. The larvae recovered from each mouse were counted and were classed as live, live plus adherent peritoneal cells or dead. The larvae were fixed and mounted as described by Wharton (1959) and measurements were made from scaled drawings prepared with the aid of a camera lucida. Comparisons of the lengths and numbers of larvae recovered from different mouse strains were made by the Mann-Whitney 'U' test (Armitage, 1971).

Table 1. Recoveries and mean lengths of live *B. pahangi* larvae on day 28/29 post infection from six inbred mouse strains, the Mongolian Jird, *Meriones unguiculatus* and the domestic cat. All mice received 50 infective larvae ip

Host	No. infected/ examined	Percent larval recovery (Mean \pm S.E.) ¹	Mean lengths (mm) ²	
			♀ (\pm S.D.)	♂
BALB/C	5/5	19.2 \pm 0.025	10.5 \pm 1.8 (19)	8.7 \pm 1.0 (9)
Dh/+ ³	7/7	38.0 \pm 0.026	11.5 \pm 1.5 (41)	8.5 \pm 1.0 (12)
+/+	5/8	2.5 \pm 0.008	10.9 \pm 0.7 (2)	8.5 (1)
101	3/5	8.0 \pm 0.017	10.0 \pm 1.4 (12)	9.8 \pm 0.1 (3)
C3H/He	5/5	5.2 \pm 0.014	10.7 \pm 1.6 (7)	7.8 \pm 1.3 (2)
C57BL/10	5/5	9.6 \pm 0.065	8.7 \pm 1.0 (8)	7.0 (1)
JIRD ⁴	3/3	33.3 \pm 0.027	13.14 \pm 2.2 (26)	10.35 \pm 1.9 (26)
CAT		n.d.	11.7 ⁵	10.3 ⁵

¹ The standard errors should be treated with some caution because of the variation in recovery between mice within strains. Comparisons between strains are based on a non-parametric test.

² The differences in lengths of larvae recovered from the six mouse strains were not significant ($P>0.05$).

³ 4 of 7 Dh/+ mice examined were female (see Materials and Methods).

⁴ Jirds infected with 100 L₃.

⁵ Length of male and female worms on day 27 pi after Schacher (1962).

n.d. = no data available

Results

The mean lengths and percentage recoveries of larvae from six inbred strains of mice at day 28/29 pi are presented in Table 1. All mice were infected on the same day from a single pool of infective larvae. The highest recoveries were obtained from the Dh/+ and BALB/C mice. The homozygous (+/+) mice which possessed spleens and each of the other strains examined were highly refractory to infection.

The mean lengths of the larvae recovered from all strains were similar. CBA/Ca mice were infected with a different batch of infective larvae to those employed for the animals included in Table 1. The larval recovery from CBA/Ca mice on day 27 was $12.2 \pm 14.2\%$, not significantly different to that from BALB/C mice ($p>0.05$).

The growth curve of *B. pahangi* in the BALB/C mouse is illustrated in Fig. 1. These data were obtained from mice infected at different times and with different batches of larvae. Data derived from the study of Schacher (1962) on the growth of the parasite in the cat are also presented in that Figure. During the first month of infection the rates of growth of the worms appeared similar in both hosts but by day 60 female worms from the cat were 43 mm long compared to 20 mm in the mouse. Male worms also attained a greater length in cats than in mice but the differences were less pronounced than observed with females.

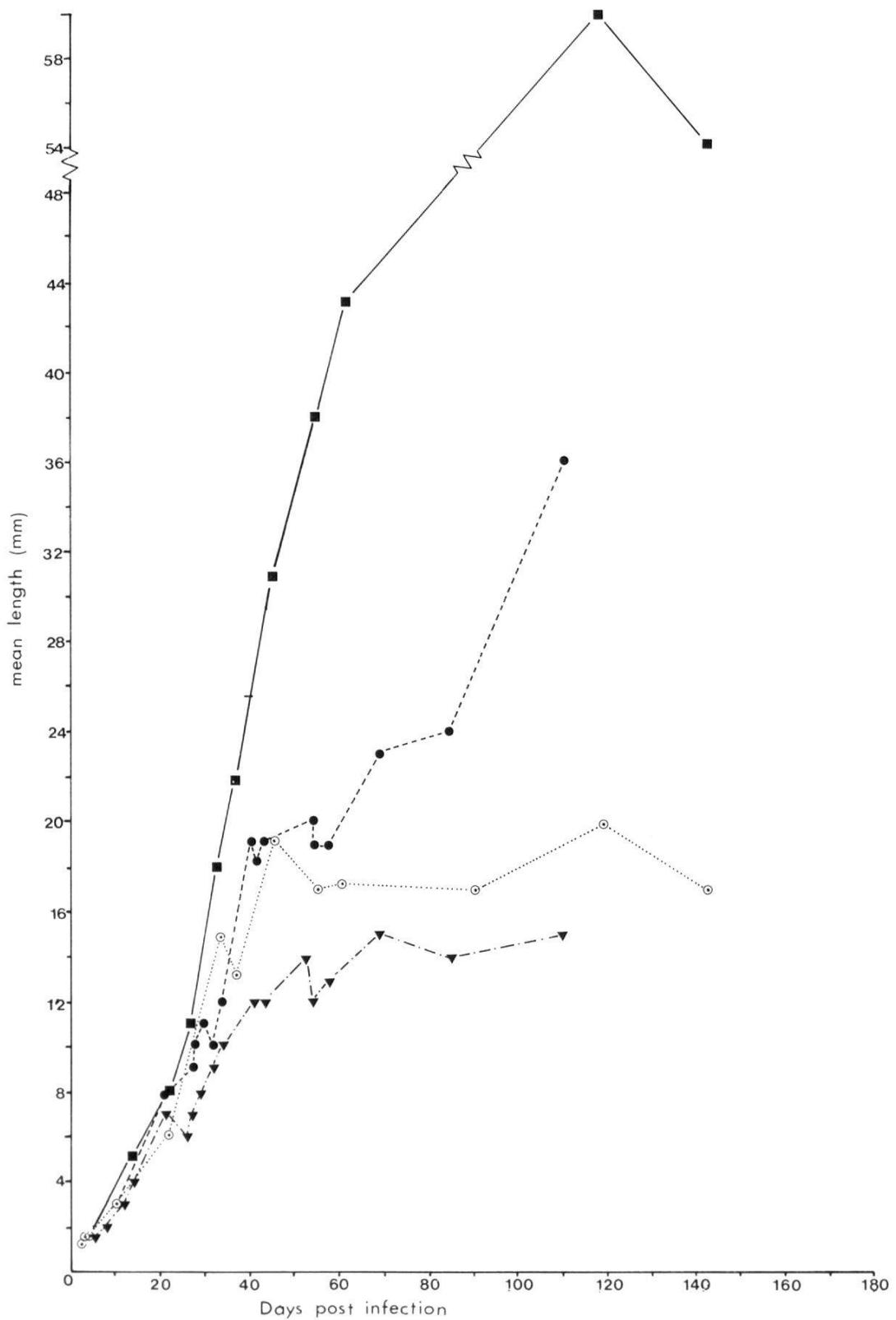


Fig. 1. The growth curve of *B. pahangi* in the BALB/C mouse compared with that in the cat. Data on cat infections taken from Schacher (1962). ■ = Female worms in cat; ● = female worms in mouse; ○ = male worms in cat; ▲ = male worms in mouse.

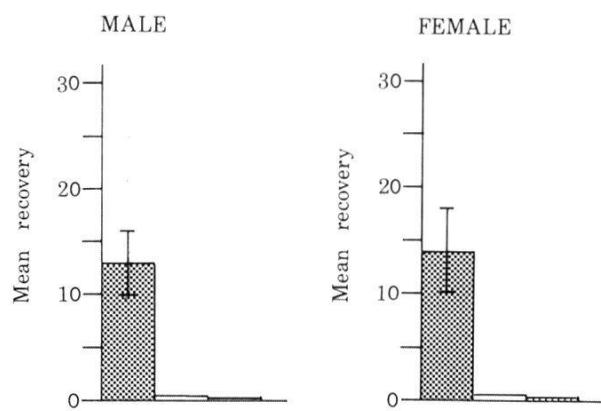


Fig. 2. The recovery of *B. pahangi* larvae from male and female BALB/C mice. Mice were employed in groups of ten and larvae were recovered 26 and 27 days pi. Bars represent \pm SE.

- = Live normal worms
- = Live larvae with adherent host cells
- ▨ = Dead larvae

Male worm growth ceased about day 60 when cat worms were 18–20 mm long and mouse worms 14–15 mm. The growth of male and female *B. pahangi* in the mouse was very similar to that described for the jird (Chen and Howells, 1979; Howells and Blainey, in press). No difference was observed in the number nor the mean lengths of larvae recovered from male and female BALB/C mice on day 26/27 pi (Fig. 2).

Comparison of the larval recoveries from C57BL/10 mice on days 14 and 29 is presented in Fig. 3. A 52% larval recovery was obtained from C57BL/10 mice on day 14 but 86% of these larvae had adherent peritoneal cells and/or were immobile. On day 29 pi the total larval recovery was reduced to 18% though the yield of normal live larvae was similar to that of day 14. In marked contrast to those results with C57BL/10 mice, the total worm burden of BALB/C was approximately the same on days 14 and 29 pi and at both times more than 89% of the larvae recovered were normal. The recoveries of larvae from BALB/C mice at various times post infection, accumulated from nine separate experiments are presented in Fig. 4. Comparisons of recovery at week 1 with subsequent recoveries were made by the Mann-Whitney 'U' test, as described in the Materials and Methods. Only at week 6 and later were the recoveries significantly different (at the 95% confidence limit) from those at week 1. At 12 weeks pi. four of six mice examined still yielded live worms. Microfilariae were not recovered from the peritoneal washings of those mice but a single female (32.4 mm long) contained apparently mature microfilariae in utero. At 16 weeks pi each of four mice examined were infected. A total of eight males and seven females were recovered. The length of female worms ranged from 22–49.6 mm (mean 36.5 ± 9.9 mm); male worms were 15.0–17.2 mm long (mean 15.8 ± 1.2 mm). In two mice which harboured male and female worms microfilariae were recovered from the peritoneum. In no mouse was a microfilaraemia observed.

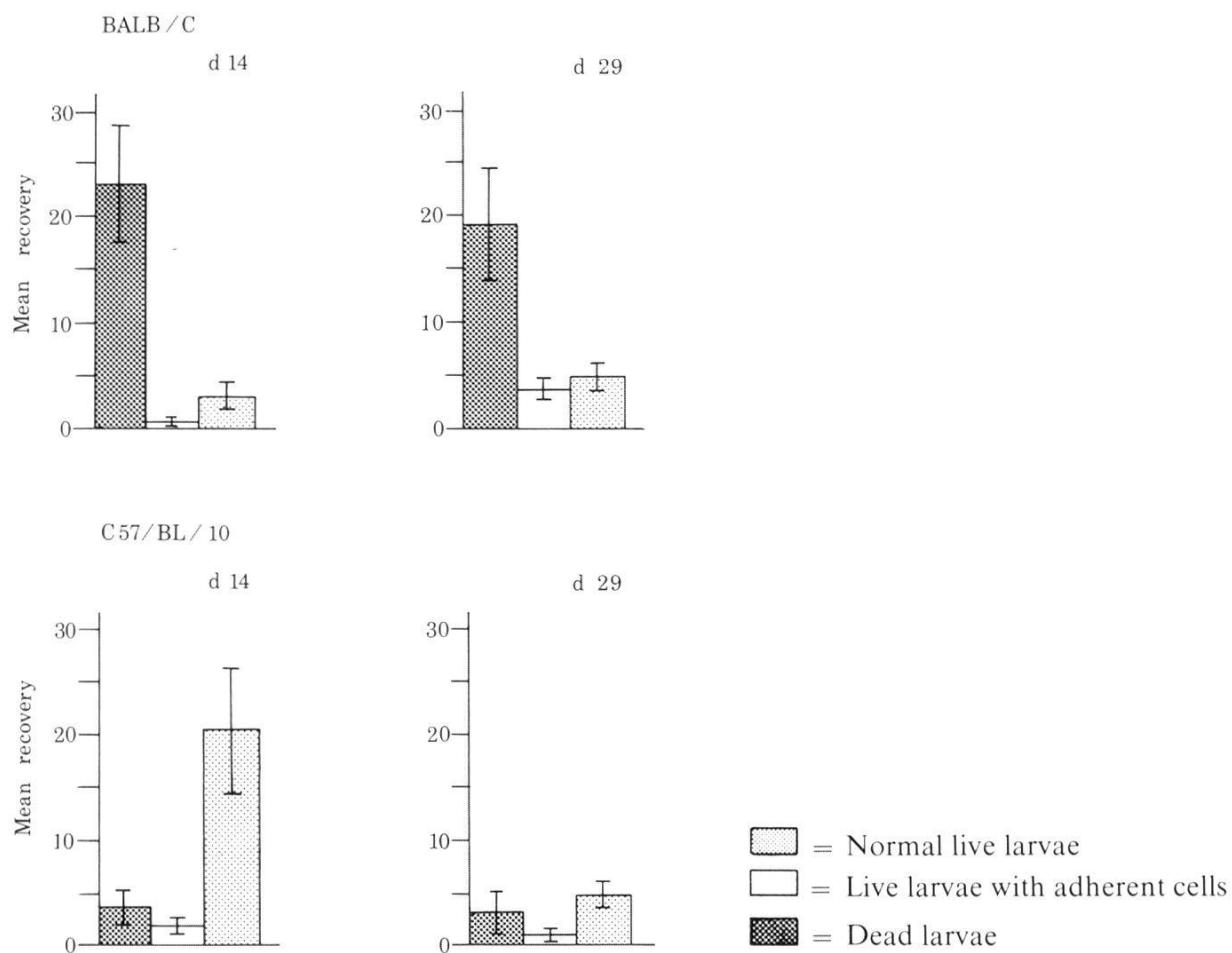


Fig. 3. Yields of normal larvae, live larvae with peritoneal cells, and dead larvae of *B. pahangi* from BALB/C and C57BL/10 mice at days 14 and 29 pi. Means \pm SE of yield from five mice each infected with 50 L_3 larvae.

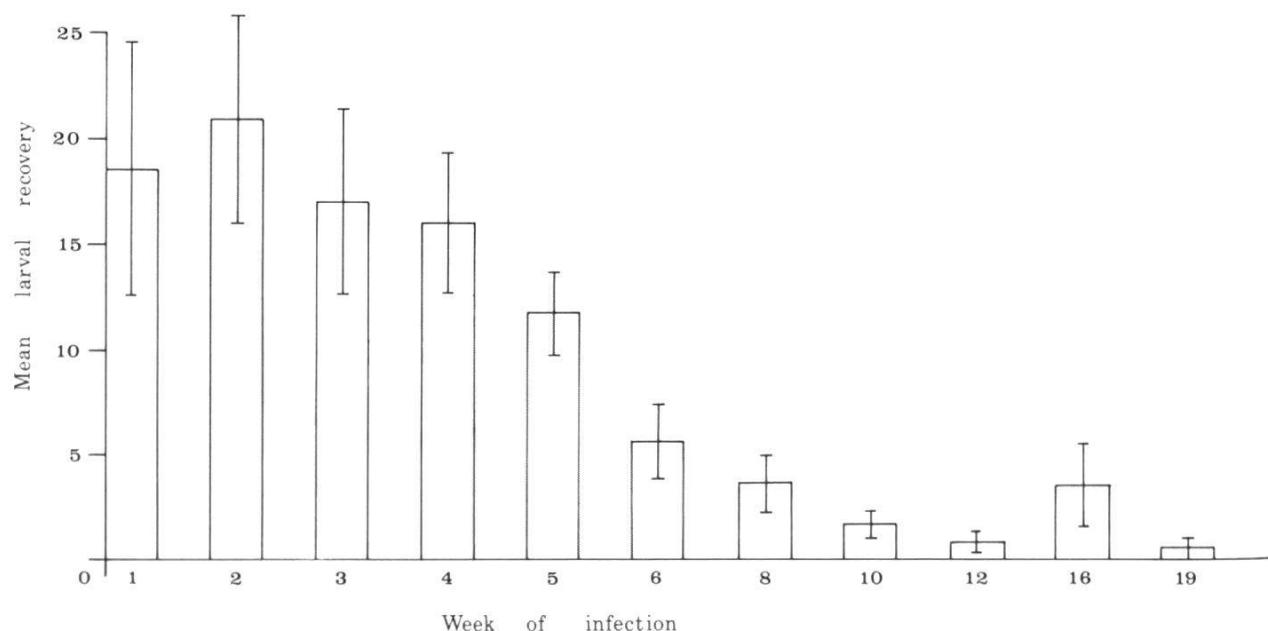


Fig. 4. The recoveries of normal live larvae from BALB/C mice with increasing time pi, presented as the mean \pm SE of yield from a minimum of five mice each infected with 50 L_3 larvae.

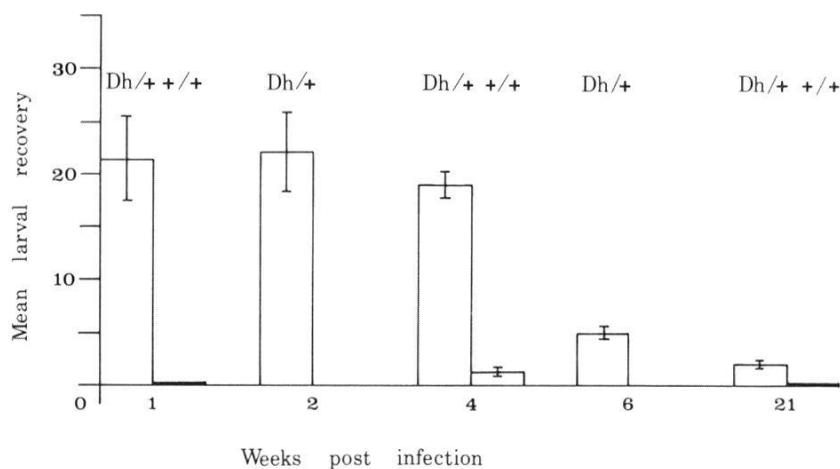


Fig. 5. The recoveries of normal, live larvae from Dh/+ and +/+ mice with increasing time pi presented as the means \pm SE of yield from five mice each infected with 50 L₃ larvae.

The pattern of larval recovery with time in Dh/+ mice (Fig. 5) was similar to that described for the BALB/C strain (Fig. 4). Five of eight Dh/+ mice examined 21 weeks pi were infected with a mean of 2.1 (range 2–6) adult worms per mouse. The lengths of female and male worms were 23.6–32.8 mm (mean 28.2 ± 2.6 mm) and 14–18.4 mm (mean 16.0 ± 2.2 mm), respectively. One of the five infected mice had microfilariae in the peritoneal cavity but no microfilariaemia. The remaining four had single sex infections.

Discussion

The innate susceptibility of BALB/C mice to infection with third stage larvae of *B. pahangi* demonstrated here contrasts with the observations of Suswillo et al. (1980) who found no sign of infection in mice autopsied three months after the ip inoculation of 50 infective larvae. An undisclosed number of BALB/C mice were employed in the latter study and no examinations were made earlier than three months pi. The time of examination post infection probably accounted for the failure of those authors to detect infection.

The primary objective of this study was to identify an inbred mouse strain which would support the development of *B. pahangi*. The variation in susceptibility to this parasite of the several mouse strains examined may indicate that susceptibility in mice is genetically controlled though we have not yet attempted to correlate susceptibility with the mouse genotype. In an analysis of familial predisposition to filarial infection in a group of 225 Polynesians, Ottesen et al. (1981) failed to demonstrate a correlation with HLA-A or -B locus specificities. A relationship of mouse susceptibility to filarial infection with the H-2 haplotype has yet to be established. Wakelin and others (see Wakelin and Donachie, 1981) have shown that the susceptibility of mice to *Trichinella spiralis* infection is complex and is influenced by both non H-2 and H-2-linked genes.

The observations of previous workers that thymus deficient nude mice (Suswillo et al., 1980; Vincent et al., 1980) and thymectomised mice (Suswillo et al., 1981) are more susceptible to *B. pahangi* infection than immune competent animals indicated that refractoriness may be T-cell dependent. Susceptibility has here been shown to be enhanced by the asplenic condition, though our results with the Dh/+ mice contrast with those of Ahmed (1967) who found splenectomised white mice fully resistant to infection with *B. phangi*. The susceptibility of young jirds to *B. pahangi* was considered to be sex-linked (Ash, 1971) but male and female BALB/C mice were equally susceptible.

Studies on the infection of surrogate hosts with filarial worms have identified the immediate post-infection period as a significant barrier to infection, transplanted post-infective larval and adult worms being capable of development in hosts fully resistant to infection by the third stage larval forms (Olson, 1959; Suswillo et al., 1980). From the evidence of those studies we thought it probable that mice identified as naturally susceptible to the infective larvae of *B. pahangi* would prove capable of supporting all subsequent developmental forms. The results obtained with the BALB/C and Dh/+ mice have shown that concept to be untenable, for although the larval recoveries from these mice within the first 28 days of infection were similar to those from the jird (Table 1) high mortality rates were observed in the mice during the later stages of infection. Wong et al. (1982) observed a decrease in worm recoveries from mice (CWS/CWB and DBA/1J) after 12 weeks of infection. We have not determined whether those larvae which died during the second and subsequent months of infection had completed development to the fifth stage or were arrested fourth stage worms.

The yield of adult worms and of microfilariae in BALB/C and Dh/+ mice was low and in neither strain was a microfilaraemia observed. The recovery of adult worms was greater from ip infected thymectomised (Suswillo et al., 1981) and nude mice (Suswillo et al., 1980) than from our BALB/C mice. Interestingly, Suswillo et al. (1980) recovered adult worms from the lymphatics, heart and lungs of ip infected nude mice; in our study only the peritoneal cavity was searched for adult parasites as no microfilaraemia was detected. Microfilariae were observed in the peritoneal cavity of BALB/C mice examined on day 110 pi but not on day 85. Suswillo et al. (1980) observed microfilariae in the nude mouse at three months pi and they also observed a microfilaraemia in nude mice, even when the adult parasites were apparently confined to the peritoneal cavity. In the BALB/C mouse microfilariae were recovered from the peritoneum but were not detectable in the bloodstream.

The BALB/C mouse has been identified as the most susceptible to *B. pahangi* of the immunocompetent inbred mouse lines so far tested. In terms of adult worm recovery it is a poorer host than the jird or cat yet it provides a unique basis for investigation of the genetics and immunology of experimental filariasis in a host of known genotype.

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