INFECTION AND IMMUNITY, Oct. 1986, p. 56–62
0019-9567/86/100056-07$02.00/0

Vol. 54, No. 1

Genetic Control of Natural Resistance to Nontuberculous Mycobacterial Infections in Mice

IAN M. ORME,* RICHARD W. STOKES, AND FRANK M. COLLINS
Trudeau Institute, Saranac Lake, New York 12983

Received 16 April 1986/Accepted 17 June 1986

Results show that various inbred strains of mice can be segregated into two distinct groups, based on their capacity to allow a number of nontuberculous mycobacterial infections to grow in target organs following experimental intravenous infection. The first group, which allowed these infections to grow progressively, was thus designated as naturally susceptible to these infections; in contrast, those strains which were able to exert detectable bacteriostasis were designated as naturally resistant. It was then found that segregation of mouse strains based on this distinction also mirrored the capacity of these animals to generate acquired immunity to the mycobacterial infections. For example, *Mycobacterium simiae* grew progressively in susceptible C57BL/6 mice, subsequently triggering acquired mechanisms of immunity, whereas no evidence for acquired immunity could be found in resistant A/Tru mice infected with this organism. The possibility that acquired immunity could not be expressed in the latter strain as a result of a defect in macrophage activation was excluded. Moreover, it was found that the trait of resistance to these infections could be transferred by bone marrow cells into radiation chimeras, thus indicating that this trait was expressed by the progeny of hemopoietic precursor cells. Subsequent backcross analysis to determine the mode of inheritance of the trait of resistance to these mycobacterial infections revealed data that were consistent with the hypothesis that this resistance is controlled by more than one gene. Statistical analysis of the data by the maximum likelihood method suggested polygenic control, although in some cases the probability values suggested control by a major gene, influenced by modifier genes. These findings suggest that the previous hypothesis that the growth of mycobacterial infections in inbred strains of mice is controlled by a single gene should be reevaluated.

It is now established that various inbred strains of mice differ widely in their ability to control the proliferation of a number of intravenously administered mycobacterial infections. For example, it was found that small intravenous inocula of *Mycobacterium bovis* BCG Montreal grew progressively in the spleens of certain susceptible strains (for example, C57BL/6, BIO.A, BALB/c), while they grew poorly or not at all in resistant strains (for example, A/J, C3H/He, DBA/2) (3). In subsequent studies the mechanisms underlying this phenomenon have been investigated, and it has been ascribed to the action of a single, autosomal, dominant gene which has been mapped to chromosome 1 in the mouse and which has been given the designation *Bcg* (5, 14). Accumulative evidence to date suggests that the *Bcg* gene controls an heretofore unidentified mechanism of antimicrobial resistance that is expressed by resident host macrophages (6, 14).

Results of initial reports concerning the activity of the *Bcg* gene suggest that expression of this gene is absolute, in that it completely prevents mycobacterial proliferation in vivo in mice bearing the resistant allele (Bcg^r), thus obviating the need for the generation of acquired mechanisms of immunity (13). More recent reports from this laboratory have challenged this viewpoint, however, by showing that some degree of mycobacterial proliferation does in fact occur in resistant Bcg^r mouse strains and that this leads to the generation of acquired T-cell-mediated immunity in these animals, albeit at a much slower rate than in susceptible Bcg^s mouse strains (11, 12). Furthermore, results of these studies also showed that the bacteriostatic activity of the *Bcg* gene is only effective against certain vaccine strains of BCG (notably, BCG Montreal and BCG Australian), while other strains (BCG Pasteur and several others) grew progressively in the spleens of Bcg^r mice.

In this study four nontuberculous mycobacterial infections are described that were found to grow at different rates in various mouse strains. Analysis of the genetic control of resistance to three of these infections was performed by using segregating backcross populations, derived by initially mating parental strains that were designated as naturally susceptible (NS) or naturally resistant (NR) to these infections. It was found that the data obtained by this experimental method support a hypothesis for multiple gene control of resistance to these infections.

MATERIALS AND METHODS

Mice. Experiments were performed with 6- to 9-week-old specific-pathogen-free BALB/c, DBA/2, C3H/He, C57BL/6, and A/Tru male mice and F_1 and backcross mice derived from these parental strains. In addition, B6D2 (C57BL/6 × DBA/2)F_1 hybrid mice were used in radiation chimera experiments. These mice were bred in the Trudeau Institute Animal Breeding Facility. In addition, A/J, BALB/cJ, and BIO.AJ mice were obtained from Jackson Laboratories, Bar Harbor, Maine. Results of periodic screening for antibodies to viruses were invariably negative. Animals were maintained under barrier conditions and fed acidified water and autoclaved mouse chow ad libitum.

Bacteria. *M. simiae* (Trudeau Mycobacterium Culture Collection (TMC) strain 1226; ATCC 25275), *M. avium* (TMC 724; ATCC 25292), *M. avium* (TMC 702; Weybridge), *M. intracellulare* (D673; Dunbar), *M. bovis* BCG (TMC 1011; Pasteur), and *M. tuberculosis* (TMC 107; Erdman) were grown as described previously (9). *Listeria monocyto-*

* Corresponding author.

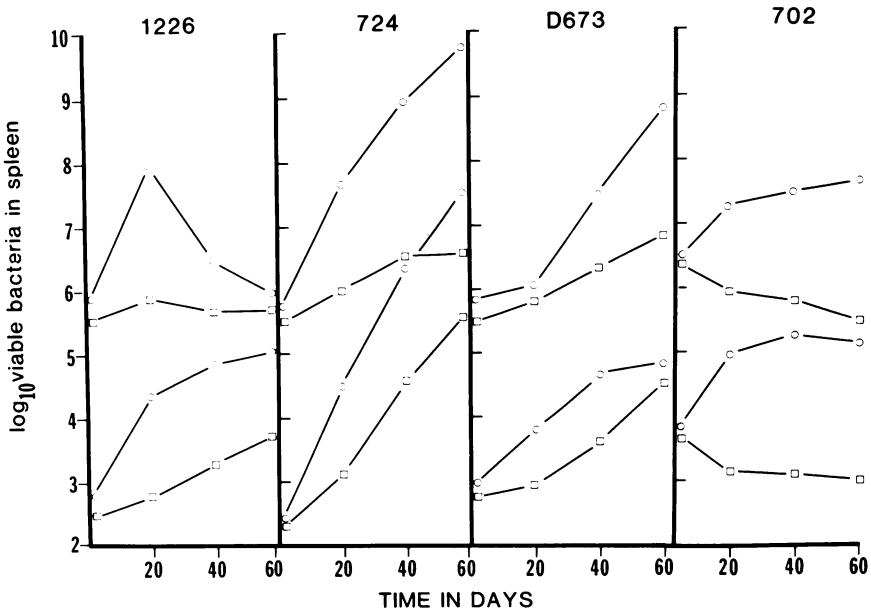

FIG. 1. Growth of a high-dose (10^7 intravenously) or a low-dose (10^4 intravenously) inoculum of *M. simiae* 1226, *M. avium* 724, *M. intracellulare* D673, or *M. avium* 702 in the spleens of C57BL/6 (○) and A/Tru (□) mice. Data are expressed as mean values (n = 4 to 5); the SEM was omitted; it never exceeded 0.31.

genes EDG (serotype 3b) was grown in tryptic soy broth (Difco Laboratories, Detroit, Mich.), harvested in log-phase growth (5×10^8/ml), and stored frozen at −70°C until required.

Mice were infected via a lateral tail vein with indicated numbers of bacteria suspended in 0.2 ml of phosphate-buffered saline. The course of the test infection was followed against time by sacrificing groups of mice (n = 4 to 5) at various intervals and by plating serial dilutions of individual whole-target organ homogenates on nutrient Middlebrook 7H11 agar (GIBCO Laboratories, Grand Island, N.Y.); plates were examined for bacterial colony formation after 14 to 20 days of incubation at 37°C in humidified air.

Determination of acquired nonspecific resistance. The generation of nonspecific resistance to secondary challenge in mycobacteria-infected mice was determined at various time intervals by intravenously infecting groups (n = 4 to 5) of test and normal control animals with a dose (10^5) of *L. monocytogenes* that was uniformly lethal for both *L. monocytogenes*-susceptible (A/Tru) and *L. monocytogenes*-resistant (C57BL/6) mouse strains (9). Resistance to the challenge infection was determined 48 h later by plating serial dilutions of individual whole-spleen homogenates on tryptic soy agar and counting bacterial colony formation after 24 h of incubation at 37°C. These data were then expressed as the $\log_{10}$ difference in the mean numbers of *L. monocytogenes* recovered from the spleens of control animals and those recovered from infected test animals.

Radiation chimeras. Bone marrow cells were harvested from the femurs of C57BL/6 and B6D2 F_1 mice. Cells were washed in ice-cold RPMI 1640 tissue culture medium supplemented with 1% heat-inactivated fetal calf serum and then treated with monoclonal anti-Thy-1.2 antibody plus complement, as described previously (10). Lethally irradiated (1,000 rad) C57BL/6 donors were infused intravenously with 2×10^7 donor bone marrow cells. Nonreconstituted animals died of the effects of irradiation within 10 days. Surviving chimeric recipients were used 90 days later.

Backcross analysis. Backcross analysis of the genetic control of resistance to the mycobacterial infections was performed by conventional procedures. Data were analyzed by the chi-square test applied to the maximum likelihood method (1, 2). In backcross experiments in which both male and female animals were used, no evidence for sex-linked effects was noted.

RESULTS

Screening for the growth of nontuberculous mycobacterial infections in various inbred mouse strains. In an initial experiment, various mouse strains were tested for their capacity to allow the growth of two test infections, following intravenous inoculation with a low dose (10^4) of these organisms. Two distinct patterns emerged when bacterial numbers in the spleens of these mice were determined after 30 days of each infection (Table 1). Two BALB/c sublines (BALB/cJ, BALB/cTru) and two closely related C57 strains (C57BL/6, BIO.A) permitted progressive growth of the infection and

TABLE 1. Growth of nontuberculous mycobacteria in various strains of mice

Strain	No. of bacteria recovered from spleens on day 30 of infection (type)[a]	
	M. simiae	*M. avium*
C57BL/6Tru	4.89 ± 0.16 (NS)	5.34 ± 0.09 (NS)
BALB/cTru	4.92 ± 0.08 (NS)	5.25 ± 0.08 (NS)
BALB/cJ	4.79 ± 0.07 (NS)	4.89 ± 0.06 (NS)
BIO.AJ	5.00 ± 0.10 (NS)	5.10 ± 0.02 (NS)
A/J	3.02 ± 0.03 (NR)	2.93 ± 0.12 (NR)
A/Tru	2.92 ± 0.12 (NR)	3.08 ± 0.09 (NR)
DBA/2Tru	3.36 ± 0.09 (NR)	3.74 ± 0.11 (NR)
C3H/HeTru	3.23 ± 0.06 (NR)	3.72 ± 0.09 (NR)
B6D2F_1	3.40 ± 0.09 (NR)	3.89 ± 0.14 (NR)

[a] Values are means ± standard error of the mean (SEM) (n = 5); mice were infected intravenously with ~10^4 viable bacteria. Typing was based on allowance of progressive growth (NS) or ablility to exert bacteriostasis (NR).

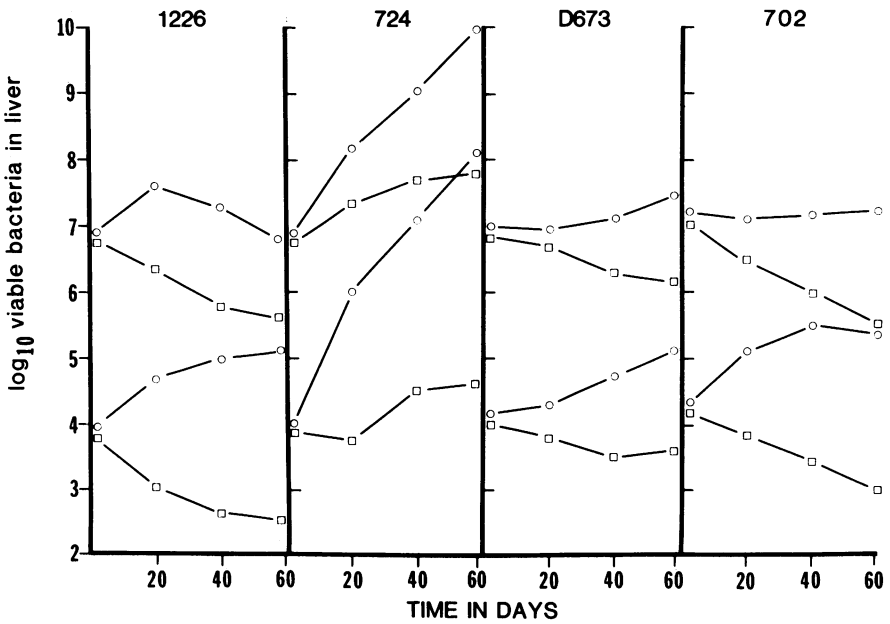

FIG. 2. Growth of the four test organisms in the livers of C57BL/6 (○) and A/Tru (□) mice. Data are expressed as mean values (n = 4 to 5); the SEM was omitted; it never exceeded 0.27.

thus were designated as NS strains. Three other strains (A/J, DBA/2Tru, C3H/HeTru) plus a subline (A/Tru) exerted bacteriostatis against *M. simiae* and permitted *M. avium* to grow only at a considerably slower rate, and thus were designated as NR. In addition, an F_1 hybrid strain (B6D2 F_1; C57BL/6 × DBA/2) was typed as NR.

Course of infections in NS and NR mice. Following the designation of C57BL/6 Tru and A/Tru mice as NS and NR strains, respectively, the course of four mycobacterial test infections was determined in these two representative strains. Each strain of mouse received a high-dose infection (10^7 viable bacteria intravenously) or a low-dose infection (10^4 intravenously). In mice infected with the higher dose, the *M. simiae* infection grew progressively in the spleens of the C57BL/6 Tru mice for 20 days before showing evidence of progressive elimination (Fig. 1). The three other organisms, *M. avium* 724 and 702 and *M. intracellulare*, showed no evidence of elimination and grew progressively in this strain (at various rates) throughout the course of the experiments. In contrast, no evidence for the growth of *M. simiae* was observed in the spleens of A/Tru mice, whereas *M. avium* 724 and *M. intracellulare* showed a very slow increase in bacterial numbers. In addition, no growth of *M. avium* 702 was observed, with the infection showing evidence of progressive elimination throughout the course of the experiment. Similar profiles to those described above were observed in mice infected with the lower dose of each organism.

A somewhat different profile was observed in the livers of these animals (Fig. 2). At either infectious dose, only *M. avium* 724 possessed the capacity to grow in the C57BL/6Tru mice, while the other three organisms remained in an apparent bacteriostasis (at the higher dose) or grew very slowly (at the lower dose). *M. avium* 724 also grew slowly in the livers of the A/Tru mice, while the other infections were slowly, but progressively, eliminated from this organ. Again, similar profiles were observed in mice inoculated with 10^4 isolates of each test infection.

Generation of acquired nonspecific resistance in NS and NR mice. The generation of acquired specific immunity to mycobacteria is associated with the emergence of a popula-

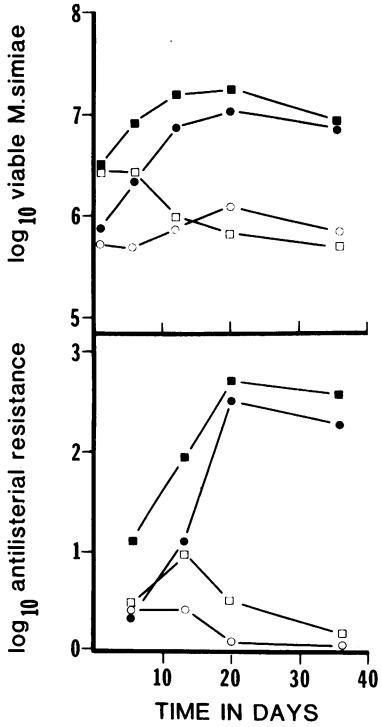

FIG. 3. Evidence that progressive growth of *M. simiae* 1226 infection was associated with an increase in acquired antilisterial resistance. Symbols: ●, spleens of strain C57BL/6; ■, livers of strain C57BL/6; ○, spleens of strain A/Tru; □, livers of strain A/Tru. In all cases n = 4 to 5; the SEM of the growth of *M. simiae* never exceeded 0.22.

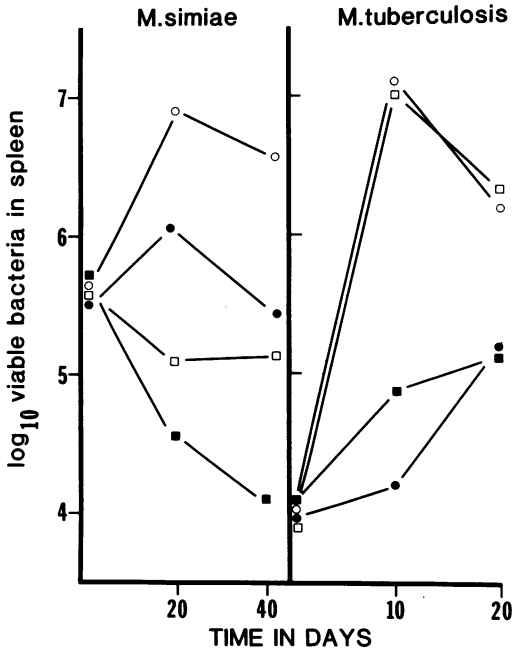

FIG. 4. Demonstration that prior infection of C57BL/6 or A/Tru mice with 10^6 *M. bovis* BCG Pasteur isolates increased the resistance of these animals to secondary mycobacterial infection. Data show the growth of the two secondary infections in the spleens of control C57BL/6 mice (○), BCG-infected C57BL/6 mice (●), control A/Tru mice (□), and BCG-infected A/Tru mice (■). In all cases n = 4 to 5; the SEMs never exceeded 0.29.

tion of mononuclear phagocytes which are able to express enhanced antimicrobial activity against both the specific infection and a secondary infection with other intracellular bacterial parasites. This latter, nonspecific component of acquired resistance can be readily measured by determining the capacity of the animal to destroy a lethal inoculum of *L. monocytogenes* (9).

Taking the *M. simiae* infection as an example, experiments were performed to determine the extent to which NS and NR mouse strains were able to generate acquired immunity when infected intravenously with a high dose (10^7) of this organism. It was found (Fig. 3) that the progressive growth of the infection over the first 20 days in NS (C57BL/6Tru) mice was temporally associated with a rapid increase in levels of acquired nonspecific resistance, which were expressed in both the spleen and liver. In contrast, in NR (A/Tru) mice, in which the primary infection was characterized by bacteriostasis in the spleen and by a slow decline in numbers in the liver, low or negligible levels of antilisterial resistance were detected in these animals. These results suggest, therefore, that the *M. simiae* infection resulted in the generation of considerable levels of acquired immunity in the NS mice, while little or no acquired immunity was induced in mice expressing the NR phenotype.

Induction of acquired nonspecific resistance in NR mice. The observation presented above that a large infectious dose of *M. simiae* is unable to proliferate in the spleens of NR (A/Tru) mice and fails to result in the generation of acquired immunity in these animals could be taken as evidence in support of the hypothesis that the bacteriostatic activity expressed by these mice obviates the need for the generation of an acquired population of activated macrophages. These data were initially viewed with caution, however, in view of evidence which suggested that mice possessing the A strain background may carry a defect in macrophage activation. This possibility was based on the observation elsewhere that macrophages from A/J mice (from which the A/Tru colony was originally derived), unlike such cells from a number of other strains, are unable to lyse fibrosarcoma cells following activation by heat-killed *Corynebacterium parvum* (7). It followed from this evidence, therefore, that the lack of antilisterial resistance observed in A/Tru mice infected with *M. simiae* might not necessarily reflect an absence of acquired immunity.

To exclude this possibility, C57BL/6 (NS) and A/Tru (NR) mice were infected intravenously with 10^8 *M. bovis* BCG Pasteur (a procedure that results in the generation of very high levels of macrophage activation [9]), and then 14 days later they were challenged intravenously with either *M. simiae* or *M. tuberculosis*. It was found (Fig. 4) that prior activation of macrophages by the BCG infection substantially inhibited the growth of *M. simiae* in C57BL/6 mice and accelerated its clearance in the A/Tru mice. Similar results were observed in mice infected with *M. tuberculosis*, in which equivalent levels of bacteriostasis were exerted by both strains of animals against the challenge infection. It was concluded, therefore, that the A/Tru mouse was fully capable of expressing acquired antimicrobial resistance, following appropriate stimulation.

Growth of *M. simiae* in radiation chimeras. Findings reported elsewhere (6) have indicated that the cell population responsible for the phenotypic expression of natural resistance to mycobacterial infections is bone marrow derived and can be transferred by these cells into radiation chimeras. To test this possibility in this study, lethally irradiated C57BL/6 mice (B6 mice) were reconstituted with bone marrow cells from either syngeneic donors (B6; NS) or from F_1 animals (B6D2; NR). These mice and controls were infected intravenously with 10^7 viable *M. simiae*, and the growth of the infection was monitored in the spleens and livers of these mice 20 days later.

It was found (Fig. 5) that the *M. simiae* infection grew similarly in both C57BL/6 controls and in mice reconstituted

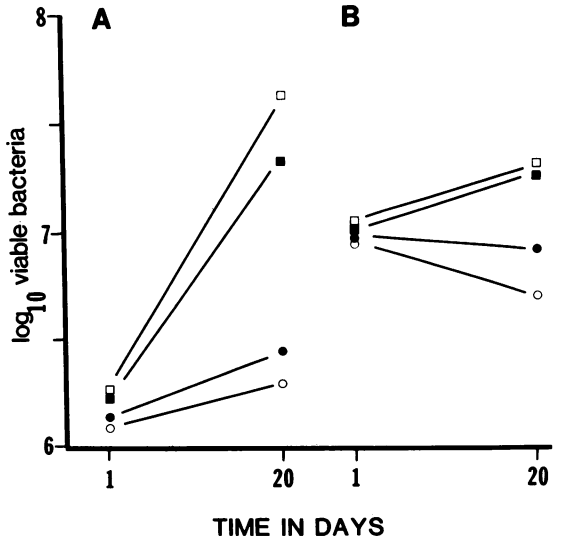

FIG. 5. Growth of *M. simiae* 1226 infection in C57BL/6 radiation chimeras reconstituted with C57BL/6 bone marrow cells (□) or with B6D2 F_1 hybrid bone marrow cells (●) and in C57BL/6 (■) or B6D2 (○) control animals. Data are expressed as mean growth in spleen (A) and liver (B); n = 4 to 5; the SEMs never exceeded 0.37.

with syngeneic cells (B6 → B6). In contrast, the infection was inhibited from growing both in B6D2 F_1 controls and in C57BL/6 mice reconstituted with bone marrow cells from these animals (F_1 → B6). Thus, it was concluded that susceptibility or resistance to the *M. simiae* infection was expressed phenotypically by bone marrow-derived progenitor cells.

Backcross analysis of the genetic control of native resistance. In an attempt to determine the basis of the genetic control of the findings described above, susceptible parent and F_1 mice and backcross mice derived from them were infected with low doses of three of the mycobacterial test organisms and the numbers of bacteria enumerated in the spleens and livers of these animals after 30 days of each infection subjected to formal backcross analysis. A fourth organism, *M. intracellulare*, was not included in view of the minimal differences in growth of infection by this organism in the spleens of NS and NR mice following low-dose inoculation (Fig. 1).

Three separate backcross experiments were performed; a representative result is shown in Fig. 6, and statistical analysis of the data obtained is summarized in Table 2. A consistent finding throughout the three experiments was the observation that the distribution of the backcross values

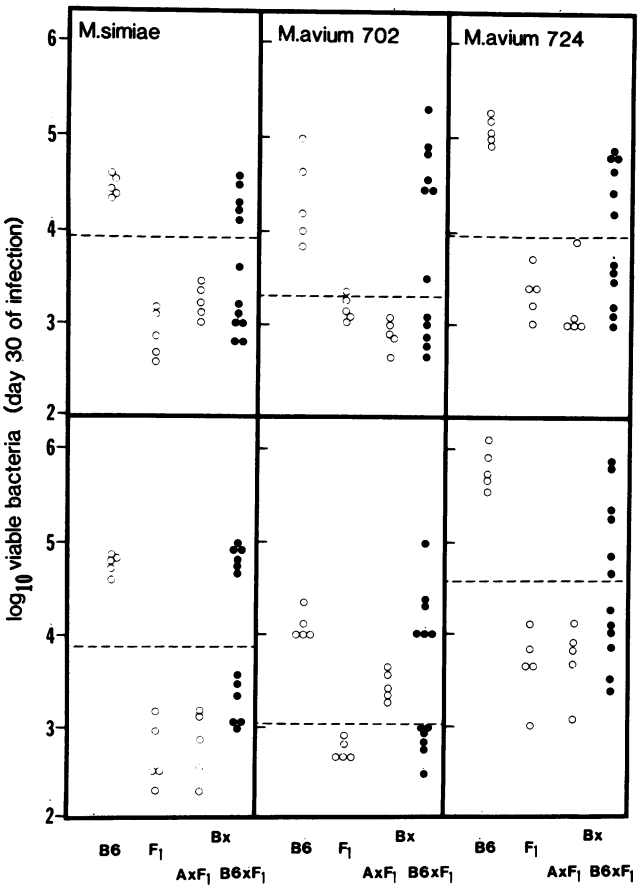

FIG. 6. Backcross analysis of the genetic control of the growth of three test organisms. Data show log numbers of bacteria harvested from the spleens (top panels) and liver (bottom panels) of C57BL/6 (B6) and A/Tru × C57BL/6 F_1 hybrids (F_1), and from A/Tru × F_1 and C57BL/6 × F_1 backcross mice. Dotted lines represent the values of two standard deviations above the mean value for the F_1 group of mice (see text).

TABLE 2. Probability of inheritance modes by maximum likelihood analysis

Backcross animals infected with:	Probability based on:		
	Single gene control	Major gene plus modifier genes	Multiple gene control
M. simiae	NS[a]	$P < 0.01$	$P < 0.01$
M. avium 702	NS	$P < 0.02$	$P < 0.05$
M. avium 724	NS	NS	$P < 0.001$

[a] NS, Not significant.

rarely aligned with those of the susceptible or resistant parents, and in at least half of the cases values tended to concentrate toward the middle range between the susceptible parent and F_1 values. In view of this, the maximum likelihood method (1, 2) was applied to the data to determine the goodness of fit of these data to hypotheses of single or multiple gene control. It was found (Table 2) that none of the backcross data were consistent with single gene control. For the *M. simiae* infection, the liver data could be explained by control by a major gene, plus modifier genes, whereas the spleen data suggested multigenic control. In the case of *M. avium* 702, the data suggested multigenic control for both the spleen and liver, although if these values were pooled a case for a major gene plus modifiers could be made ($P < 0.02$). In contrast, the growth of *M. avium* 724 in both the spleens and livers of the backcross animals favored polygene control ($P < 0.001$).

DISCUSSION

The principle finding of this study was the identification of four mycobacterial infections, *M. simiae*, *M. intracellulare*, and two strains of *M. avium*, which grew progressively in strains designated NS and poorly in strains designated NR. Subsequent formal backcross experiments and analysis by the maximum likelihood statistical method revealed the trait of resistance to these infections to be clearly under the influence of a number of host genes.

Although no linkage experiments were performed in this study, the designation of NS and NR mouse strains in this report follow identically those described elsewhere (5, 14), in which mouse strains were infected intravenously with a low dose of the Montreal vaccine preparation of *M. bovis* BCG. In those studies, genetic linkage experiments revealed the resistance trait to be strongly influenced by a locus on chromosome 1 in the mouse which was designated *Bcg* and is now believed to be identical or very closely linked to genes that control resistance to *Salmonella* species (*Ity*) and to *Leishmania* species (*Lsh*) (14).

In view of these findings, it is tempting to speculate that the *Bcg* gene may play a major role in the control of natural resistance to the four nontuberculous mycobacterial infections described here. That it is not the only locus involved, however, is in keeping with the viewpoint expressed by previous reports from this laboratory. For example, we have shown elsewhere that while 2 BCG strains (BCG Montreal and BCG Australian) grow in previously designated Bcg^s and Bcg^r inbred strains, as would be predicted by the *Bcg* gene hypothesis, 13 other BCG strains (including the widely used BCG Pasteur strain) grow equally well in all strains tested (12).

In addition, it has been shown elsewhere that while NR (in this case Bcg^r) mice are able to express some degree of bacteriostasis against BCG Montreal and BCG Australian,

this did not ablate but only slowed the subsequent emergence of acquired immunity (12). Thus it is apparent that while genes controlling natural (macrophage-mediated) mechanisms of resistance (such as *Bcg*) clearly control early events in Bcg^r strains of mice, genes controlling the various aspects of acquired immunity are expressed shortly thereafter. This conclusion was evidenced by the observation that T cells capable of expressing antituberculous resistance were already detectable in BCG Australian-infected Bcg^r mice on day 14 of the infection and, because the generation of this population of cells takes a number of days, indicated that acquired mechanisms of immunity were triggered early during the course of the infection.

The statement by other workers that natural resistance to mycobacterial infection is controlled by a single, autosomal, dominant gene may prove to be correct (5, 14). However, the control of the host response to this class of bacterial infections in toto is almost certainly multigenic, and this hypothesis is supported by the findings of the present study and by that of others (8). Furthermore, it is now clear that the statistical approaches used to confirm or deny single gene control of natural resistance to these infections themselves require careful application and usage.

To illustrate the importance of this latter point, Curtis and colleagues (1) have discussed the methodology underlying the testing of single locus control of host resistance to infection. By applying their findings to the present case, it can be argued that the method used in recent studies of host resistance to BCG (typing as susceptible groups of mice in which the mean numbers of mycobacteria recovered from the spleen 3 weeks after infection with BCG Montreal fell above a cutoff point 2 standard deviations above the mean numbers recovered from a designated resistant strain) cannot be reliably used as evidence that a single gene is operating. Curtis et al. (1) have pointed out that in attempting to prove the single gene hypothesis, a detailed prediction of the distribution of the backcross progeny can be made from the superimposition of the observed distributions of the F_1 and parental strains. If, in this analysis, the observed backcross data deviate significantly in the direction of the middle range between the F_1 and the (in this case, susceptible) parental values, it must be concluded that more than one locus influences resistance.

In this study we consistently observed a greater variance and deviation to the middle range in backcross progeny in all three infections tested. Use of a maximum likelihood method for testing the goodness of fit of these values to a single or multigene hypothesis resulted in statistical probability values that invariably pointed to the latter. In two cases, *M. simiae* and *M. avium* 702, the statistical data indicated either multigenic control or, perhaps, control by a major gene influenced by other modifier genes, whereas in the case of infection with *M. avium* 724, multigene control was strongly suggested.

The results of this analysis, therefore, are different than those of Gros et al. (5) and Goto et al. (4), who argued for single gene control of susceptibility to *M. bovis* BCG and *M. intracellulare*, respectively, following experiments in which each used cutoff points based on 95% confidence limits. It is interesting, however, that reanalysis of the BCG infection data presented by Gros et al. (5) by the maximum likelihood method also suggests control by a major gene plus modifier genes (J. Curtis; personal communication).

These findings again raise the question of what precisely determines the phenotypic expression of susceptibility or resistance to mycobacterial infections. Accumulative evidence (5, 14) suggests that expression of this trait is at the level of bone marrow-derived mononuclear phagocytes, and the bone marrow origin of these cells is confirmed by experiments in this study with radiation chimeras. Current speculation consists of the hypothesis that resistance to mycobacterial infections reflects the expression of an active mechanism of antimicrobial resistance by resident macrophages in the spleen and liver (5, 6). Against this hypothesis, however, we have previously shown (11, 12) that only certain mycobacterial strains are influenced by the resistance trait. Thus, these findings do not exclude the possibility that resistance, in fact, reflects a passive mechanism whereby particular factors (such as, for example, the nature of the intracellular milieu of Bcg^r macrophages) are not conducive to the unrestrained growth of the infecting mycobacteria.

In conclusion, evidence is presented that suggests that the control of the growth of four nontuberculous mycobacterial infections in designated susceptible and resistant mouse strains is under multigene control. These findings thus support the hypothesis that the phenotypic expression of resistance or susceptibility to intravenous mycobacterial infections is multifactorial.

ACKNOWLEDGMENTS

We are grateful to Jill Curtis for helpful discussions and for drawing our attention to the maximum likelihood statistical method. In addition, we thank Linda Auclair, Alan Roberts, and Paula Lanthier for excellent technical assistance and David Niederbuhl for providing backcross animals.

This work was supported by U.S. Public Health Service Grant AI-14065 (U.S.-Japan Cooperative Program) and HL-19774 from the National Institutes of Health.

LITERATURE CITED

1. **Curtis, J., C. F. Curtis, and N. H. Barton.** 1985. E. Skamene (ed.), Genetic control of host resistance to infection and malignancy, pp. 65–70. Alan R. Liss, Inc., New York.
2. **Elston, R. C., and J. Stewart.** 1973. The analysis of quantitative traits for simple genetic models from parental, F_1 and backcross data. Genetics **73**:695–711.
3. **Forget, A., E. Skamene, P. Gros, A. Miailhe, and R. Turcotte.** 1981. Differences in response among inbred mouse strains to infection with small doses of *Mycobacterium bovis* BCG. Infect. Immun. **32**:42–47.
4. **Goto, Y., R. M. Nakamura, H. Takahashi, and T. Tokunaga.** 1984. Genetic control of resistance to *Mycobacterium intracellulare* infection in mice. Infect. Immun. **46**:135–140.
5. **Gros, P., E. Skamene, and A. Forget.** 1981. Genetic control of natural resistance to *Mycobacterium bovis* (BCG) in mice. J. Immunol. **127**:2414–2422.
6. **Gros, P., E. Skamene, and A. Forget.** 1983. Cellular mechanisms of genetically controlled host resistance to *Mycobacterium bovis* (BCG). J. Immunol. **131**:1966–1972.
7. **James, S. L., E. Skamene, and M. S. Meltzer.** 1983. Macrophages as effector cells of protective immunity in murine schistosomiasis. V. Variation in macrophage schistosomulacidal and tumoricidal activities among mouse strains and correlation with resistance to reinfection. J. Immunol. **131**:948–953.
8. **Nickonenko, B. V., A. S. Apt, A. M. Moroz, and M. M. Averbakh.** 1985. E. Skamene (ed.), Genetic control of host resistance to infection and malignancy, pp. 291–298. Alan R. Liss, Inc., New York.
9. **Orme, I. M., and F. M. Collins.** 1983. Resistance of various strains of mycobacteria to killing by activated macrophages *in vivo*. J. Immunol. **131**:1452–1454.
10. **Orme, I. M., and F. M. Collins.** 1983. Protection against *Mycobacterium tuberculosis* infection by adoptive immunotherapy. J. Exp. Med. **158**:74–83.

11. **Orme, I. M., and F. M. Collins.** 1984. Demonstration of acquired resistance in *Bcg*^{r} inbred mouse strains infected with a low dose of BCG Montreal. Clin. Exp. Immunol. **56**:81–88.
12. **Orme, I. M., and F. M. Collins.** 1985. E. Skamene (ed.), Genetic control of host resistance to infection and malignancy, pp. 285–289. Alan R. Liss, Inc., New York.
13. **Pelletier, M., A. Forget, D. Bourassa, P. Gros, and E. Skamene.** 1982. Immunopathology of BCG infection in genetically resistant and susceptible mouse strains. J. Immunol. **129**:2179–2185.
14. **Skamene, E., P. Gros, A. Forget, P. A. L. Kongshavn, C. St. Charles, and B. A. Taylor.** 1982. Genetic regulation of resistance to intracellular pathogens. Nature (London) **297**:506–509.