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SCID Mouse Models of Acute and Relapsing Chronic *Toxoplasma gondii* Infections

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Lymphodeficient *scid/scid* (SCID) mice died from acute infection with a strain of *Toxoplasma gondii* that causes chronic infection with mild symptoms in immunocompetent non-SCID mice. However, most SCID mice reconstituted with spleen cells from immunocompetent mice 1 month prior to *T. gondii* infection survived in good health after a transient period during which they appeared ill. Unreconstituted SCID mice given sulfadiazine in their drinking water from day 10 of *Toxoplasma* infection onward survived the acute phase of infection and lived for many weeks without overt symptoms. Histological examination revealed *Toxoplasma* cysts in their brains. However, if sulfadiazine was withdrawn from the drinking water of these chronically infected SCID mice, the mice died within 1 week with large numbers of trophozoites throughout their brains. These findings establish SCID mice as a potentially useful resource with which to study various aspects of immunological control of *T. gondii* infection during either its acute or chronic phase. Furthermore, the ability to produce chronic infections with avirulent *T. gondii* in SCID mice and to cause acute relapsing infections at will suggests that SCID mice may be helpful in evaluating potential therapies for acute and chronic *T. gondii* infections in immunocompromised patients.

Toxoplasma gondii is a geographically widely distributed intracellular protozoan parasite. Infection in humans is often acquired by ingestion of encysted organisms frequently present in undercooked pork or lamb (15). Much of what is known about pathological aspects of the early stages of *T. gondii* infection has come from studies on experimental animals. After release from cysts in the digestive tract of experimentally infected mice, *T. gondii* organisms invade host cells as a rapidly proliferating form (trophozoite) that may spread to various organs, causing tissue injury and disease (5, 15, 16). Within 1 or 2 weeks in immunocompetent laboratory mice, the infection enters a chronic phase in which, through a poorly understood process, some intracellular parasites become encysted, often within the central nervous system or skeletal muscle (4, 6, 7, 13). A developing immune response apparently controls the remaining proliferating trophozoites. In the chronic phase, both in humans and in mice, the infection may persist lifelong in an asymptomatic state. Large percentages of adult humans in a given population may be chronically infected (15).

Although not ordinarily a problem for immunocompetent individuals, *T. gondii* infections may cause severe disease in an immunocompromised host. About 10% of AIDS patients develop serious neurological impairment from recurrent relapsing *T. gondii* infections probably acquired prior to the onset of AIDS (17). Although treatable with sulfonamides and pyrimethamine, drugs that act against the trophozoites but not against encysted organisms, *T. gondii* infections in AIDS patients require lifelong drug therapy that is not always tolerated well.

It is clear that good animal models are needed to facilitate the development of alternative therapies for *T. gondii* infections. Of particular interest are models in which mechanisms of control of *T. gondii* infections can be studied, especially in the chronic phase. The approach used most commonly to date has been to deplete mice of lymphocyte populations in various ways. Mice treated with antibodies that presumably depleted them of T cells were found to have reduced resistance to acute infection but very little increased mortality from chronic infection (24). More recently, the effects of treating chronically infected mice with antibodies to deplete them of $CD4^+$ T cells (10, 25) have been studied as a model potentially relevant to AIDS. Although an increased mortality of treated mice was found in one study (25), the observed immunopathological consequences of antibody treatment seemed to depend critically on when, in relation to cessation of antibody treatment, the treated mice were examined (10). In addition to the lack of dramatic effects on mortality in these models, they suffer from the defect that mice must be continually treated with antibodies to maintain the depleted state. This problem seriously complicates the design of experiments wherein lymphocytes would be reintroduced into treated hosts.

Various immunosuppressive drugs have also been used for the study of resistance mechanisms in *T. gondii* infections (23). These methods also suffer from the defect that effective drug levels must be maintained in the host. In addition, drugs such as cortisone and cyclophosphamide that have been used for this purpose are rather nonspecific in their effects. Another mouse model, developed to address questions regarding toxoplasmic encephalitis in AIDS patients, relies on direct intracerebral injection of trophozoites (9). Apart from being somewhat artificial biologically, this model also required that mice be treated with immunosuppressive drugs to produce a nonresolving infection.

It would seem that T-cell-deficient nude mice should be useful models for the study of resistance to *T. gondii* infections. Some time ago, it was shown that nude mice infected with a virulent strain of *T. gondii* and treated with sulfadiazine failed to develop immunity. In contrast *nu/+* controls were protected after drug therapy was stopped (14). Oddly, nude mice have not been used, so far as we know, to study resistance to chronic *T. gondii* infections, possibly in part because of difficulties in breeding and maintaining large numbers of healthy nude mice.

The ideal model for the study of resistance to chronic *T. gondii* infections should allow for the establishment of a chronic infection that can be made to develop into an acute

relapsing infection at will. Moreover, the host should be unable to develop specific anti-*Toxoplasma* immunity by itself so that the experimenter can administer various components of the immune system to determine their contributions, singly and in combination, to protection. The work reported here was done to determine whether the SCID mouse, which is deficient in both T- and B-lymphocyte functions by virtue of an autosomal recessive mutation (3), is a potentially useful model for the study of acute, chronic, and relapsing *Toxoplasma* infections.

MATERIALS AND METHODS

Mice. C.B-17/Smn (hereafter designated C.B-17) and C.B-17-*scid/scid* (SCID) mice were bred at the Trudeau Institute from founder stocks obtained from the Jackson Laboratory. Because SCID mice are susceptible to infection with *Pneumocystis carinii* (8, 21), SCID mice used as breeders were given 5×10^7 C.B-17 spleen cells intravenously, usually when 4 to 5 weeks old. This procedure protects them against *P. carinii* infection (8). Breeders treated in this way and their untreated progeny, which were used in the experiments described herein, were kept in modified sterilized microisolator cages into which air was introduced through high-efficiency particulate air filters. The mice received autoclaved food and water, and all maintenance functions were performed in a clean hood. Thus, the mice used for these experiments were free of *P. carinii* and were capable of healthy long-term survival. SCID mice bred and maintained under these conditions were found by flow cytofluorometric analysis to contain 1% or fewer of the number of $CD4^+$, $CD8^+$, or immunoglobulin-positive splenic lymphocytes possessed by C.B-17 control mice (data not shown). These values are virtually identical to those for SCID progeny of parents not reconstituted with non-SCID spleen cells (8).

T. gondii. The ME49 strain of *T. gondii* was obtained originally from Jack Remington, Palo Alto Medical Foundation, Palo Alto, Calif., as cysts in a suspension of mouse brain. Parasites were maintained by serial passage in C57BL/6J female mice by intraperitoneal (i.p.) injection of 0.2 ml of crude suspensions of brain in *N*-2-hydroxyethylpiperazine-*N'*-2-ethanesulfonic acid (HEPES)-buffered Hanks balanced salts solution containing 100 cysts per ml. Experimental infections were initiated in exactly the same way.

Cysts were quantified in brains by gently mashing each whole brain (or left or right half if histology was to be performed on the other half) in a plastic tube (Falcon 2057; Becton Dickinson, Fairlawn, N.J.), using a loose-fitting Teflon pestle, and then suspending the material in 2.0 ml of HEPES-buffered Hanks balanced salts solution. Twenty microliters of the resulting suspension was placed on a glass slide and covered with a coverslip (22 by 22 mm), and cysts in the entire sample were counted by phase microscopy under ×100 magnification. With this procedure, the detection limit for cysts is 100 per brain, or 200 per brain if only half of a brain is sampled.

Histology. Brain halves were fixed overnight in 10% neutral buffered formalin (Sigma Chemical Co., St. Louis, Mo.) and embedded in paraffin, and 5-μm sections were prepared and stained with hematoxylin-eosin.

RESULTS AND DISCUSSION

SCID mice are acutely susceptible to infection with a relatively avirulent strain of *T. gondii* but can be protected if given spleen cells before infection. Groups of five male or female SCID mice and C.B-17 controls were challenged i.p. with 20 ME49 *T. gondii* cysts. Survival data are shown in Table 1. Whereas C.B-17 control mice of either sex survived for the duration of the experiment with only transient mild symptoms, all SCID mice died within 2.5 to 3 weeks. Several independent experiments have confirmed the susceptibility of SCID mice and the resistance of C.B-17 controls.

TABLE 1. Susceptibility of SCID mice to infection with an avirulent *Toxoplasma* strain

Strain	Treatment	Sex[a]	Survival (days)[b]
C.B-17		M	>100[c]
SCID		M	19, 19, 19, 21, 22
C.B-17		F	>52[c]
SCID		F	18, 19, 19, 21, 22
	C.B-17 spleen cells[d]	F	14, >90, >90, >90, >90
	No cells	F	14, 15, 15, 18, 20

[a] M, male; F, female.
[b] Groups of five 8-week-old mice were challenged with 20 ME49 cysts i.p.
[c] Mice killed at the indicated times appeared healthy were asymptomatic throughout most of the infection.
[d] Mice received 5×10^7 sex-matched spleen cells intravenously 30 days before infection with 20 ME49 cysts i.p.

Evidence accumulated by other investigators indicates that lymphocytes, particularly $CD4^+$ and $CD8^+$ T cells, are crucial to the development of immunity that allows *Toxoplasma*-infected mice to survive for the long term (1, 18, 19). Experiments performed at this institute and elsewhere have shown that SCID mice can be reconstituted with C.B-17 lymphocytes (8, 22) and, once reconstituted, are able to resolve an established *P. carinii* infection (8). To determine whether C.B-17 lymphocytes are able to confer protection against *Toxoplasma* infection, SCID mice were given 5×10^7 C.B-17 spleen cells intravenously and challenged with 20 ME49 cysts i.p. 30 days later. Flow cytofluorometric analysis of spleens of similarly reconstituted uninfected mice 29 days after reconstitution revealed that $CD4^+$, $CD8^+$, and surface immunoglobulin-positive cells were present at about 10% of the numbers found in a control C.B-17 mouse, whereas unreconstituted SCID mice had fewer than 1% of the numbers in controls (data not shown). Results in Table 1 show that unlike unreconstituted SCID mice, which are susceptible to *Toxoplasma* infection, most of the mice given C.B-17 spleen cells prior to infection were resistant, although they exhibited symptoms of infection (piloerection and huddling) for several days between 2 and 3 weeks postinfection. The mice appeared healthy thereafter. In a repetition of this experiment, all of the spleen cell-reconstituted SCID mice survived for 1 year.

SCID mice treated with sulfadiazine during *Toxoplasma* infection survive and develop brain cysts. Sulfadiazine has frequently been used to allow mice to survive the early stages of infection with virulent strains of *T. gondii* by controlling trophozoites until a fully protective immunity develops. Furthermore, it has been shown that even T-cell-deficient nude mice can survive infection with virulent *T. gondii* so long as they are treated with sulfadiazine (14).

With this consideration in mind, we reasoned that SCID mice, too, might survive an acute *T. gondii* infection if given sulfadiazine. A pilot experiment was performed in which sulfadiazine therapy (400 mg/liter of drinking water) was initiated in SCID mice on day 5 or 10 of infection. Mice in both groups survived, but far more cysts were found in the group in which sulfadiazine was started on day 10 (approx-

TABLE 2. Brain cyst burdens in sulfadiazine-treated SCID mice at progressive times of infection

Wk of infection	Cysts/brain[a]		
	Sulfa-treated SCID	Sulfa-treated C.B-17	Untreated C.B-17
2	<200, <200	<200, <200	<200, <200
4	1,600, 3,200	200, 600	<200, 200
6	600, 1,400	<200, <200	<200, <200

[a] SCID or C.B-17 females were challenged with 20 ME49 cysts i.p. and given sulfadiazine (400 mg/liter of H_2O) as indicated from day 10 of infection onward. Pairs of mice in each treatment group were killed at the indicated times. Cysts were counted in one-half of the brain, and the other half was processed for histological examination.

imately 10^3 per brain). Therefore, sulfadiazine therapy was initiated on day 10 in the remaining experiments.

To characterize the chronic infection produced in SCID mice, groups of mice were infected with 20 ME49 cysts i.p. and given sulfadiazine therapy as described above. Infected C.B-17 control mice were also sulfadiazine treated or their drinking water was left untreated. At 2, 4, and 6 weeks of infection, two mice in each group were killed, cysts were counted in one-half of each brain, and the other half was processed for histological examination. Untreated SCID mice were not included in this aspect of the study since they do not survive beyond the time when cysts are first detectable in brains of immunocompetent mice, about 2 to 3 weeks into infection. Sulfadiazine-treated SCID mice did survive for the duration of the experiment (with only mild symptoms) and developed substantial numbers of cysts in their brains (Table 2). This experiment also revealed that cyst formation in vivo is not a parasite response to immunological pressure generated by responding T and B lymphocytes. This finding thus provides an in vivo counterpart to observations made by others who found that cysts can form in vitro in the absence of host immune cells (12). In additional experiments, *Toxoplasma*-infected SCID mice given sulfadiazine in their drinking water have survived for more than 10 weeks (data not shown), although occasionally mice have died shortly after initiation of sulfadiazine therapy.

Sulfadiazine-treated *T. gondii*-infected SCID mice succumb quickly if sulfadiazine treatment is stopped. If $CD4^+$ and $CD8^+$ T-cell-dependent mechanisms are responsible for the protection of mice against *T. gondii* infections in the chronic state, one would predict that SCID mice would be unable to control their *T. gondii* infection if sulfadiazine was withdrawn. In an experiment to verify this prediction, it was found that five of five healthy-appearing *T. gondii*-infected SCID mice treated with sulfadiazine from days 10 to 28 of infection died 7 days after sulfadiazine treatment was stopped. Death was not an artifact due to sulfadiazine treatment per se, judging by the survival of five of five uninfected, sulfadiazine-treated control SCID mice to beyond 70 days in apparently good health. In numerous additional experiments (data not shown), it has been observed that *T. gondii*-infected SCID mice consistently die within 6 to 9 days after sulfadiazine treatment is stopped, even if sulfadiazine treatment is maintained for as long as 10 weeks.

Brains of *T. gondii*-infected SCID mice and controls were evaluated histologically. Beyond week 2 of infection, there was evidence of an inflammatory response in all of the brains, which was somewhat more extensive and intense in C.B-17 control brains (Fig. 1a and b), regardless of sulfadiazine treatment, than in SCID brains (Fig. 1c). SCID brains exhibited a relatively mild meningitis and encephalitis, as well as vasculitis in some areas. Most of the inflammatory cells in these areas appeared to be lymphoid. In addition, occasional foci of inflammatory necrosis containing mixed mononuclear and polymorphonuclear cells could be found in SCID brains. During the period of sulfadiazine therapy, trophozoites were not readily apparent in brain sections from any of the mice, whereas after sulfadiazine therapy was stopped, numerous foci containing large numbers of trophozoites were evident in SCID mice (Fig. 1d) but not in immunocompetent controls. The trophozoites were easily detectable in SCID mouse brain sections from 2 days after cessation of sulfadiazine therapy onward.

In another experiment, a few tissues besides brain (i.e., heart, lung, kidney, liver, and spleen) from chronically infected SCID mice were examined histologically. Neither in SCID mice maintained on sulfadiazine nor in SCID mice from which sulfadiazine was removed 5 days before tissues were taken for histology was there any evidence of *T. gondii* infection (cysts, trophozoites, or foci of inflammation) in any tissue except brain (data not shown). The brains of mice in the two groups appeared much like those described above, however.

The results of this study establish that SCID mice infected with an ordinarily avirulent strain of *T. gondii* (i) die of acute infection, (ii) can be protected by an infusion of spleen cells from immunocompetent mice prior to infection, (iii) survive to a chronic stage of infection and develop brain cysts if given sulfadiazine in their drinking water, and (iv) succumb to acute relapsing disease if sulfadiazine therapy is stopped.

Several features of SCID mice make them particularly attractive as experimental animals in which to study mechanisms of resistance to infection. Unlike immunodeficient nude mice, which are deficient only in $CD4^+$ and $CD8^+$ T lymphocytes, SCID mice are deficient in B-cell functions as well (3). This property allows T-cell and B-cell roles in infection to be studied independently. Moreover, as a practical matter, the C.B-17 SCID mice used in this study breed well, have large litters, and remain healthy so long as they are kept in an environment free of *P. carinii* and other pathogens, as is necessary for any severely immunocompromised experimental animal. Maintained in the way described in this study, SCID mice have been found to compare very favorably with nude mice with regard to husbandry, productivity, and cost.

The method used to produce *Pneumocystis*-free SCID mice for this study relies on reconstitution of their parents with lymphoid cells from immunocompetent C.B-17 mice (8). It could be asked whether this process affects the SCID progeny in ways that might affect their usefulness in studies of this type. While we have not performed an exhaustive comparison of SCID progenies from reconstituted and unreconstituted parents, fluorescence-activated cell sorting analysis of spleen cell populations of a few progeny of reconstituted breeders revealed no noticeable differences in the numbers or percentages of various lymphocyte subpopulations from those found in progeny of unreconstituted SCID breeders at this institute (8). Moreover, since the reconstituted parents of mice used in these studies were never exposed to *T. gondii* and thus should have developed no *T. gondii*-specific immunity (for example, in the form of antibodies), it is difficult to imagine a mechanism by which the immunological constitution of the parents could affect their progeny any differently than occurs with any immunocompetent parent mice.

Although SCID mice are rather susceptible to acute infec-

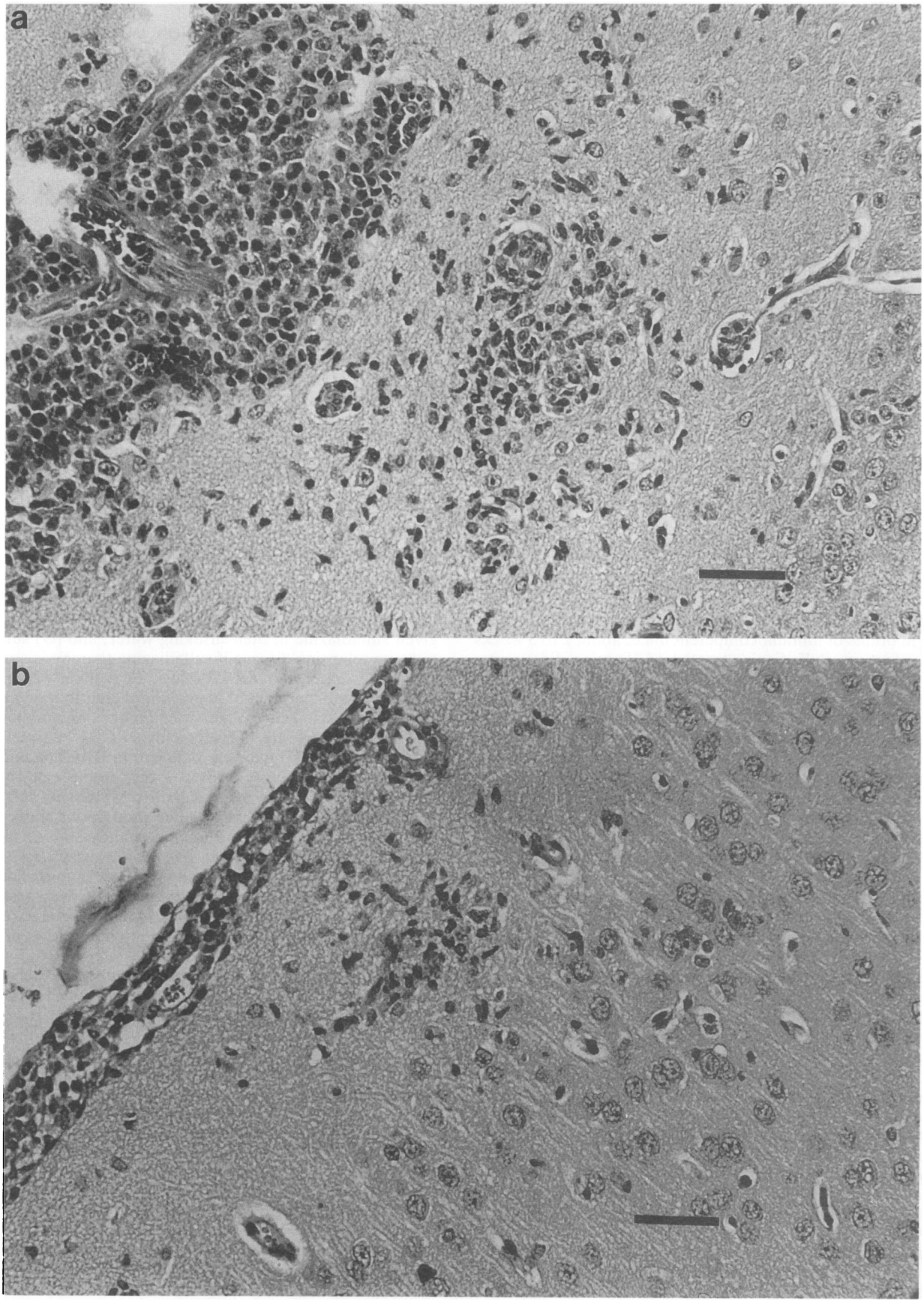

FIG. 1. Brain sections of *Toxoplasma*-infected, sulfadiazine-treated C.B-17 and SCID mice. (a) Extensive inflammation in C.B-17 brain at 4 weeks of infection; (b) meningitis and focal encephalitis in C.B-17 brain at 4 weeks of infection; (c) focus of inflammation in SCID brain at 6 weeks of infection during sulfadiazine therapy; (d) trophozoites and cyst (arrow) in SCID brain 5 days after withdrawal of sulfadiazine at 6 weeks of infection. Bars equal 50 μm.

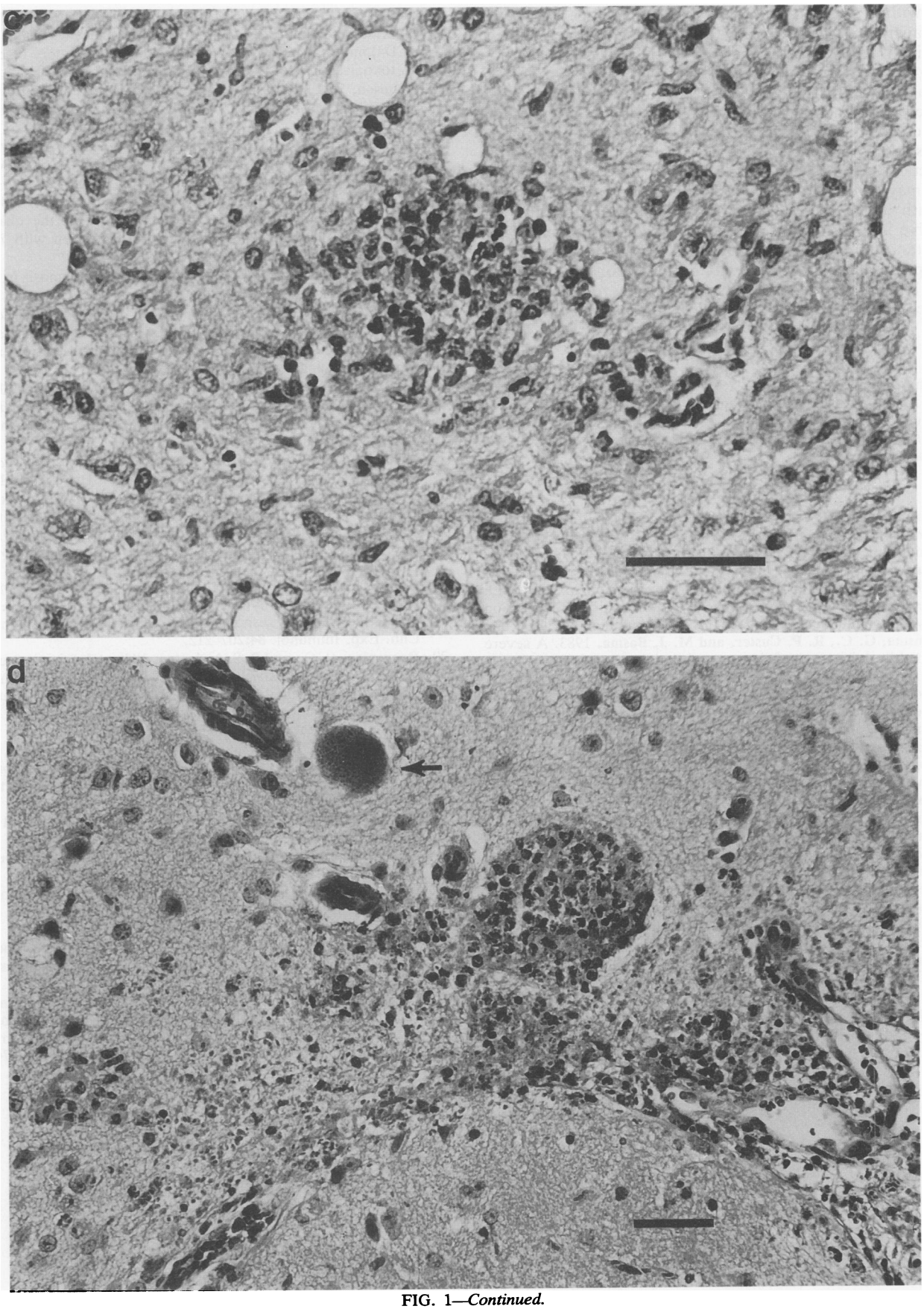

FIG. 1—*Continued.*

tion with *T. gondii*, they survive somewhat longer (for about 18 days) than the 7 to 9 days that immunocompetent mice survive if given a single injection of antibodies that neutralize gamma interferon 6 h before infection with *T. gondii* is initiated (11). This finding suggests that despite their deficiency in T- and B-lymphocyte functions, SCID mice may possess a gamma interferon-dependent mechanism that provides temporary incomplete resistance to acute *T. gondii* infections. It has been suggested that a mechanism of this sort may come into play in other infections as well (2).

With the knowledge that transferred B and T cells will survive in SCID mice (22) and can mediate immunological resistance to pathogens (8, 21; this study) and allografts (20), it appears that SCID mice will be useful tools in elucidating the lymphocyte-dependent mechanisms responsible for acute and chronic resistance to *Toxoplasma* infections.

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