Anti-immunoglobulin E Treatment Decreases Worm Burden and Egg Production in *Schistosoma mansoni*-infected Normal and Interferon γ Knockout Mice

By Payman Amiri,[‡] Mary Haak-Frendscho,[||] Kimberly Robbins,[*] James H. McKerrow,[¶] Timothy Stewart,[§] and Paula Jardieu[*]

From the Departments of [*]Immunology, [‡]Cell Culture and Fermentation R&D, and [§]Endocrinology, Genentech, Inc., South San Francisco, California 94080-4990; [||]Promega Corporation, Madison, Wisconsin 53711; and the [¶]Department of Veterans Affairs Medical Center, Anatomic Pathology Service-113B, San Francisco, California 94121

Summary

The immunoglobulin E (IgE) response is generally considered an essential component of the host defense against parasitic helminths such as *Schistosoma mansoni*. In contrast, work on antischistosome vaccines suggests that interferon γ (IFN-γ) is the critical immune mediator for vaccine-induced immunity to the parasite. In this study, the total IgE response to a primary *S. mansoni* infection was suppressed by anti-IgE treatment in both normal mice and in mice with defective IFN genes (gene knockout [GKO]). Reduction of the IgE response resulted in decreased worm burden and a decrease in the number of eggs produced per worm in both normal and GKO mice. Whereas anti-IgE treatment also resulted in reduced hepatosplenomegaly, granulomas around existing schistosome eggs showed normal cellularity. Serum interleukin 4 levels fell in response to the reduction in serum IgE as well. The data suggest that IgE plays a detrimental, rather than beneficial, role for the host in schistosomiasis. Furthermore, the absence of IFN-γ was found to be of little consequence to the host–response to adults or eggs in a primary schistosome infection.

An elevated IgE antibody response is a hallmark of infection with parasitic helminths, including *Schistosoma mansoni*, which infect an estimated 250 million people worldwide (1–3). It is a widely accepted hypothesis that this IgE response evolved as a host defense against metazoan parasites (4, 5). Certainly, numerous studies support the hypothesis that IgE is important in acquired resistance to secondary schistosome infection: B cell depletion prevents development of immunity (6), effective immunity can be adoptively transferred by IgE antibodies (7, 8), and in vitro IgE can directly mediate resistance through eosinophil, macrophage, and platelet-mediated cytotoxicity (4, 9, 10). In addition, recent epidemiological reports suggest a correlation between high schistosome-specific IgE antibody levels and resistance to reinfection (11–13). On the other hand, studies of vaccine-induced immunity suggest that IFN-γ, rather than IgE, is the important effector molecule for acquired immunity (14, 15). Indeed, treatment with an anti-IFN-γ antibody has been shown to reduce immunity to schistosomiasis (16). IFN-γ has also been implicated in schistosome egg–induced granuloma formation (17).

In this study, we evaluated the contributions of IgE and IFN-γ in the host defense against a primary infection with *S. mansoni*. The relative roles of IgE and IFN-γ were examined in a murine model of schistosomiasis in which IgE was eliminated using a monoclonal anti-IgE antibody, and IFN-γ was eliminated via gene knockout (GKO)[1] (18). We report that anti-IgE mAb treatment of both wild type and GKO mice completely blocked production of IgE, yet reduced the number of adult worms and dramatically reduced egg production leading to amelioration of hepatosplenomegaly. These findings suggest that in primary infections, the IgE response stimulated by *S. mansoni* infection is an immunopathological consequence of the host–parasite interaction rather than a protective immune response.

Materials and Methods

Collection of S. mansoni Cercariae. The life cycle *S. mansoni* is maintained in the laboratory of Dr. McKerrow at the Veteran's

P. Amiri and M. Haak-Frendscho contributed equally to this work.

[1] *Abbreviation used in this paper:* GKO, gene knockout.

Affairs Medical Center by using golden Syrian hamsters as the final host, and *Biomphalaria glabrata* snails as the intermediate host. Cercariae of *S. mansoni* were collected by placing infected snails in a darkroom for 3–4 d. Shedding of cercariae into spring water (with 100 μg/ml gentamycin) was induced by placing snails under an incandescent light for 2 h.

Infection of Mice with S. mansoni Cercariae. BALB/c and (129/SvXC57BL/6)F_2 (wild-type) mice were purchased from Charles River Laboratories (Portage, MI). IFN-γ (GKO) mice were obtained from a breeding colony at Genentech. All the mice were housed under microisolator caps in a quarantine room. Once acclimated to our facility, the 5–7-wk-old mice were treated intravenously with either 100 μg anti-IgE mAb (R35-92, rat IgG1; Pharmingen, San Diego, CA) or an isotype-matched control antibody (rat IgG1,κ; PharMingen). The next day, all the mice were injected subcutaneously with 90 ± 5 cercariae of *S. mansoni*. At weekly intervals, mice were bled and then retreated intravenously with 20 μg anti-IgE mAb or isotype-matched control antibody at weeks 1, 2, 3, 4, and 5 and with 100 μg at weeks 6 and 7 (total of 400 μg), or with 20 μg anti-IgE mAb weekly (total of 240 μg). GKO mice (5–9 per group) were treated with a total of 400 μg of the anti-IgE mAb or the isotype control. Total serum IgE was determined by ELISA. There was no effect of the rat anti-IgE Ab on the ability to detect IgE using this assay format.

Quantitation of Adult Worms. Mice were killed by interperitoneal injection of 15 mg of pentobarbital (Fort Dodge Laboratories, Inc., Fort Dodge, IA) and 60 U of heparin (Elkins-Simm Inc., Cherry Hill, NJ). After 10 min, adult worms were recovered by perfusion of the portal venous system (19). Numbers reported are the mean number of worms per mouse (n = 7–12 per group) ± standard deviation.

Quantitation of S. mansoni Eggs in the Liver. Livers were removed from the mice after the perfusion (above) and placed in Earl's Basic Salt Solution (GIBCO BRL Life Technologies, Inc., Gaithersburg, MD) containing 1% type III trypsin (Sigma Chemical Co., St. Louis, MO) and 0.1% collagenase A (Boehringer Mannheim Biochemicals, Indianapolis, IN). The liver was homogenized for 20–30 s using a Polytron homogenizer (Brinkmann Instruments, Westbury, NY). The mixture was allowed to incubate at 37°C for 12 h. At the end of the incubation period, the mixture was shaken well, 20-μl samples were removed, and the total number of eggs in the sample was counted under a microscope at a magnification of 5. The results are reported as the mean total egg number of 10 independently counted samples per liver ± standard deviation.

Evaluation of Histopathology. Liver and spleen were removed and weighed after perfusion of portal venous system and tissue samples (portion of liver and spleen) were fixed for 12 h in 10% phosphate-buffered formalin followed by embedding in paraffin blocks. Paraffin sections were cut at 5 μm and stained with hematoxylin and eosin.

Antibodies. Rabbit polyclonal anti-mouse IgE, hamster anti-recombinant murine (mIFN-γ), rabbit anti-recombinant mIFN-γ, recombinant mIFN-γ, and biotinylated IgE receptor I-IgG immunoadhesin (20) were manufactured at Genentech. Mouse IgE, rat anti-mouse IL-4 mAb, biotin-conjugated rat anti-mouse IL-4, and FITC-conjugated rat anti-mouse CD23 were purchased from PharMingen. Mouse IL-4 was from R&D Systems, Inc. (Minneapolis, MN). Horseradish peroxidase–conjugated donkey anti-rabbit Ig was obtained from Amersham Corp. (Arlington Heights, IL). mAb recognizing CD45R-Red613 was from GIBCO BRL. Horseradish peroxidase–conjugated streptavidin was purchased from Zymed Laboratories (S. San Francisco, CA).

FACS® Analysis. Spleens were removed from anti-IgE mAb and control antibody treated mice after 8 wk of infection with *S. mansoni*. Cells were dispersed with frosted glass slides and washed with PBS containing 1% BSA and 0.1% sodium azide (staining buffer). 10^6 cells were stained with appropriate dilutions of mAbs recognizing CD45R (RA3-6B2, Red613) and CD23(B3B4, FITC conjugated) for 30 min at 4°C. Splenocytes from uninfected mice were used for reference B cell expression of CD23. Cells were washed and fluorescence intensity was measured on a FACScan® flow cytometer (Becton Dickinson & Co., Mountain View, CA). Cells were gated to eliminate dead cells and debris by using forward and side light scatter.

Con A Stimulation of Splenocytes. Spleen cells were dispersed with frosted glass slides and 10^6 cells/ml were cultured in DMEM containing 10% FBS, 5 × 10^{-5} M 2-ME, 100 U/ml penicillin, and 100 mg/ml streptomycin (GIBCO BRL) at 37°C, 5% CO_2. 5 μg/ml Con A was added at initiation of the culture, and supernatants for ELISA were harvested after 72 h.

ELISA. Microtiter plates (Immuno MaxiSorp; Nunc, Roskilde, Denmark) were coated overnight at 4°C with either 2 μg/ml polyclonal rabbit anti-mouse IgE, 1 μg/ml rat anti-mouse IL-4 mAb (BVD4-1D11, IgG2b), or 1 μg/ml hamster anti-recombinant mIFN-γ, depending on the assay format, in 0.05 M sodium carbonate/bicarbonate, pH 9.6. Plates were washed with PBS/0.1% Tween 20 and unbound protein sites were blocked for 1 h at room temperature with 100 μl of 50 mM TBS/0.5% BSA/2 mM EDTA/0.05% Tween 20 (ELISA buffer). After washing three times, twofold dilutions of serum from treated mice or supernatants from cultured splenocytes were added for 2 h and then washed.

To detect total serum IgE, biotinylated IgE receptor I-IgG immunoadhesin (1:1,000 in ELISA buffer) was added and plates were incubated for 90 min at room temperature. The plates were washed and incubated for 1 h with horseradish peroxidase conjugated to streptavidin (1:4,000 in ELISA buffer) followed by washing and the addition of the developing substrate *o*-phenylenediamine dihydrochloride (OPD, Sigma Chemical Co.).

IL-4 concentrations were determined using biotin-conjugated anti-mouse IL-4 (BVD6-24G2, rat IgG1; 1 μg/ml in ELISA buffer). After washing, the plates were incubated for 1 h with horseradish peroxidase conjugated to streptavidin (1:4,000 in ELISA buffer) followed by OPD.

IFN-γ in supernatants from Con A–stimulated splenocytes was detected with rabbit anti-recombinant mIFN-γ followed by a 90-min incubation with horseradish peroxidase–conjugated donkey anti-rabbit Ig (1:5,000 in ELISA buffer) before the developing substrate OPD was added.

Results

We began with an examination of the role of IgE in primary schistosome infection. In the first series of experiments, normal BALB/c mice were infected with *S. mansoni* cercariae and treated weekly with a total of 400 μg of anti-IgE mAb (high dose). This treatment reduced serum IgE to undetectable levels (<3 ng/ml) during the 8-wk course of the infection (Fig. 1). The assay used for quantitation of IgE detects both free IgE and IgE complexed to the antibody and, as such, measures the total serum IgE concentration. A second group of mice treated with a lower dose of anti-IgE mAb weekly (240 μg/total) had measurable IgE responses (<50 μg/ml) during the last 2 wk of the infection. The IgE levels in the antibody treated mice were markedly reduced compared with infected mice treated with the isotype control an-

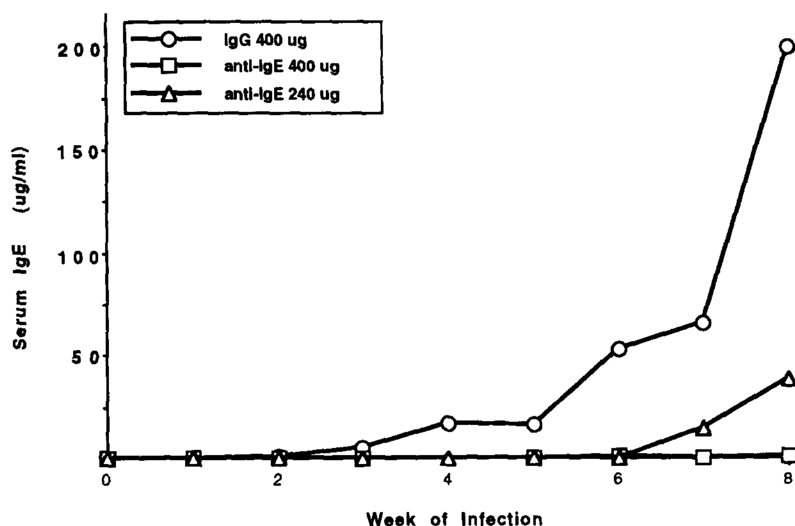


Figure 1. Effect of anti-IgE mAb or control antibody treatment on total serum IgE levels in BALB/c mice. All the mice were treated with 100 μg of anti-IgE mAb or the isotype-matched control IgG antibody 1 d before exposure to parasites. At weekly intervals, mice were bled and then retreated intravenously with a total of 400 or 240 μg of anti-IgE mAb or IgG. Total serum IgE was determined by ELISA using polyclonal rabbit anti-mouse IgE.

tibody which exhibited typically high serum IgE levels (240 μg/ml) by the eighth week of infection.

In agreement with previous reports, a significant but incomplete reduction in serum IgE levels had little effect on either parasite burden or the number of eggs produced per worm (Table 1). In contrast, infected mice, which had undetectable IgE levels as a result of treatment with the higher dose of anti-IgE mAb, had a significant reduction in the number of adult worms and the number of eggs produced, as compared with the control group.

The reduction in egg production resulting from antibody treatment had a measurable effect on the cellular response to infection. Granuloma formation around schistosome eggs trapped in the portal venules of the liver is the key pathological event in schistosomiasis (21, 22). Histopathological examination of the infected animals revealed that organ size correlated with the tissue inflammatory response (Fig. 2 *A*). In the high dose mAb-treated mice, hepatosplenomegaly was diminished by ∼50% when compared with control IgG treated mice. This was due to the decrease in egg production which in turn resulted in marked reductions in the number of granulomas in the livers of the high dose anti-IgE mab treated mice (Fig. 2 *B*).

The cellular composition of the granulomas was not appreciably altered. Well developed granulomas with numerous macrophages and eosinophils were observed in all groups of mice. However, the high dose treatment group did show decreased granuloma-associated fibrosis (Fig. 2, *C* and *D*). Additional immunohistochemical staining of the inflammatory infiltrate for reticulin fibers (data not shown) revealed little fibrosis around the eggs in the anti-IgE treated mice, whereas a distinct fibrotic reaction was evident around the eggs in the IgG controls.

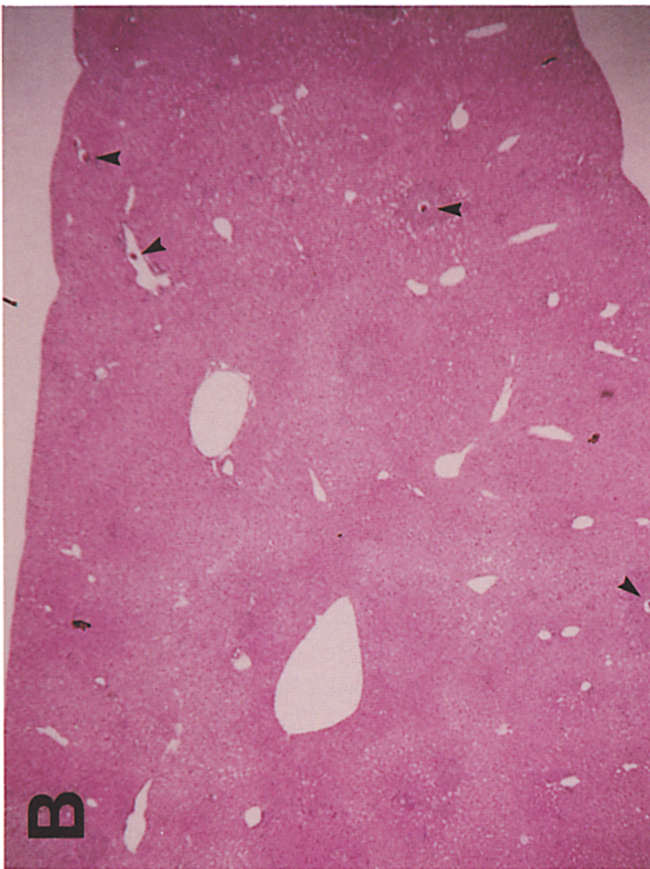
In addition to eliciting a potent inflammatory response, schistosome eggs are a powerful stimulus for clonal expansion and activation of the Th2 subclass of $CD4^+$ T cells (23, 24) which release specific cytokines, including IL-4 (25). In these experiments, serum IL-4 rose to detectable levels during the seventh and eighth weeks of infection in control antibody treated mice (Fig. 3). This rise coincided with egg production (26). However, there was no similar spike of IL-4 in the sera of infected mice treated with anti-IgE mAb (Fig. 4).

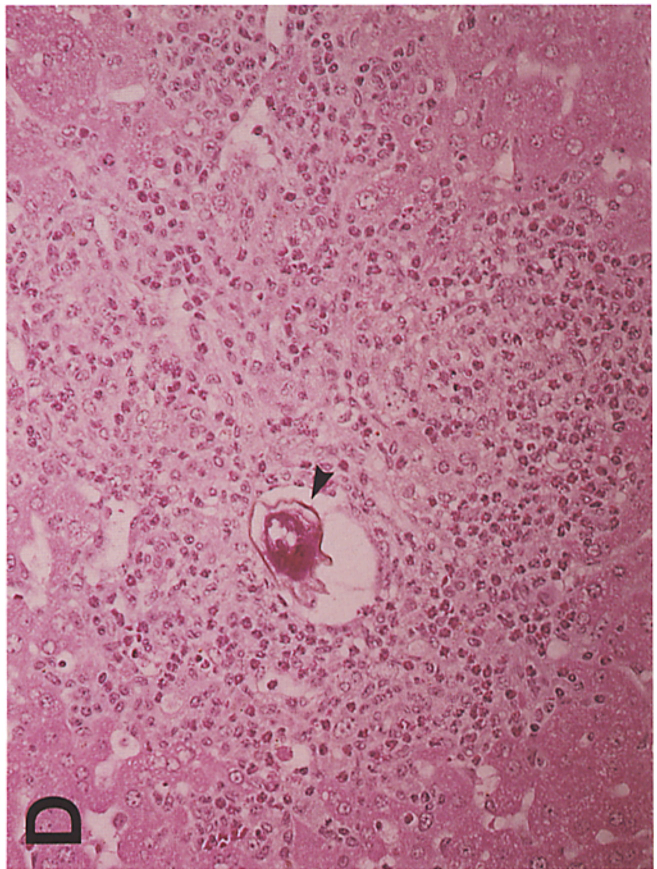
The decrease in IL-4 levels after anti-IgE treatment of schistosome-infected mice was reflected in differential surface marker expression of splenic B cells in the treated mice examined at 8 wk after infection with cercariae. Examination of FcεRII (CD23), the low affinity receptor for IgE, on splenic B cells revealed that the receptor level was elevated in response

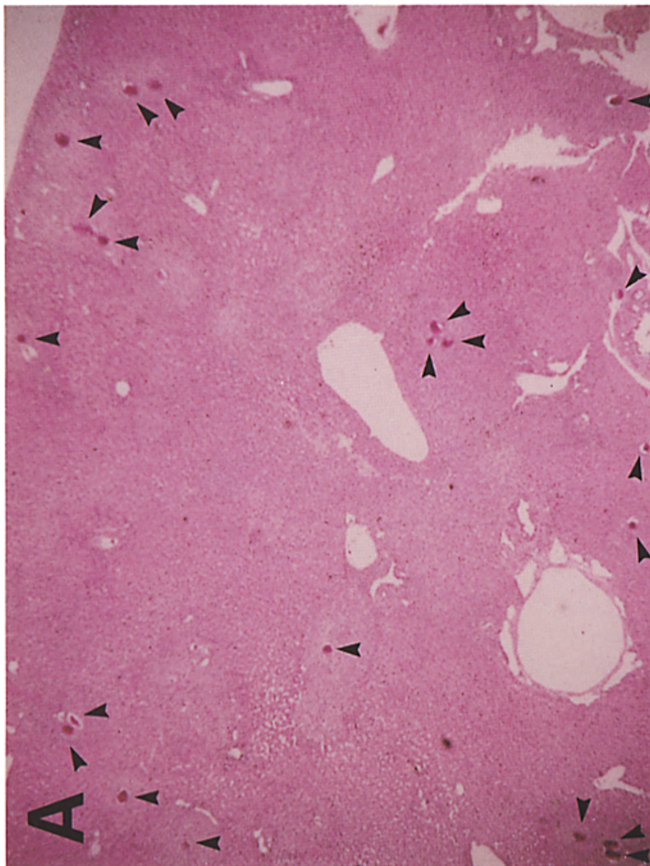
Table 1. *Effect of Anti-IgE on Egg-laying by S. mansoni Worms In Vivo*

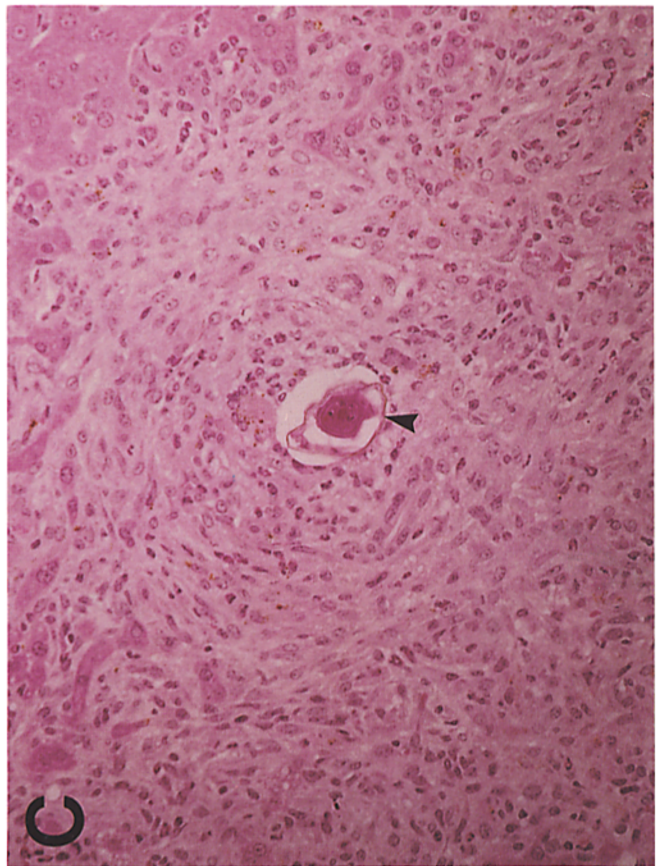
Treatment (400 μg)	Control Ab (400 μg)	Anti-IgE (400 μg)	Anti-IgE (240 μg)
Number of adult worms	41 ± 10	20 ± 2*	42 ± 10
Total no. of eggs/liver	27,061 ± 1,128	5,557 ± 1,595*	23,369 ± 4,927
Mean no. eggs/adult	656 ± 162	268 ± 72*	556 ± 69

* Significant at $P < 0.05$ as determined by analysis of variance; comparisons were performed using the Student-Newman-Keul Test.


B


D


A


C

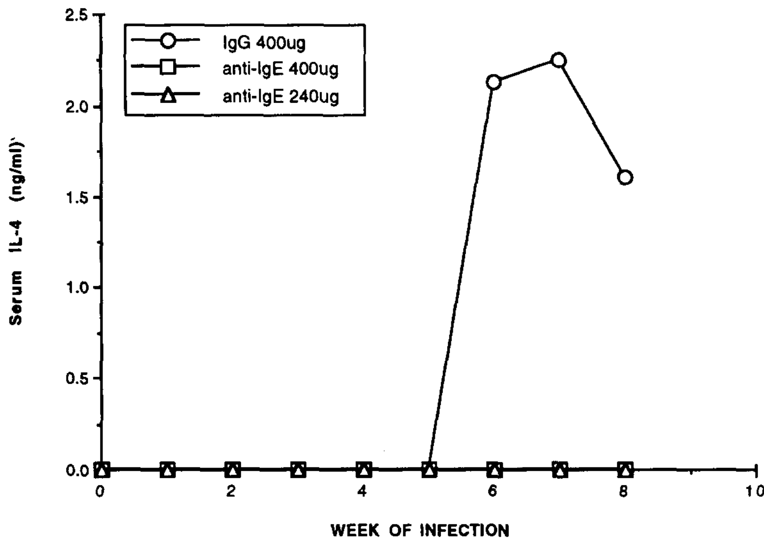


Figure 3. Effect of anti-IgE mAb or control antibody treatment on serum IL-4 levels of schistosome-infected BALB/c mice. Serum IL-4 level was determined by ELISA using anti-mouse IL-4 mAb.

to schistosome infection in the control mice. This increased expression was not seen in mice treated with the anti-IgE mAb (Fig. 4). Since IL-4 is known to increase cell surface expression of CD23 (27), the lack of enhanced CD23 expression is consistent with the absence of detectable IL-4 levels in the anti-IgE treated mice.

To investigate the relative contribution of Th1-derived cytokines in this system, sera were assayed for IFN-γ which has been shown to confer vaccine-induced protective immunity to *S. mansoni* (28). Although the ELISA used was sensitive to 15 pg/ml, no circulating IFN-γ was detected in any of the serum samples collected during the 8-wk course of primary schistosome infection (data not shown). However, IFN-γ levels were measurable in the supernatants of Con A–stimulated spleen cells taken from either uninfected mice or from infected mice treated with anti-IgE or control antibody. In agreement with published findings (29), IFN-γ levels in the cultures were greatly suppressed 8 wk after infection (560 pg/ml uninfected mice vs. 18 pg/ml infected mice). It is interesting to note that treatment with the anti-IgE antibody partially reversed this suppression elevating IFN-γ to 67 pg/ml in the supernatants of splenocytes from infected mice.

To investigate the role of IFN-γ in the immune response to primary *S. mansoni* infection in the anti-IgE treated mice, GKO mice were infected with the parasite and treated with the anti-IgE or control antibody (Fig. 5). It is surprising that GKO and wild-type mice treated with the control antibody were found to have equivalent responses to the parasites (Fig. 6). Almost identical numbers of worms and eggs were recovered from each group. Furthermore, there were no differences in the number or appearance of granulomas in the two

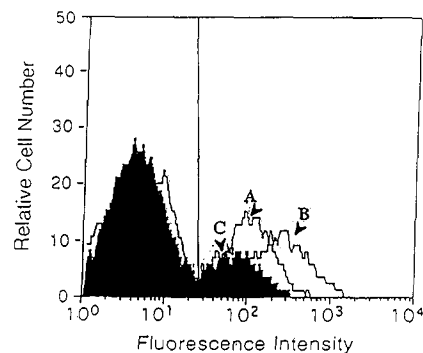


Figure 4. CD23 cell surface expression on splenocytes. Splenocytes from uninfected mice were used for reference for B cell expression of CD23 (*A*). Cells from mice treated with control antibody (*B*) showed a marked upregulation of CD23 expression in response to schistosome infection. In contrast, CD23 expression on spleen cells was reduced as a result of anti-IgE mAb treatment (*C*).

groups. However, similar to the results seen in the BALB/c mice, treatment of the GKO mice with the anti-IgE antibody did result in a decrease in worm burden and egg production. Thus, the effect of anti-IgE treatment would appear to be independent of IFN-γ.

The lack of IFN-γ production in the GKO mice was confirmed by the absence of IFN-γ after Con A stimulation of splenocytes (Fig. 7 *A*). Given the well-established suppressive effects of IFN-γ on IgE synthesis, it is noteworthy that serum IgE levels in the GKO mice were not elevated compared with wild-type mice. This may reflect lower IL-4 levels in these mice since in this experiment, splenocytes from the GKO

Figure 2. Cellular reaction to schistosome eggs trapped in the liver of schistosome-infected BALB/c mice. Livers from control antibody treated mice contained multiple large coalescing foci of granulomas predominately composed of macrophages and eosinophils (*A*). Livers of anti-IgE mAb treated animals had fewer eggs and therefore fewer granulomas (*B*). The histologic characteristics, notably the presence of macrophages and numerous eosinophils, were similar in both groups. However, the granulomas of the anti-IgE treated group (*D*) did appear to have less fibrosis than those from control mice (*C*).

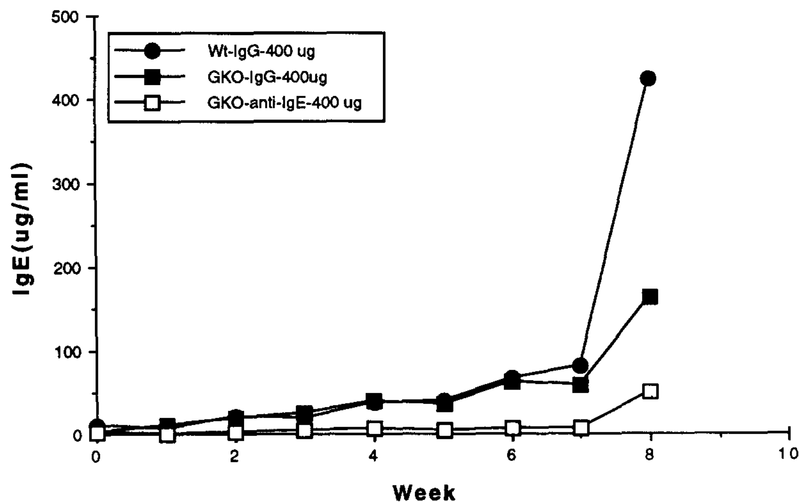


Figure 5. Serum IgE levels of schistosome infected GKO or wild-type mice (five to nine per group) treated with a total of 400 μg of the anti-IgE mAb or the control (IgG) antibody.

mice produced decreased levels of IL-4 in response to Con A stimulation (Fig. 7 *B*).

Discussion

It has been difficult to determine the precise role of IgE in models of parasite infection since most of the studies have employed systems in which IgE is deficient as a result of genetic mutation(s) or via elimination of the pluripotent lymphokine IL-4 which acts as a switch factor for IgE and IgG1 and is required for IgE synthesis (30). Treatment of mice with anti-IL-4 antibodies reduced serum IgE along with IL-4, but failed to alter immunity against *S. mansoni* (15). Since both IL-4 and IgE levels were affected in this study, it is difficult to separate the effects of removal of IgE alone from the pluripotent effects of IL-4 removal. Likewise, attempts to suppress only IgE levels using a polyclonal anti-IgE antiserum showed no detrimental effect on curing a primary infection of *S. mansoni* in rats (31). However, since that study measured only worm-specific IgE responses, it is unclear to what degree the nonspecific IgE response or the IgE response to the other forms of the parasite was suppressed by the dose of anti-IgE antibody used. It has been shown that schistosome-specific IgE constitutes <10% of the total IgE made in response to the infection (32). The suggestion has been made that the presence of this disproportionately high level of total non-parasite IgE may be protective for the parasite since these IgE molecules would saturate the available FcεRs and prevent parasite antigen-specific mediator release (33). Here we measured the total IgE response to assure that the nonspecific IgE levels were completely suppressed throughout the entire course of the infection. Measurement of antigen-specific IgE titers confirmed this result (data not shown). Clearly, suppression of the total IgE response to undetectable levels, rather than a partial reduction in IgE levels, was beneficial for the host as measured by decreases in worm burden and egg production. This reduction in egg production does not appear to

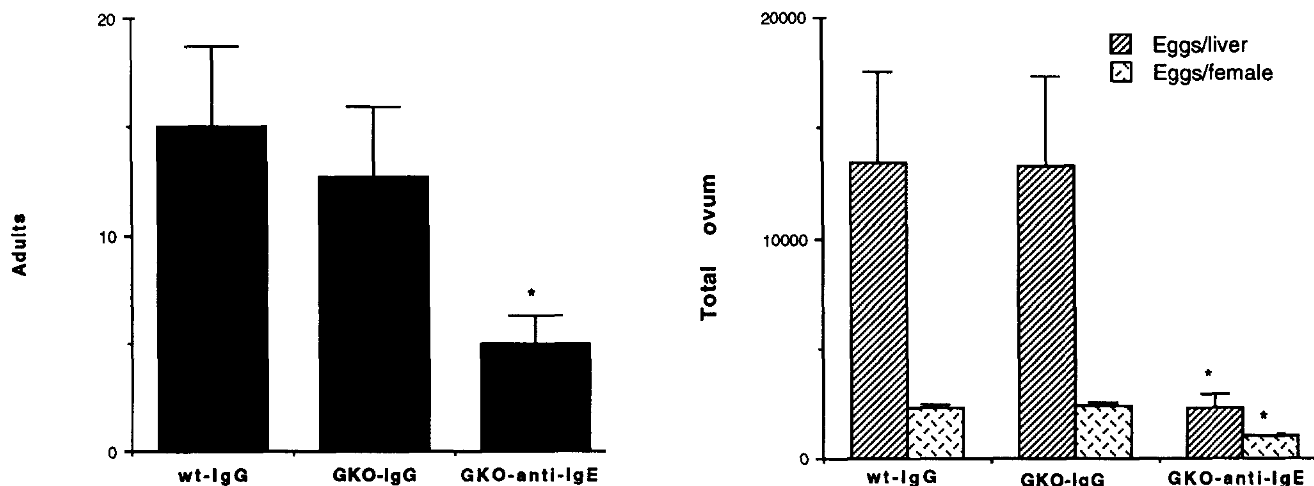


Figure 6. Effect of anti-IgE on *S. mansoni* ovum and worms in GKO or wild-type mice. Numbers reported are mean ± SD. (*) Significance at $p < 0.05$ or better.

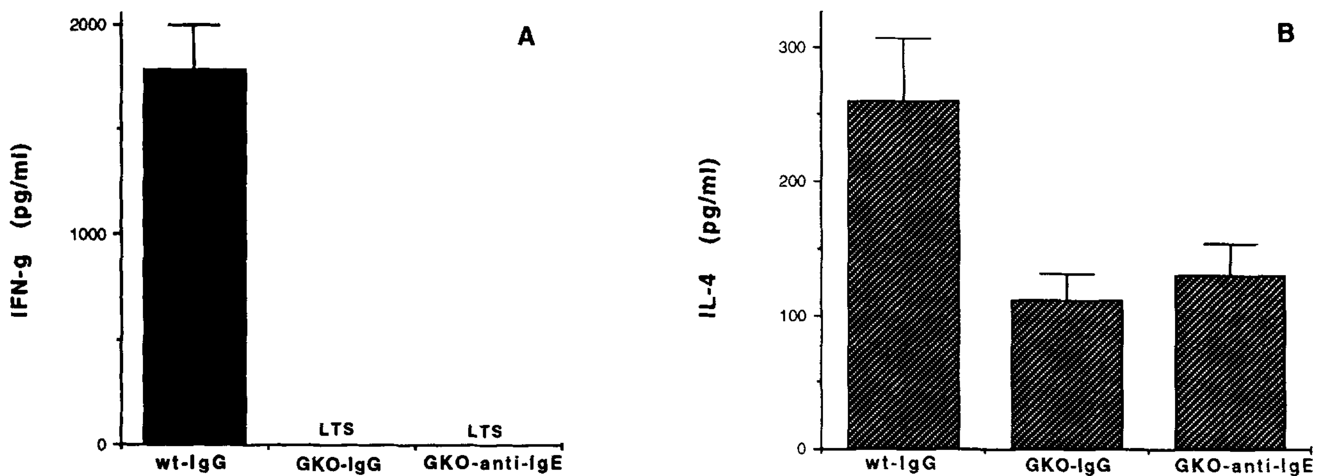


Figure 7. Con A-stimulated IFN-γ and IL-4 production by splenocytes from schistosome-infected GKO or wild-type mice treated with either anti-IgE mAb or isotype control.

be due to a shift in kinetics, since in other reinfection experiments, identical results were seen as late as 15 wk after infection (our unpublished results).

The reduction in egg production in the anti-IgE treated mice is striking. Since it has been shown that TNF-α is required for egg laying by schistosomes (34) the reduction in IgE levels after antibody treatment may have resulted in a reduction in the IgE-dependent release of TNF-α by peritoneal mast cells (35, 36). The lack of IgE to trigger mast cell degranulation would lead to lower TNF-α levels and could account for the decreased egg production in the anti-IgE treated mice. This conclusion is supported by the results seen in the low dose anti-IgE treated mice. In this experiment, when IgE was detectable during the last 2 wk of the infection, egg production and the resultant hepatosplenomegaly were equivalent to the control antibody treated animals.

The decrease in egg production would be expected to have an impact on the cellular response to this parasite since schistosome eggs are known to be potent inducers of Th2 cells. Thus, the decreased egg numbers may have resulted in decreased Th2 stimulation thereby decreasing IL-4 production since Th2 cells are a primary source of this cytokine. This could account for the decreased IL-4 levels observed in the anti-IgE treated mice. Alternatively, as suggested for TNF-α, decreased IgE levels after antibody treatment could lead to decreased mast cell degranulation and release of IL-4 from the granules since it has been shown that mast cells are an important source of IL-4 which is released after receptor cross-linking (37). Indeed, FcεR-positive cells are a major source of IL-4 in spleens of mice infected with *S. mansoni* (38). These findings suggest that in addition to IL-4 directing IgE synthesis, IgE feeds back to amplify IL-4 release, thus modulating its own production.

Decreased IL-4 levels could also account for the observed decrease in CD23 expression since IL-4 is known to be involved in upregulation of CD23 expression. CD23 can act quite efficiently in the capture and preferential presentation of antigens to Th2 cells (39) leading to induction of IgE responses. Thus, a reduction in CD23 expression would lead to a further decrease in Th2 stimulation.

Previous reports have established an association with Th1 stimulation and protection against adult worms versus Th2 stimulation and egg-induced immunopathology (40). It has also been suggested that the Th2 response to schistosome eggs results in downregulation of the Th1 response (37). The improved response to the parasite after elimination of IgE via anti-IgE treatment may result from shifting the balance from a Th2 towards a Th1 response, resulting in the production of cytokines that are reported to be more effective in controlling the parasite infection (17). The increase in IFN-γ levels observed after anti-IgE treatment suggested this shift toward a Th1 response was occurring.

We tested the role of IFN-γ directly by treating schistosome-infected mice, defective in the IFN-γ gene, with the anti-IgE antibody. Since there was little difference in the ability of wild-type or GKO mice to respond to infection, the data suggest that IFN-γ does not play a central role in the development of immunity to primary schistosome infection. Nevertheless, elimination of IFN-γ with an anti-IFN-γ antibody has been shown to reduce vaccine-induced immunity to schistosomiasis (15).

Treatment of the GKO mice with the anti-IgE antibody did result in a decrease in worm burden and egg production. Thus it would appear that the protective effect of the anti-IgE treatment is independent of IFN-γ production. IFN-γ is well accepted as a downregulator of IgE synthesis (41). If IgE plays a negative role in immunity to schistosomiasis, then one may speculate that the reduction in immunity as a consequence of decreased IFN-γ levels resulted from an increase in IgE production. Indeed, in other experiments in mice unable to produce IFN-γ because of disruptions of their IFN genes, we observed enhanced IgE production in response to bacillus Calmette Guérin infection (our unpublished observations).

Our results demonstrate that suppression of IgE synthesis lowers worm burden, egg production, and hepatosplenomegaly in murine schistosomiasis and support the notion that the IgE response stimulated by *S. mansoni* may be parasite rather than host protective, at least in primary infections (33). We are currently investigating the role of IgE and cytokines like IFN-γ in resistance to secondary infection and vaccine-induced immunity.

Address correspondence to P. Jardieu, Department of Immunology, Genentech, Inc., 460 Point San Bruno Boulevard, South San Francisco, CA 94080-6000.

Received for publication 9 November 1993 and in revised form 18 March 1993.

References

1. Finkelman, F.D., E.J. Pearce, J.F. Urban, Jr., and A. Sher. 1991. Regulation and biological function of helminth-induced cytokine responses. *Immunol. Today.* 12:462.
2. Capron, A., J.-P. Dessaint, M. Capron, and H. Bazin. 1975. Specific IgE antibodies in immune adherence of normal macrophages to *Schistosoma mansoni* schistosomules. *Nature (Lond.).* 253:474.
3. World Health Organization. 1985. *Seventh Program Report. Tropical Disease Research.* World Health Organization, Geneva. 3/1-3/25.
4. Capron, A., J.-P. Dessaint, A. Haque, and M. Capron. 1982. Antibody-dependent cell-mediated cytotoxicity against parasites. *Prog. Allergy.* 31:234.
5. Joseph, M., C. Auriault, A. Capron, H. Vorng, and P. Veins. 1983. A new function for platelets: IgE-dependent killing of schistosomes. *Nature (Lond.).* 303:810.
6. Bazin, H., A. Capron, M. Capron, M. Joseph, J.-P. Dessaint, and R. Pauwels. 1980. Effect of neonatal injection of anti-μ antibodies on immunity to schistosomes (*S. mansoni*) in the rat. *J. Immunol.* 124:3273.
7. Capron, A., and J.-P. Dessaint. 1985. Effector and regulatory mechanisms in immunity to Schistosomes: a heuristic view. *Annu. Rev. Immunol.* 3:455.
8. Vignali, D.A.A., Q.D. Bickle, and M.G. Taylor. 1989. Immunity to *Schisistosoma mansoni* infection *in vivo*: contradiction or clarification? *Immunol. Today.* 10:410.
9. Capron, M., H.L. Spiegelberg, L. Prin, H. Bennich, A.E. Butterworth, R.J. Pierce, M.A. Quaissi, and A. Capron. 1984. Role of IgE receptors in effector function of human eosinophils. *J. Immunol.* 132:462.
10. Auriault, C., M. Damonneville, C. Verwaerde, R. Pierce, M. Joseph, M. Capron, and A. Capron. 1984. Rat IgE directed against schistosomula-released products is cytotoxic for *Schistosoma mansoni* schistosomula *in vitro*. *Eur. J. Immunol.* 14:132.
11. Hagan, P., U.J. Blumenthal, D. Dunn, A.J.G. Simpson, and H.A. Wilkins. 1991. Human IgE, IgG4 and resistance to reinfection with *Schistosoma haematobium*. *Nature (Lond.).* 349:243.
12. Rihet, P., C.E. Demeure, A. Bourgios, A. Prata, and A.J. Dessein. 1991. Evidence for an association between human resistance to *Schistosoma mansoni* and high anti-larval IgE levels. *J. Immunol.* 21:2679.
13. Dunne, D.W., A.E. Butterworth, A.J.C. Fulford, H.C. Kariuke, J.G. Langley, J.H. Ouma, A. Capron, R.J. Pierce, and R.F. Sturrock. 1992. Immunity after treatment of human schistosomiasis: association between IgE antibodies to adult worm antigens and resistance to reinfection. *Eur. J. Immunol.* 22:1483.
14. James, S.L., and A. Sher. 1990. Cell mediated immune response to schistosomiasis. *Curr. Top. Microbiol. Immunol.* 21:31.
15. Sher, A., R.L. Coffman, S. Hieny, and A.W. Cheever. 1990. Ablation of eosinophil and IgE responses with anti-IL-5 or anti-IL-4 antibodies fails to affect immunity against *Schistosoma mansoni* in the mouse. *J. Immunol.* 145:3911.
16. Smythies, L.E., P.S. Coulson, and R.A. Wilson. 1992. Monoclonal antibody to IFN-γ modifies pulmonary inflammatory responses and abrogates immunity to *Schistosoma mansoni* in mice vaccinated with attenuated cercariae. *J. Immunol.* 149:3658.
17. Chensue, W.S., P.D. Terebuh, K.S. Warmington, S.D. Hershey, H.L. Evanoff, S.L. Kunkel, and G.I. Higashi. 1992. Role of IL-4 and IFN-γ in *Schistosoma mansoni* egg-induced hypersensitivity granuloma formation. *J. Immunol.* 148:900.
18. Dalton, D.K., S. Pitts-Meek, S. Keshav, I.S. Figari, A. Bradley, and T.A. Stewart. 1993. Multiple defects of immune cell function in mice with disrupted interferon-γ genes. *Science (Wash. DC).* 259:1739.
19. Duval, R.H., and W.B. DeWitt. 1967. An improved perfusion technique for recovering adult schistosomes from laboratory animals. *Am. J. Trop. Med. Hyg.* 16:483.
20. Haak-Frendscho, M., J. Ridgway, R. Shields, K. Robbins, C. Gorman, and P. Jardieu. 1993. Human IgE receptor alpha chain-IgG chimera blocks passive cutaneous anaphylaxis reaction *in vivo*. *J. Immunol.* 151:351.
21. Olds, G.R., and T.F. Kresina. 1989. Immunoregulation of hepatic fibrosis in murine schistosomiasis japonica. *J. Infect. Dis.* 159:798.
22. Parkash, S., A.E. Postlethwaite, G.P. Stricklin, and D.J. Wyler. 1990. Fibroblast stimulation in schistosomiasis. IX. Schistosomal egg granulomas from congenitally athymic mice deficient in production of fibrogenic factors. *J. Immunol.* 144:317.
23. Pearce, E.J., P. Caspar, J.M. Grzych, F.A. Lewis, and A. Sher. 1991. Down-regulation of Th1 cytokine production accompanies induction of Th2 responses by a parasitic helminth, *Schistosoma mansoni*. *J. Exp. Med.* 173:159.
24. Gryzch, J.M., E. Pearce, A. Cheever, Z. Caulada, P. Caspar, S. Heiny, F. Lewis, and A. Sher. 1991. Egg deposition is the major stimulus for the production of Th2 cytokines in murine *Schistosomiasis mansoni*. *J. Immunol.* 146:1322.
25. Mosmann, T.R., and R.L. Coffman. 1989. Th1 and Th2 cells: different patterns of lymphokine secretion lead to different functional properties. *Annu. Rev. Immunol.* 7:145.
26. Vella, A.T., and E.J. Pearce. 1992. $CD4^+$ Th2 response induced by *Schistosoma mansoni* eggs develops rapidly, through an early, transient, Th_0-like stage. *J. Immunol.* 148:2283.

27. Kikutani, H., S. Inui, R. Sato, E. Barsumian, H. Owaki, K. Yamasaki, T. Kaisho, N. Uchibayashi, R.R. Hardy, T. Hirano, et al. 1986. Molecular structure of human lymphocyte receptor for immunoglobulin E. *Cell.* 47:657.
28. Pancre, V., H. Schellekens, P. Van der Meide, H. Vorng, A. Delanoye, A. Capron, and C. Auriault. 1990. Biological effect of interferon-gamma during the course of experimental infection of rats by *Schistosoma mansoni*. *Cell Immunol.* 125:58.
29. Sher, A., R. Coffman, S. Heiny, P. Scott, and A. Cheever. 1990. Interleukin-5 (IL-5) is required for the blood and tissue eosinophilia but not granuloma formation induced by infection with *Schistosoma mansoni*. *Proc. Natl. Acad. Sci. USA.* 87:61.
30. Stavnezer, J., G. Radcliffe, Y. Lin, J. Nietupski, L. Berggren, R. Sitia, and E. Severson. 1988. Immunoglobulin heavy chain switching may be directed by prior induction of transcripts from constant region genes. *Proc. Natl. Acad. Sci. USA.* 85:7704.
31. Kigoni, E.P., P.X. Elsas, H. Lenzi, and A. Dessein. 1986. IgE antibody and resistance to infection II. Effect of IgE suppression on the early and late skin reaction and resistance of rats to *Schistosoma mansoni* infection. *Eur. J. Immunol.* 16:589.
32. Dessaint, J.-P., M. Capron, D. Bout, and A. Capron. 1975. Quantitative determination of specific IgE antibodies to schistosome antigens and serum IgE levels in patients with schistosomiasis (*S. mansoni* or *S. hamatobium*). *Exper. Immunol.* 20:427.
33. Prichard, D.I. 1993. Immunity to helminths: is too much IgE parasite- rather than host-protective? *Parasite Immunol. (Oxf.).* 15:5.
34. Amiri, P., R.M. Locksley, T.G. Parslow, M. Sadick, E. Rector, D. Ritter, and J.H. McKerrow. 1992. Tumor necrosis factor-α restores granulomas and induces parasite egg-laying in schistosome-infected SCID mice. *Nature (Lond.).* 356:604.
35. Ohkawara, Y., K. Yamauchi, Y. Tanno, G. Tamura, H. Ohtani, H. Nagura, K. Ohkuda, and T. Takishima. 1992. Human lung mast cells and pulmonary macrophages produce tumor necrosis factor-α in sensitized lung tissue after IgE receptor triggering. *Am. J. Respir. Cell Mol. Biol.* 7:385.
36. Gordon, J.R., and S.J. Galli. 1990. Mast cells as a source of both preformed and immunologically inducible TNF-α/cachectin. *Nature (Lond.).* 346:274.
37. Paul, W.E. 1991. Interleukin-4: a prototypic immunoregulatory lymphokine. *Blood.* 77:1859.
38. Williams, M.E., M.C. Kullberg, S. Barbieri, P. Gaspar, J.A. Berzofsy, R.A. Seder, and A. Sher. 1993. Fcϵ receptor positive cells are a major source of antigen induced interleukin-4 in spleens of mice infected with *S. mansoni*. *Eur. J. Immunol.* 23:1910.
39. Kehry, M.R., and L.C. Yamashita. 1989. Low-affinity IgE receptor (CD23) function on mouse B cells: role in IgE-dependent antigen focusing. *Proc. Natl. Acad. Sci. USA.* 86:7556.
40. Scott, P., E. Pearce, A.W. Cheever, R.L. Coffman, and A. Sher. 1989. Role of cytokines and $CD4^+$ T-cell subsets in the regulation of parasite immunity and disease. *Immunol. Rev.* 112:161.
41. Coffman, R., and J. Carty. 1986. A T cell activity that enhances polyclonal IgE production and its inhibition by interferon-γ. *J. Immunol.* 136:949.