INFECTION AND IMMUNITY, May 1984, p. 282–286
0019-9567/84/050282-05$02.00/0

Vol. 44, No. 2

Susceptibility and Resistance of Inbred Mice to *Giardia muris*

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Received 9 November 1983/Accepted 23 January 1984

The susceptibility and resistance of inbred mice to *Giardia muris* was studied during the acute and elimination phases of infection. The infection in susceptible A/J and C3H/He mice was characterized by a short latent period, high cyst output during the acute phase of infection, and prolonged periods of cyst release. In contrast, resistant B10.A and DBA/2 mice had a longer latent period, a lower cyst output during the acute phase, and relatively rapid resolution of infection. The trait of susceptibility and resistance during both acute and elimination phases of the infection was found to be under complex multigenic control as determined by examination of the response of F_1 hybrid mice and backcross analyses. The genes controlling this trait did not appear to be linked to the *H-2* locus. In addition, the control of the response of mice to *G. muris* during the acute phase of infection was probably mediated by mechanisms independent from those controlling the response during the elimination phase of infection.

Genetic differences in the response of mice to various intracellular protozoan infections are well documented (4–9, 11). However, there are only a few studies which have examined genetic differences in the susceptibility of mice to extracellular gut-dwelling protozoa. The contribution of Roberts-Thomson and Mitchell (14) to studies on the course of infection with *Giardia muris* in inbred mice has illustrated the potential importance of genetic factors in the control of this infection. The key observation in their study was that there were marked differences in the duration of the infection among different strains of mice. For example, C3H/He mice released *G. muris* cysts for several months, whereas BALB/c and DBA/2 mice eliminated the parasites after 4 to 6 weeks of infection. In a different study, Roberts-Thomson et al. (15) have shown that the pattern of cyst release in (BALB/c × C3H/He)F_1 mice was similar to that of the resistant BALB/c animals, indicating that this trait is inherited in a dominant fashion. In addition, these authors reported that the level of cyst output during the infection of most (BALB/c × C3H/He) × C3H/He backcross mice was intermediate when compared with the parental strains. Failure of backcross mice to segregate into two distinct groups, chronic cyst releasers (C3H/He-like) or those which eliminate the infection (BALB/c-like), has led Roberts-Thomson et al. (15) to conclude that the susceptibility to prolonged infection with *G. muris* is under the control of several genes.

In the present study, the pattern of cyst release of seven inbred strains and three F_1 hybrids are characterized further by (i) determination of the length of the latent period, (ii) quantification of cyst release during the acute phase of infection, and (iii) examination of the elimination phase of the infection. Segregation analyses, using as a criterion cyst release during the acute and elimination phases of infection, are also presented in an attempt to determine the number of genes responsible for control of susceptibility and resistance.

MATERIALS AND METHODS

Parasite. The strain of *G. muris* used in this study was originally passaged by Roberts-Thomson et al. (16), and it was obtained from B. J. Underdown, University of Toronto, Toronto, Ontario. The parasite was maintained by 20-day passages in CD-1 Swiss mice.

Animals. Eight-week-old male and female mice were used in the experiments, BALB/cAnNCr1BR, C57BL/6NCr1BR, C3H/HeNCrlBR, DBA/2NCr1BR, and B6C3F1/Cr1BR mice were purchased from Charles River Canada Inc. (St. Constant, Quebec). B10.A/SgSn, SJL/J, and A/J mice were obtained from Jackson Laboratories (Bar Harbor, Maine). All F_1, F_2, and backcross animals were bred in the animal facility of the Montreal General Hospital Research Institute (Montreal, Quebec).

Upon arrival from the animal breeder, mice used in this study were free of *Giardia* sp. infection as shown by three consecutive fecal examinations. Thus far, over 1,000 mice received from the supplier were examined and the mice were always found to be free of *Giardia* sp. infection. However, these mice were not derived from a specific-pathogen-free facility, and for this reason they were treated for 3 consecutive days with metronidazole solution (10 mg/mouse per day) per os. This treatment ensured that mice were free of protozoan infection in the gut. One week after treatment, three fecal examinations of every experimental animal and examinations of the small intestine of mice chosen at random were performed before experimental infections. In all cases mice treated with metronidazole were free of intestinal protozoa.

The infective dose for all experiments was 1,000 cysts per mouse administered orally in 0.2 ml of normal saline to unanasthetized mice.

Enumeration of cyst release. For enumeration of cyst release, individual mice were placed in separate containers, and the feces released over a 2-h period were weighed (wet weight) and collected in glass tubes (12 by 75 mm). Each mouse was earmarked and given a code number at the beginning of the experiment. The procedure for the isolation and counting of cysts was that of Belosevic and Faubert (1).

Definitions. The latent period was defined as the time when 50% or more mice began to release cysts; the level of infection was defined as log10 geometric mean cyst output per gram of feces per mouse for 8 consecutive days, from days 7 to 14 of infection. This period was selected because cyst output of all mouse strains was at its peak, enabling clear determination of maximum cyst release for each strain

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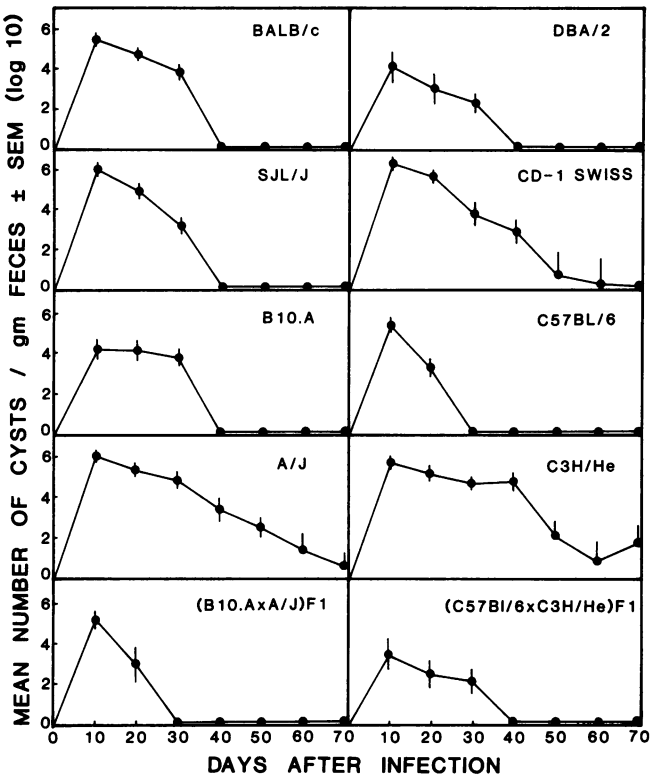

FIG. 1. Pattern of cyst release in mice infected orally with 1,000 cysts of *G. muris*. Each point represents the geometric mean cyst output of 10 female mice ± standard error.

of mice; the beginning of the elimination phase of infection was considered to be the time when 50% or more mice did not release cysts.

Experimental protocol. (i) Strain survey. The course of infection with *G. muris* was studied in CD-1 Swiss, seven inbred strains, and two groups of F_1 hyrid mice. The pattern of cyst release was examined for 10 female mice of each strain. The number of cysts released by individual mice was monitored daily for the first 22 days, on alternate days until day 30, and then at 5-day intervals until day 70 of infection. The course of infection with *G. muris* in mice can be divided into two phases, using the intensity of cyst release as the criterion (1). The acute phase of infection is characterized by the proliferation of trophozoites in the small intestine and the peak period of cyst release during week 2 of infection. The elimination phase of infection is characterized by a decrease in both the trophozoite load in the small intestine and intensity of cyst release. Throughout the infection trophozoite load in the small intestine is related to the intensity of cyst output. Eventually, the parasites are eliminated from the small intestine, and most mice acquire complete resistance against reinfection (2). Since the infection with *G. muris* in mice has two distinct phases, the response of inbred mice to the parasite was studied for each phase separately.

(ii) Response during the acute phase of infection. The acute phase of infection was assessed by using two biological characters: the duration of the latent period and the level of infection.

The segregation analysis of response to *G. muris* during the acute phase of infection was done with the crosses derived from the most susceptible strain (A/J) with the most resistant strains, namely, DBA/2 and B10.A. The criterion used to separate mice into susceptible or resistant was level of infection. Individual F_1, F_2, and backcross mice were classified as resistant if $\log_{10}$ geometric mean cyst output was ≤ 5.75 (2 standard deviations below the mean of susceptible A/J strain controls). In these experiments the responses of male and female mice were not significantly different; thus the data were combined for analysis.

(iii) Response during the elimination phase of infection. The criterion used to separate individual mice into susceptible or

TABLE 1. Duration of latent period and level of infection of inbred and F_1 hybrid mice during the acute phase of infection with *G. muris*[a]

Strain	*H-2* haplotype	*n*	Latent period [days (Range)]	Level of infection[b] + SEM
DBA/2	*d*	21	10 (7–11)	3.59 + 0.27
B10.A	*a*	25	7 (6–9)	4.35 + 0.13
C57BL/6	*b*	10	6 (4–7)	5.07 + 0.31
BALB/c	*d*	10	5 (4–8)	5.23 + 0.62
C3H/He	*k*	10	5 (4–6)	5.75 + 0.22
SJL/J	*s*	10	5 (4–5)	6.16 + 0.17
A/J	*a*	35	4 (4–5)	6.19 + 0.03
CD-1 Swiss		10	3 (3–4)	6.25 + 0.12
F_1 hybrids				
(C57BL/6 × C3H/He)F_1	*b/k*	10	7 (4–9)	3.59 + 0.21
(B10.A × A/J)F_1	*a/a*	31	6 (5–7)	4.72 + 0.10
(A/J × DBA/2)F_1	*a/d*	12	ND[c]	5.37 + 0.10

[a] Infection dose, 1,000 cysts per mouse.
[b] Log_{10} mean cyst output per gram of feces per mouse for 8 consecutive days, from days 7 to 14 of infection.
[c] ND, Not determined.

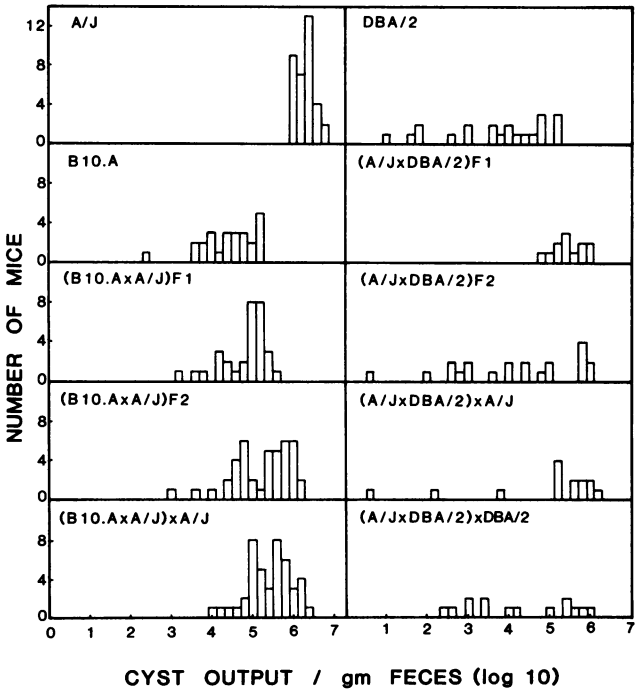

FIG. 2. Cyst release of inbred mice and their progeny during the acute phase of infection with *G. muris*. Geometric mean cyst output per gram of feces of individual mice was calculated by using the number of cysts released for 8 consecutive days, from days 7 to 14 of infection.

TABLE 2. Segregation analysis of response of inbred mice to *G. muris* during the acute phase of infection

Segregating population	*n*	No. susceptible[a]		No. resistant[b]		χ_2	*P*
		Obtained	Expected[c]	Obtained	Expected		
F_1(B10.A × A/J) × A/J	46	8	23	38	23	19.56	<0.001
F_2(B10.A × A/J)	46	9	11.5	37	34.5	0.72	>0.05
F_1(A/J × DBA/2) × A/J	14	3	7	11	7	4.56	<0.05
F_1(A/J × DBA/2) × DBA/2	14	2	0	12	14	10.29	<0.001
F_2(A/J × DBA/2)	21	3	5.25	18	15.75	1.28	>0.05

[a] > mean − 2 SD of A-strain response.
[b] < mean − 2 SD of A-strain response.
[c] Number of mice expected from a trait controlled by a single dominant gene. The expected value for backcross mice to the susceptible parent is 50% susceptible/50% resistant. The expected value for the backcross mice to the resistant parent is 0% susceptible/100% resistant. The expected value for the F_2 mice is 25% susceptible/75% resistant.

resistant groups was the presence or absence of cysts in feces on day 40 after infection. The segregation analysis of response to *G. muris* was done with F_1, F_2, and backcross mice of a (B10.A × A/J) progenitor pair. Preliminary experiments have indicated that the duration of cyst release in male mice was significantly longer than in female mice. As a result, in all experiments dealing with the elimination phase of infection only female mice were used.

Segregation analysis. To determine the number of genes responsible for control of susceptibility and resistance in murine giardiasis, we performed segregation analysis. Our null hypothesis was that the resistance in this infection is controlled by a single dominant gene. If so, then according to Mendelian genetics, 100% of F_1 generation mice derived from a resistant and a susceptible progenitor [e.g., (B10.A × A/J)F_1] should type as resistant. In addition, 75% of the F_2 population should be resistant and 25% of F_2 mice would be expected to be susceptible. In backcross analysis (where genes can be expected to be segregating), 50% of mice derived from the cross of the F_1 hybrids to the susceptible progenitor [e.g., (B10.A × A/J) × A/J] would be expected to be resistant and 100% of backcross mice to the resistant progenitor should be resistant. By using a chi-square test to compare the observed values with the expected values derived above, one either accepts or rejects the hypothesis of single gene control.

Statistics. The data were analyzed by Student's *t* test, one-way analysis of variance, and the chi-square test. The probability level of $P < 0.05$ was considered significant.

RESULTS

Strain surveys. Oral administration of *G. muris* cysts to mice of different strains resulted in an infection which was assessed by counting cysts released in feces. Typically, peak cyst release was observed at some point during week 2 of infection, followed by a gradual decline in cyst output and eventual elimination of the parasites from the small intestine. The course of infection varied markedly among strains of mice studied (Fig. 1). For example, the susceptible A/J, C3H/He, and CD-1 Swiss mice exhibited a continuous high cyst output during the first 4 weeks of infection compared with the most resistant DBA/2 and B10.A mice, in which the cyst output was significantly lower during the same period (Fig. 1). There were also marked differences in the ability of mice to eliminate the infection with *G. muris* (Fig. 1). Since the response of inbred strains of mice to *G. muris* differed during both the acute and elimination phases of infection, comparative studies of susceptibility and resistance were done separately for each phase.

(i) Response during the acute phase of infection. Studies of the acute phase of infection using two biological characters, the length of the latent period and the level of infection, has revealed marked differences in the response of inbred mice to *G. muris*. For example, the length of the latent period varied from 4 days in susceptible A/J mice to 7 and 10 days in resistant B10.A and DBA/2 mice, respectively (Table 1). An association between the long latent period and the release of fewer cysts was apparent. Mouse strains which exhibited a long latent period also released fewer cysts during week 2 of infection (Table 1).

Inbred strains of mice, when tested for the trait of susceptibility and resistance, using level of infection as the criterion, formed a spectrum of responders, with the most susceptible strain (A/J) passing 100-fold more cysts than the most resistant DBA/2 mice (Table 1). The pattern of continuous variation in the expression of this trait, without clear segregation into two or three categories (i.e., groups of mice with similar cyst output) suggested to us a complex multigenic control. This impression was further enhanced on studying the level of susceptibility and resistance of F_1 hybrids derived from several of the progenitor inbred strains. Some of the genes controlling resistance were clearly dominant as seen in the (B10.A × A/J) cross, in which F_1 hybrids resembled resistant B10.A progenitors (Table 1, Fig. 2). On the other hand, the gene(s) controlling a high level of resistance in DBA/2 mice was recessive, because F_1(A/J × DBA/2) hybrids resembled more closely their susceptible (A/J) progenitor (Fig. 2). Gene complementation was seen in the (C57BL/6 × C3H/He) cross, in which the F_1 hybrid was significantly more resistant than either parent (Table 1). Finally, the multigenic mode of inheritance of susceptibility

TABLE 3. Response of female inbred and F_1 hybrid mice to *G. muris* during the elimination phase of infection[a]

Strain	*n*	Presence of cysts on day 40 post-infection	Last positive day (no. of mice)	Classification
DBA/2	10	−	35 (4)	Resistant
B10.A	10	−	35 (5)	Resistant
C57BL/6	10	−	35 (4)	Resistant
BALB/c	10	−	35 (3)	Resistant
SJL/J	10	−	30 (8)	Resistant
C3H/He	10	+	70 (5)	Susceptible
A/J	10	+	70 (3)	Susceptible
CD-1 Swiss	10	+	65 (5)	Susceptible
F_1 hybrids				
C57BL/6 × C3H/He) F_1	10	−	35 (5)	Resistant
(B10.A × A/J) F_1	10	−	28 (1)	Resistant

[a] Infection dose, 1,000 cysts per mouse.

TABLE 4. Segregation analysis of response of female inbred mice to *G. muris* during the elimination phase of infection[a]

Segregating population	n	No. susceptible[b]		No. resistant[c]		χ_2	P
		Observed	Expected[d]	Observed	Expected		
F_1(B10.A × A/J) × A/J	20	4	10	16	10	7.20	<0.01
F_2(B10.A × A/J)	23	3	5.75	20	17.25	1.74	>0.05

[a] Infection dose, 1,000 cysts per mouse.
[b] > mean − 2 SD of A-strain response.
[c] < mean − 2 SD of A-strain response.
[d] Number of mice expected from a trait controlled by a single dominant gene. The expected value for backcross mice to the susceptible parent is 50% susceptible/50% resistant. The expected value for the F_2 mice is 25% susceptible/75% resistant.

and resistance during the acute phase of infection was confirmed in backcross analysis in which the resistant/sensitive ratios of the backcross populations were not compatible with the hypothesis of single gene control (Table 2). In addition, these genes are not linked to the *Ir* genes that map within the *H-2* locus because an association between the *H-2* haplotype and the trait of resistance to *G. muris* was not apparent. For examle, both A/J and B10.A mice have the same haplotype, but A/J mice are susceptible to infection whereas B10.A mice are resistant. This, however, does not exclude the possibility of minor involvement of *H-2* locus genes.

(ii) Response during the elimination phase of infection. Inbred strains of mice differed in their ability to eliminate the infection (Fig. 1). For example, C3H/He and A/J mice released cysts continuously during the first 70 days of infection, whereas the infection ended 40 days after inoculation or earlier in C57BL/6, BALB/c, SJL/J, B10.A, and DBA/2 mice (Fig. 1). The examination of the course of infection in F_1(C57BL/6 × C3H/He) and F_1(B10.A × A/J) hybrid mice revealed that the gene(s) controlling the trait of resistance (= elimination of *G. muris* infection) is dominant because the response of all F_1 hybrid mice resembled more closely that of the resistant parents (Table 3). In addition, backcross analysis of response to *G. muris* during the elimination phase of infection has indicated that the resistance against *G. muris* is under the control of several genes (Table 4).

DISCUSSION

In the present study, the course of infection with *G. muris* in inbred mice was examined, using the length of the latent period, the cyst output during the acute phase of infection, and duration of cyst release as biological parameters. The infection in susceptible A/J and C3H/He mice was characterized by a relatively short latent period, a high cyst output during week 2 of infection, and a prolonged period of cyst release. In contrast, resistant B10.A and DBA/2 mice had a longer latent period, a lower cyst output during the acute phase of infection, and a relatively rapid resolution of infection. These results support, in part, the findings of Roberts-Thomson and Mitchell (14) in that there are marked differences in the duration of *G. muris* infection among mouse strains. Chronic infection in C3H/He mice were not observed and SJL/J mice were shown to have a shorter infection in this study in contrast to the previous report (14). The discrepancy in findings could be due to different substrains of C3H/He mice and SJL/J mice.

The course of infection with *G. muris* in C57BL/6, BALB/c, and SJL/J mice was characterized by a relatively short latent period and high cyst output during the acute phase of infection. However, these strains of mice had the capacity to resolve the infection in a relatively short time. These findings may indicate that the response of mice to infection with *G. muris* involves two stages. The control of the acute phase of infection, exemplified by the lower cyst output and longer latent period in resistant mice, may be mediated by innate mechanisms. On the other hand, the elimination phase of the infection may be under the control of acquired mechanisms independent from those which control the response during the acute phase of infection. Due to this possibility, the tests of susceptibility and resistance of inbred mice to *G. muris* were performed independently for the acute and elimination phases of infection.

The susceptibility and resistance of inbred mice to *G. muris* was tested, using the duration of the latent period and level of infection as parameters. Our results indicate that the two parameters are related such that mouse strains which exhibited a longer latent period also released fewer cysts during week 2 of infection. Thus the rate of excystment, establishment, and eventual proliferation of the trophozoites in the small intestine may differ among strains of mice examined. Numerous physiological factors may affect the rate of establishment of the trophozoites in the small intestine. For example, inbred strains of mice may differ in stomach pH, stomach emptying time, production of bile, enzyme levels, and intestinal motility. In addition, variable conditions for the encystment of the parasites in the ileum such as the pH and redox potential may also affect the degree of cyst production. On the other hand, the immunological response of mice at the intestinal level may also affect the establishment and eventual cyst production. Mitchell et al. (12) reported that the failure of susceptible C3H/He mice to eliminate *G. muris* infection may reflect specific immunological unresponsiveness to *Giardia* sp. antigens. They found that sera of infected or immunized BALB/c mice immunoprecipitated a major surface protein of the trophozoite, whereas the sera of similarly treated C3H/He mice did not. Owen et al. (13) reported that *G. muris* trophozoites are phagocytosed by macrophages in Peyer's Patch epithelium. Moreover, they observed a close association of lymphoblasts and macrophages containing *G. muris* remnants. These authors suggested that this macrophage activity represents intraepithelial antigen processing as well as possible defense against uncontrolled entrance of microorganisms and other antigenic particles into Peyer's Patch lymphoid follicle. Thus, the differential ability of inbred mice tested in this study to recognize or process *G. muris* antigen may affect the immunological response against the parasite at the gut level, resulting in increased establishment of the trophozoites and a higher rate of cyst production.

Persistent infection with *G. muris* is the mast cell-deficient W/W mice (17) indicates that local anaphylaxis may be a component of the host response against *G. muris*. If mast cell degranulation is an integral part of the host response against *G. muris*, this would presumably be mediated by

antiparasite immunoglobulin E. It is possible that strains of mice which are susceptible to *G. muris* during the acute phase of infection are unable to mount a strong local anaphylactic response. In our study, a mouse strain which is known to be a low producer of immunoglobulin E (10), SJL/J, exhibited a high cyst output during the acute phase of infection. In addition, C3H/He mice, which also exhibited a high cyst output during the acute phase of infection, were reported to be unusually nonresponsive to the histamine-sensitizing factor of *Bordetella pertussis* (3). It remains to be determined whether the rate of establishment and high cyst output during the acute phase of infection with *G. muris* are related to the ability of susceptible mice to mount an adequate anaphylactic response.

When tested for the trait of susceptibility and resistance during the acute phase of infection, inbred strains of mice formed a spectrum of responders, which suggested to us that this trait is under complex multigenic control. The response of F_1 hybrid mice and backcross analysis confirmed that the susceptibility and resistance to *G. muris* during this phase is under the control of several genes not linked to the *H-2* locus.

In an attempt to determine the number of genes which influence the resolution of infection with *G. muris*, Roberts-Thomson et al. (15) examined the pattern of cyst release in F_1 and backcross mice of the (BALB/c × C3H/He) progenitor pair. These authors found that the resolution of the infection is inherited in a dominant fashion since the length of the infection in F_1 mice was similar to that of the resistant BALB/c progenitor. By using two different progenitor combinations, (B10.A × A/J) and (C57BL/6 × C3H/He), we confirmed in these experiments that the resolution of *G. muris* infection has a dominant mode of inheritance since F_1 hybrid mice exhibited the pattern of cyst release which resembled more closely that of the resistant progenitors.

The complex pattern of genetic control of resistance in murine giardiasis during both the acute and elimination phases of infection indicates that the responses of the host against this parasite are diverse, probably involving both immunological and non-immunological defense mechanisms.

ACKNOWLEDGMENTS

The technical skills of Suzanne Gauthier and Rebecca Guy are gratefully acknowledged.

M.B. holds a McConnell Fellowship (McGill University). This work was supported by grants from the Medical Research Council of Canada to G.M.F. and J.D.M. (MRC no. 8146) and E.S. (MRC no. 6431). Research at the Institute of Parasitology is supported by the Natural Sciences and Engineering Research Council of Canada and the Fonds FCAC pour l'aide et le soutien a la recherche.

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