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Depression of the Immune Response to Sheep Erythrocytes in Mice Infected with *Taenia crassiceps* Larvae

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Intraperitoneal infection of mice with larvae of the cestode parasite *Taenia crassiceps* results in depression of both primary and secondary antibody responses to sheep erythrocytes in vivo. The depression is not associated with a shift in kinetics of the response. Both immunoglobulin M (IgM) and IgG responses are depressed, but IgG is depressed more than IgM in the secondary response. Secondary in vitro sheep erythrocyte responses are consistently depressed in both spleen and mesenteric lymph node cell preparations from infected mice, whereas primary in vitro sheep erythrocyte responses are consistently depressed in mesenteric lymph node cell preparations but not always in spleen cell preparations. These results are consistent with antigenic competition. The cell type or types involved in mediation of the immunological defect in the infected animals remain to be identified.

Infection with parasitic helminths is often associated clinically with increased susceptibility of the host to certain bacterial and viral diseases, both in humans and in animals (25). One possible contributing mechanism for such an association is depression of the host's immune system as a result of the helminth infection. Depression of the immune response of the host to apparently unrelated antigens has been reported in two nematode infections. Mice infected with larvae of the nematode *Trichinella spiralis* show depressed humoral antibody responses to sheep erythrocytes (SRBC) (1, 5, 15) and Japanese B encephalitis virus (2, 15) and are more susceptible than normal mice to the pathological effects of the virus. More recently, depression of the antibody response to orally administered SRBC has been reported in mice infected with the lumen-dwelling nematode *Heligmosomoides polygyrus* (*Nematospiroides dubius*) (20).

This investigation was undertaken to determine whether suppression of the immune response to apparently unrelated antigens is a feature of infection with helminths other than nematodes and to examine the feasibility of using in vitro methods to study the mechanism of such suppression. The larval form of the cestode *Taenia crassiceps* (7) was chosen for study. Our results show that infection of mice with *T. crassiceps* depresses both the primary and the secondary humoral response to SRBC in vivo and that secondary in vitro SRBC responses are consistently depressed in both spleen and mesenteric lymph node preparations from infected mice, whereas primary in vitro SRBC responses are consistently depressed in preparations of mesenteric lymph node cells but not always in spleen cell preparations.

MATERIALS AND METHODS

Mice. BALB/c mice, 2 to 4 months old, were used for all experimental work. Both Swiss Webster female mice and BALB/c male mice were used for propagation of *T. crassiceps* larvae.

Parasites. *T. crassiceps* larvae of the ORF strain were obtained from C. J. Weinmann, Division of Entomology and Parasitology, University of California, Berkeley. Larvae were propagated by intraperitoneal inoculation of 6 to 8 larvae in 0.5 ml of normal saline with a tuberculin syringe and no. 16 needle. Larvae were harvested 3 to 8 months later.

Parasite counts. *T. crassiceps* larvae from experimental mice were washed from the peritoneal cavity with normal saline and counted directly in a ruled petri dish. Pleural cavities and subcutaneous tissues along the route of injection were also examined for larvae.

Representative mice from the colony were screened for the presence of other helminth parasites in the intestinal tract. *Syphacea obvelata* and *Aspicularis tetraptera* (pinworms, normally present in conventionally maintained laboratory mice) were counted under ×10 magnification in a ruled petri dish after zinc sulfate flotation (9) of the contents of the colon from rectum through the cecum. The colons were opened longitudinally and vigorously stirred on a magnetic stirrer in 4 ml of zinc sulfate (specific gravity, 1.180) until the fecal contents were thoroughly dispersed. After removal of the colons and centrifugation, the entire supernatant was decanted into a ruled petri dish, and both juvenile and

adult worms were counted. Cover slip preparations were examined for eggs under ×100 magnification.

Immunizations. Mice were immunized by intravenous injection of 4×10^8 washed SRBC in a lateral tail vein at appropriate intervals after infection with *T. crassiceps*.

In vitro cultures. The Mishell-Dutton (16) culture system was employed with slight modifications. Cell suspensions were prepared in Eagle minimal essential medium without bicarbonate (no. 109S, Grand Island Biological Co., Grand Island, N.Y.) containing glutamine, penicillin, and streptomycin. The culture medium used was RPMI 1640 (Grand Island Biological Co., N.Y.) supplemented with 8% fetal bovine serum (Microbiological Associates, Bethesda, Md., lot 84182), asparagine (20 μg/ml), penicillin, streptomycin, and 2-mercaptoethanol (J. T. Baker Chemical Co.) at a final concentration of 5×10^{-5} or 10^{-4} M. (We found that lymph node cultures did not respond well in the absence of 2-mercaptoethanol.) Unless otherwise noted, cultures contained 1×10^7 to 2×10^7 cells in 1 ml. All cultures were harvested and assayed for plaque-forming cells (PFC) on day 5. Cell recoveries and viabilities as determined by trypan blue dye exclusion were similar in cultures from normal and infected mice.

Assay for PFC. Spleens were weighed and washed in minimal essential medium, and cell suspensions were obtained by teasing against a fine stainless steel wire mesh. Cultured cells were washed once in minimal essential medium. Direct and developed PFC were measured by the method of Jerne et al. (13), except that antibiotics were omitted from the medium and the amount of diethylaminoethyl-dextran in both top and bottom layers was increased to a final concentration of 1 mg/ml. A correction factor for the inhibitory effect of rabbit anti-mouse immunoglobulin serum on immunoglobulin M (IgM) plaques was used in the calculation of developed plaques. There was no significant difference between the amount of inhibition of IgM plaques in infected and control mice.

Antibody titrations. Agglutination titers against SRBC were measured in duplicate on sera from individual mice by the microtiter method of Sever (19), using 0.025 ml of 1% SRBC in a final volume of 0.10 ml. Titers were expressed as $\log_2$ of the last well showing 1+ agglutination.

Statistics. The significance of experimental results was evaluated by the Wilcoxon matched-pairs signed-ranks test and by the Behrens-Fisher test for evaluating the significance of the difference between means of samples of unequal variance. Results of the Behrens-Fisher test were confirmed by the nonparametric Mann-Whitney U test. A probability of <0.05 was considered significant.

RESULTS

Effects of *T. crassiceps* infection on host mice. The effect of infection with *T. crassiceps* on body weight, weight of lymphoid organs, and number of pinworms in the large intestine was followed for 9 weeks in 66 mice given 7 *T. crassiceps* larvae by intraperitoneal inoculation, 64 mice given 20 *T. crassiceps* larvae, and 66 mice given injections of saline alone at the time of inoculation. These mice were also used to study the effect of *T. crassiceps* infection on the primary antibody response to SRBC.

During the 9 weeks of the experiment, replication of *T. crassiceps* larvae by budding regularly occurred after week 1 but was not sufficient to cause abdominal distension or any symptoms of physical illness. At the end of the 9-week period, mice inoculated with 7 larvae contained an average of $114 \div 1.09$ larvae, and mice inoculated with 20 larvae contained an average of $343 \div 1.10$ larvae per mouse. There was no significant difference in body weight, weight of thymus, or weight of mesenteric lymph nodes between either group of infected mice and the control mice.

An increase in spleen weight was apparent in some of the infected mice 1 week after inoculation of the larvae, and enlarged spleens were consistently found in the infected mice from week 3 onwards (Table 1). Enlarged parathymic and mediastinal nodes were present from week 3 onwards in mice given 20 larvae and from week 4 onwards in mice given 7 larvae. At the end of week 9, parathymic nodes averaged 0.024 ± 0.011 g in both groups of mice. Infection with *T. crassiceps* had no apparent effect on pinworm burdens in the infected mice. There was no significant difference in the mean number of pinworms recovered per mouse between the control group ($53 \div 1.16$) and either group of mice infected with *T. crassiceps* ($59 \div 1.13$ and $47 \div 1.17$). There was also no indication that pinworm infestation alone led to immunodepression: in the 66 control mice no negative correlation was found between logarithmically transformed pinworm counts and logarithmically transformed PFC per 10^6 nucleated cells (correlation coefficient $r = 0.030$; for 95% confidence of significant correlation, $r \geq |0.25|$).

Effect of infection with *T. crassiceps* on the primary antibody response to SRBC. The effect of infection with *T. crassiceps* on the primary antibody response to SRBC was tested on day 4 after intravenous immunization, since the IgM PFC response is normally at its peak on this day. In an initial experiment, three groups of 36 BALB/c mice were injected intraperitoneally on day 0 with 0.5 ml of normal saline, 7 *T. crassiceps* larvae, or 20 *T. crassiceps* larvae from Swiss Webster female donor mice. At appropriate intervals six mice from each of the three groups were immunized by intravenous injection of 4×10^8 SRBC. Four days later, on days 7, 14, 21, 28, 35, and 42 after infection, the mice were autopsied and the number of direct and developed PFC per spleen

TABLE 1. *Effect of T. crassiceps infection on the primary IgM PFC response to SRBC*[a]

Time after infection (weeks)	Control mice		Infected mice					
			7 Larvae			20 Larvae		
	Spleen weight (g)[b]	PFC/spleen $\times 10^{-5}$[c]	Spleen weight (g)[b]	PFC/spleen $\times 10^{-5}$[c]	Ratio of infected PFC/ control PFC	Spleen weight (g)[b]	PFC/spleen $\times 10^{-5}$[c]	Ratio of infected PFC/ control PFC
1	0.238 ± 0.010	2.27 (1.09)	0.264 ± 0.009	1.82 (1.11)	0.80	0.289 ± 0.014	2.36 (1.22)	1.04
2	0.239 ± 0.017	1.83 (1.15)	0.293 ± 0.018	1.99 (1.14)	1.09	0.232 ± 0.013	0.80 (1.39)	0.44
3	0.232 ± 0.020	1.84 (1.17)	0.243 ± 0.019	1.53 (1.21)	0.83	0.300 ± 0.015	1.44 (1.35)	0.78
4	0.227 ± 0.020	1.18 (1.25)	0.305 ± 0.012	1.39 (1.22)	1.18	0.282 ± 0.020	1.02 (1.09)	0.86
5 (a)	0.259 ± 0.007	2.03 (1.09)	0.288 ± 0.017	1.10 (1.20)	0.54	0.322 ± 0.021	0.95 (1.16)	0.47
5 (b)	0.262 ± 0.010	2.78 (1.11)	0.308 ± 0.016	1.15 (1.13)	0.41	0.381 ± 0.017	2.66 (1.09)	0.96
6 (a)	0.261 ± 0.009	2.09 (1.21)	0.302 ± 0.022	1.89 (1.10)	0.90	0.324 ± 0.024	1.30 (1.19)	0.62
6 (b)	0.252 ± 0.011	1.32 (1.33)	0.325 ± 0.013	1.07 (1.23)	0.81	0.320 ± 0.032	0.98 (1.27)	0.74
7	0.247 ± 0.013	1.91 (1.37)	0.310 ± 0.020	1.22 (1.28)	0.64	0.346 ± 0.020	1.37 (1.17)	0.72
8	0.262 ± 0.022	2.62 (1.24)	0.413 ± 0.013	3.44 (1.18)	1.31	0.344 ± 0.018	1.87 (1.14)	0.71
9	0.267 ± 0.013	2.57 (1.17)	0.318 ± 0.006	1.53 (1.12)	0.60	0.301 ± 0.031	2.47 (1.16)	0.96

[a] Measured on day 4 after intravenous inoculation of 4×10^8 SRBC. All experimental groups contained six mice, except for weeks 6b and 9 for mice infected with 20 *T. crassiceps* larvae. These two groups each contained five mice. Two separate sets of experiments were run for weeks 5 and 6.

[b] Arithmetic mean of experiment group ± standard error of the mean.

[c] Geometric mean of experimental group. $\times/\div$ factor for standard error of the mean is indicated in parentheses.

was measured. In a second experiment, three groups of 30 BALB/c mice were similarly treated and assayed for 4-day direct and developed PFC to SRBC on days 35, 42, 49, 56, and 63 after infection.

The effect of *T. crassiceps* infection on the IgM PFC response to SRBC is shown in Table 1. Since there was a high level of variability in the responses of the control mice (see below), responses of infected mice were compared with those of matched groups of control mice assayed at the same time. With only three exceptions (weeks 2, 4, and 8 in mice receiving seven *T. crassiceps* larvae at the time of inoculation), the IgM PFC responses were depressed in the infected mice as compared with control mice from week 2 through 9 after infection. Although the magnitude of the difference between mean PFC responses in infected and control mice was relatively small, the consistency of the difference was highly significant by the Wilcoxon matched-pairs signed-rank test ($P < 0.05$ for mice receiving 7 larvae, and $P < 0.005$ for mice receiving 20 larvae). There was no obvious correlation between the degree of depression of the anti-SRBC response and the interval between infection with *T. crassiceps* larvae and injection of SRBC. For most subsequent studies, mice infected with 20 *T. crassiceps* larvae 3 to 7 weeks prior to antigen injection were used, since immunodepression was most reliably demonstrated under these conditions (Table 1 and unpublished data). The degree of depression of the anti-SRBC response was not related to the degree of splenic enlargement in the infected mice since there was no consistent correlation between spleen weight and PFC response to SRBC in either group of infected mice (see Table 1, especially weeks 2 and 5).

Primary IgG responses in both groups of infected mice, although usually lower than in control mice, were not always depressed to a significant degree when assayed 4 days after intravenous injection of SRBC. Kinetic data (Fig. 1B) show that significant depression of the IgG response is more likely to be observed on day 5 or 6 after intravenous immunization rather than on day 4.

To exclude the possibility that infection with *T. crassiceps* resulted in a shift of the time of the peak antibody response to SRBC, a kinetics experiment was performed during week 3 to 5 after injection of 20 *T. crassiceps* larvae when immunodepression was to be expected in the infected mice. Groups of four control (saline-injected) mice and four infected mice were immunized with 4×10^8 SRBC intravenously 14, 7, 6, 5, 4, 3, 2, and 1 day prior to assay. All mice were assayed at the end of week 5 after infection with *T. crassiceps* larvae. The results are shown in Fig. 1. There was no shift in kinetics of either the IgM or the IgG response in the infected mice as compared with control mice. In

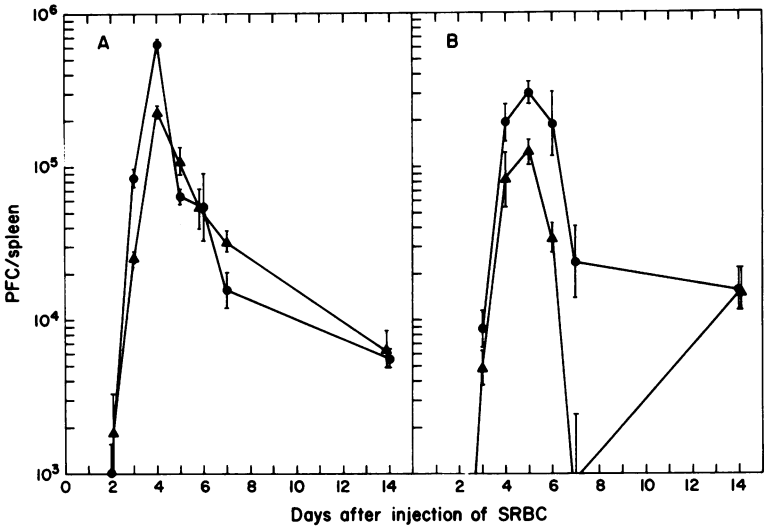

FIG. 1. *Effect of infection with T. crassiceps larvae on the kinetics of the PFC response after intravenous injection of 4 × 10⁸ SRBC. Symbols: ●, control mice; ▲, infected mice. (A) IgM response; (B) IgG response.*

TABLE 2. *Effect of larval dose on primary IgM response to SRBC*[a]

Treatment	IgM antibody response	
	PFC/spleen[b]	P[c]
Saline	2.42 × 10⁵ (1.09)	
3 Live larvae	0.83 × 10⁵ (1.37)	<0.05
20 Live larvae	1.35 × 10⁵ (1.21)	<0.05

[a] Measured on day 4 after intravenous inoculation of 4 × 10⁸ SRBC and 6 weeks after infection with *T. crassiceps*.

[b] Geometric mean of six animals. ×/÷ factor for standard error of the mean is indicated in parentheses.

[c] *P* values calculated by the Behrens-Fisher method for samples of unequal variance.

both groups of mice, the IgM response reached its peak on day 4 and the IgG response peaked on day 5. However, the IgM response on days 3 and 4 in the infected mice was only 31 to 36% of the control response ($P < 0.01$ by the Behrens-Fisher test). The number of IgM PFC decreased somewhat more slowly in infected mice than in control mice, possibly as a result of the reduction in feedback inhibition of IgM synthesis due to depression of IgG levels in the infected mice. The IgG PFC response in infected mice was less than that in control mice on all days tested and was significantly depressed by the Behrens-Fisher test on days 5 ($P < 0.01$) and 6 ($P < 0.05$).

Since there was some suggestion in the data of Table 1 that infection with 20 *T. crassiceps* larvae resulted in more consistent depression of the SRBC response than infection with 7 *T. crassiceps* larvae, the ability of a low dose of *T. crassiceps* to elicit immunodepression was tested in mice 6 weeks after injection of larvae (Table 2). Infection with 3 *T. crassiceps* larvae proved to be at least as effective as infection with 20 larvae in depressing the PFC response to SRBC. The experiment in Table 2 differs from that in Table 1 in that both donor and recipient mice were BALB/c, whereas in the earlier experiments of Table 1 donor mice were Swiss Webster and recipients were BALB/c.

Effect of infection with *T. crassiceps* on the secondary antibody response to SRBC. Twelve BALB/c mice were initially immunized with 4 × 10⁸ SRBC intravenously. Twelve days after immunization, half of the mice were given 20 *T. crassiceps* larvae intraperitoneally. Five weeks after the initial immunization, all mice were bled and then given a booster injection of 4 × 10⁸ SRBC. Serum antibody titers were done on individual mice through day 6, when all mice were killed for PFC assays. The results are presented in Fig. 2.

Serum titers in the infected mice were significantly lower than those in the control mice even before the booster injection was given ($P < 0.01$ by the Behrens-Fisher method), indicating that infection with *T. crassiceps* is capable of depressing an established antibody response to SRBC. Depression of the secondary response was more pronounced than depression of the primary response. Hemagglutination titers in the infected mice remained depressed through

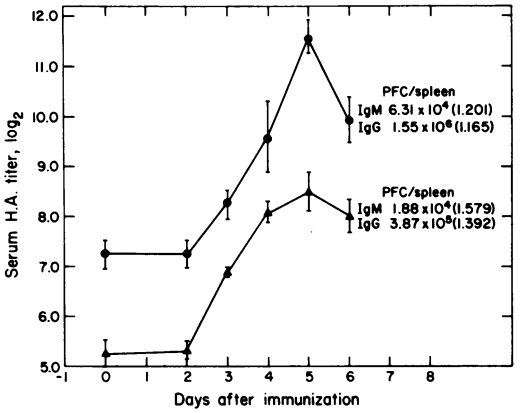

FIG. 2. *Effect of infection with T. crassiceps larvae on a secondary antibody response to SRBC. The day 0 sample was taken before administration of the booster injection of SRBC. Symbols: ●, serum hemagglutination titers in control mice; ▲, serum hemagglutination titers in infected mice.*

day 6, when the number of IgG PFC per spleen in infected mice ($3.87 \times 10^5 \div 1.392$) was only 25% of the number found in the control group ($1.55 \times 10^6 \div 1.165$; $P < 0.01$). IgM PFC were also lower in infected mice ($1.88 \times 10^4 \div 1.579$ versus $6.31 \times 10^4 \div 1.201$ for the control mice; $P < 0.05$), but the effect on IgM was not as dramatic as that on IgG. In both groups of mice, mean spleen weights (0.456 ± 0.032 g for the control mice and 0.527 ± 0.023 g for infected mice) were considerably greater than mean spleen weights for any of the groups of mice examined during a primary response.

In vitro antibody response of spleen and mesenteric lymph node cells from mice infected with *T. crassiceps*. Initially we tested spleen and mesenteric lymph node cell suspensions from mice infected with 20 *T. crassiceps* larvae 4 to 7 weeks previously for their ability to give a primary PFC response to SRBC in vitro. Cell suspensions from single mice or from pools of three to four mice were cultured in the Mishell-Dutton culture system and assayed for direct PFC to SRBC on day 5. The results are shown in Table 3. Mesenteric lymph node cells from infected mice consistently gave a depressed primary PFC response to SRBC as compared with similar preparations from saline-injected control mice. Spleen cells, however, behaved in a variable manner in primary responses: in some experiments significant depression of the response of spleen cells from infected mice was noted, whereas in other experiments the response was normal

For secondary in vitro responses, mice were initially primed by intravenous injection of 4×10^8 SRBC. Ten days later, half of the mice were given 20 live *T. crassiceps* larvae intraperitoneally in saline, whereas control mice received injections of saline alone. After 3 to 7 weeks, cell suspensions from the spleens and mesenteric lymph nodes of these mice were cultured and tested for their ability to respond to SRBC in vitro. The results are shown in Table 4. Both spleen and mesenteric lymph node cell suspensions from infected mice consistently give depressed secondary responses to SRBC in vitro. The IgG secondary response was more dramatically depressed than the IgM response in vitro as well as in vivo.

DISCUSSION

Our results demonstrate that depression of the immune response to an apparently unrelated antigen can be a feature of cestode as well as nematode infections. Infection of mice with *T. crassiceps* results in depression of both the

TABLE 3. *Primary in vitro response to SRBC in normal and infected mice*[a]

Expt no.	PFC response/10^6 recovered cells			
	Spleen		Mesenteric nodes	
	Control	Infected	Control	Infected
5	326	84	1,310	57
	284	483	2,361	149
6	363	79	1,824	475
12	243	126	1,333	73
13	781	1,015	4,467	590

[a] Cultures contained 1×10^7 to 2×10^7 cells in a volume of 1 ml. Responses were assayed for PFC on day 5. Cell recoveries were similar in cultures from normal and infected mice.

TABLE 4. *Secondary in vitro response to SRBC in normal and infected mice*[a]

Expt no.	PFC response/10^6 recovered cells[b]			
	Spleen		Mesenteric nodes	
	Control	Infected	Control	Infected
17	4,639 (17,130)	885 (2,487)		
	4,687 (16,032)	700 (988)		
	2,511 (5,357)			
21	6,738 (16,011)	2,216 (3,569)	774 (751)[c]	304 (120)[c]
22	5,860 (4,947)	1,416 (994)	324 (41)	34 (0)

[a] Data shown are for cultures from cell suspensions from individual animals (experiment 17) or from pools of three to four animals (experiments 21 and 22). Cultures contained 1×10^7 to 3×10^7 cells in a volume of 1 ml unless otherwise noted and were assayed on day 5 of culture. Cell recoveries and viabilities were similar in cultures from normal and infected mice.

[b] IgG responses are indicated in parentheses after the corresponding IgM responses.

[c] Cultures contained 8×10^6 cells in 1 ml.

primary and the secondary antibody responses to SRBC. The secondary response is depressed to a greater extent than the primary response, and in the secondary response IgG is depressed to a greater extent than is IgM. Neither depression of the primary response nor depression of the secondary response is accompanied by a shift in kinetics. The degree of depression of the PFC response in *T. crassiceps* infection is similar to that reported for PFC responses in the spleens of mice infected with the nematodes *H. polygyrus* (*N. dubius*) (20) and *T. spiralis* (15). Unlike the humoral immunodepression associated with *T. spiralis* infection, the humoral immunodepression associated with *T. crassiceps* infection does not appear to be clearly limited to a definite time period after initial infection. This difference may be due to the fact that *T. crassiceps* continues to bud in the peritoneal cavity throughout the lifetime of the mouse, whereas most *T. spiralis* larvae are already encysted 42 days after oral infection (6) when humoral immunodepression is no longer demonstrable (15).

An important feature of both *T. crassiceps* and *T. spiralis* infections is that they are able to produce their characteristic effects on the immune response of the host, even if introduced at a time when an immune response is already established (reference 4 and Fig. 2). Some other immunosuppressive infectious agents such as malaria (11) and certain viruses (18), although capable of producing a much more dramatic degree of immunodepression than the helminth infections, normally do not exert their immunodepressive effects unless infection occurs shortly before challenge with antigen. The importance of the effects of helminth infections on commonly used clinical immunizing agents needs further study in view of their ability to depress an established immune response.

In our initial experiments, we encountered considerable variability in PFC responses in our control mice as well as in the degree of immunodepression achieved (Table 1). We believe that this variability is due in large part to environmental factors normally present in conventional animal colonies. The nematodes *A. tetraptera* and *S. obvelata* are normally present in nearly all mice maintained under usual laboratory conditions and have been shown to interact with the immune system of their hosts (12). Shimp et al. (20) have recently reported that infection with the gut-dwelling nematode *H. polygyrus* (*N. dubius*) can result in depression of the response to intraperitoneally administered SRBC. Although we were unable to demonstrate any negative correlation between pinworm burdens and PFC responses in our control mice, we cannot exclude the possibility that the presence of the pinworms contributed to the variability in our control PFC responses since we were also unable to demonstrate a clear correlation between larval dose and the degree of immunodepression induced by *T. crassiceps*.

Another factor that may affect the extent of the immunodepression obtained with *T. crassiceps* infection is the degree of adaptation of the larvae at the time they are inoculated into their recipient host. Kinetics of growth for *T. crassiceps* suggest that some degree of adaptation to the host is necessary before an optimal rate of budding is achieved (7; Siebert and Good, unpublished data). If immunodepression is dependent upon products of actively metabolizing and replicating larvae, the degree of adaptation could affect the level of immunodepression obtained in the host. Our work suggests that immunodepression is most reliably obtained when all experimental mice are inoculated with larvae taken from a single donor mouse of the same inbred strain as the recipient mice. (Compare degree and consistency of depression in Table 1, where several Swiss Webster donors were used for BALB/c recipients, with results in all remaining tables and figures, where a single BALB/c donor was used for all BALB/c recipients in each experiment.) Since different strains of mice vary in their susceptibility to particular helminth parasites (22), it is conceivable that successful adaptation and, hence, ability to produce immunodepressive products may be delayed or less consistent when donor and recipient mice are not of the same inbred strain.

A number of possible mechanisms may be suggested to account for the immunodepression associated with *T. crassiceps* infection. Secondary debilitation of the host is not a likely explanation since our infected mice showed no weight loss and immunodepression was found even in very light infections (three larvae per mouse initially). Debilitation of the host has been excluded in *T. spiralis* infection since the response to certain antigens is depressed while the response to other antigens is normal or enhanced (1–5, 15). Preliminary results with haptenated keyhole limpet hemocyanin suggest that *T. crassiceps* infection may not significantly depress the antibody response to this antigen although it does suppress the anti-SRBC response.

Since we have been unable to demonstrate any serological cross-reactivity between SRBC and *T. crassiceps* or any evidence of high background PFC to SRBC in infected mice or cell

cultures from infected mice (data not shown), it seems probable that there is no cross-reactivity between SRBC and *T. crassiceps* at the B cell level. Cross-reactivity at a regulatory cell level has not been excluded. The latter possibility warrants further investigation in view of the selectivity of the immunodepression that has been reported in other types of parasitic infections (1, 10, 24).

Many features of the immunodepression associated with *T. crassiceps* infection are consistent with classical descriptions of antigenic competition. However, antigenic competition is a complex phenomenon that can occur through a variety of mechanisms (8, 17, 21, 23). The mechanism in the case of *T. crassiceps* infection is likely to be more complex than simple competition for available space between two proliferating cell populations, since we found no correlation between degree of splenic enlargement and the degree of immunodepression of the primary anti-SRBC response in the infected mice. Moreover, depression in the primary response occurred at spleen weights well below those found in normal mice during a secondary response where spleen weights were nearly twice those in a primary response, and cell viabilities were the same in normal and infected mice in both primary and secondary responses.

In view of the suggested role of circulating complexes of antigen and antibody in antigenic competition (17, 21), mediation by soluble products released from living larvae must be considered in an analysis of the mechanisms of immunodepression by *T. crassiceps*. *T. spiralis*-induced immunodepression can be passively transferred with serum from infected animals (5), and depression of the humoral response is no longer apparent at a time when the larvae are encysted. Preliminary results with subcutaneous implantation of *T. crassiceps* larvae, where encystment of larvae occurs more frequently than with intraperitoneal inoculation, suggest that immunodepression may be less likely to occur when the larvae are encysted, but more data are needed on this point. The fact that spleen and mesenteric lymph node suspensions from infected mice give depressed responses to SRBC in vitro in the absence of added *T. crassiceps* antigen does not exclude mediation by soluble factors such as complexes of antigen and antibody. Such complexes may bind in vivo to the surface of cells by means of their Fc receptors (14). We are now investigating in vitro whether depression of the anti-SRBC response by *T. crassiceps* infection involves soluble mediators or active participation of suppressor cell populations or whether it is primarily due to a defect in function of a particular lymphocyte or accessory cell population.

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