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Differences in Response Among Inbred Mouse Strains to Infection with Small Doses of *Mycobacterium bovis* BCG

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Intravenous infection of six inbred mouse strains with small doses of dispersed cells of *Mycobacterium bovis* BCG (15.5×10^3 or 15.5×10^4 colony-forming units) separated them into resistant (C3H/HeCr, A/J, and DBA/2) and sensitive (B10.A, C57BL/6, and BALB/c) strains as assessed by the magnitude of bacterial multiplication in the spleens at 28 days. The two groups were more sharply separated after infection with the lower dose of BCG (15.5×10^3 colony-forming units), which allowed for true multiplication of the bacteria in the spleens of permissive hosts, expressed as the ratio of the number of BCG recovered from the spleens to the number of BCG injected. This coefficient of increase was less than 1 in resistant strains, whereas it was higher than 2.5 in sensitive strains. Significant splenomegaly developed only in mice of the sensitive strains infected with BCG when compared with uninfected controls. There was no correlation between the magnitude of the delayed-type hypersensitivity (DTH) to BCG and susceptibility to infection: DTH was absent in both the sensitive and the resistant strains when the smaller dose of BCG was used for infection. Moreover, significant DTH was detected in animals of the most sensitive (BALB/c) as well as of the most resistant (C3H/HeCr) strain when the higher dose of BCG (15.5×10^4) was used for immunization. These results document significant genetic differences in the ability of inbred mice to inhibit bacterial multiplication after infection with small dispersed doses of BCG. Resistance to BCG multiplication, in this model, does not appear to be related to the establishment of DTH.

It has been shown that hereditary variations in resistance to different microbial infections exist among various strains of mice. Resistance or susceptibility of mice to mycobacteria (10, 23, 26), corynebacteria (28), salmonella (29, 31), listeria (8, 31, 34), toxoplasma (3), leishmania (6), trypanosoma (22), coccidia (18), and rickettsia (15) has been demonstrated to be related to various genetic factors.

Several parameters of specific and nonspecific responses to BCG such as induction of delayed hypersensitivity (23, 29), in vivo release (24) or in vitro production (1) of lymphokines, emergence of suppressive cells (36, 39, 41), enhanced phagocytosis through stimulation of the reticuloendothelial system (35), induction of chronic pulmonary inflammation (2), enhancement of endotoxin sensitivity (40), and protection against unrelated intracellular bacterial infection (21, 41), against infection with multicellular helminth parasite *Schistosoma mansoni* (9), and against carcinogen-induced autochthonous tumors (38) have also been shown to be under genetic control in mice. In all of these studies, mice were generally inoculated intravenously with high doses of BCG (usually 10^7 or more colony-forming units [CFU] containing usually a certain amount of clumps).

It was found by several investigators that when such high doses of BCG were used for infection, the bacteria grew little or not at all in organs of infected animals (4, 12, 13, 20, 32, 33). On the other hand, BCG inocula injected in low doses (10^1 to 10^5 CFU) were shown to multiply in the spleen and liver (4, 19, 27). There was a positive correlation between the size of the infective inoculum and the rate of BCG multiplication when the doses between 10^1 and 10^3 CFU were injected (28). When somewhat higher doses (10^3 to 10^5 CFU) were used, an inverse relationship between the inoculum size and the rate of BCG multiplication could be observed (4, 19). Such relationships between the size of inoculum and the control of net bacterial growth were interpreted to be the effect of specific anti-BCG immunity which develops with a shorter latency period after a higher antigenic load (19). The variations in the development of specific cell-

mediated immunity thus seem to be the mechanism responsible for genetically controlled variations in viable counts of BCG in mice infected with large inocula (23). It is conceivable, however, that there could be other mechanisms controlling the resistance to BCG which operate independently from the postulated effects of specific immunity. The precedents for such a hypothesis are the recently discovered genetic systems of natural resistance to other intracellular pathogens such as salmonella, listeria, leishmania, or rickettsia (7, 15, 17, 30) in which the differences in net rate of bacterial multiplication in the preimmune phase of antibacterial response are responsible for the resulting level of resistance (9). To ascertain whether such genetic systems may also operate in the response to BCG, a model which allows for true multiplication of the bacteria, i.e., resistance to infection with low doses of dispersed bacterial cells, is being investigated. The observed strain differences in resistance to mycobacterial infection using this model are the subject of this report.

MATERIALS AND METHODS

Animals. Male mice, weighing 18 to 20 g, were housed in plastic cages and were fed Purina laboratory chow with water ad libitum. Inbred BALB/c, C3H/HeCr, C57BL/6, and DBA/2 mice were obtained from Canadian Breeding Farm, Montreal. A/J mice were purchased from Jackson Laboratories, Bar Harbor, Maine, and B10.A/SgSn (B10.A) mice were bred in our laboratory from breeding pairs originally obtained from Jackson Laboratories.

Preparation of dispersed low doses of BCG. *Mycobacterium bovis*, strain BCG Montreal, obtained form the BCG laboratory of the Institut Armand-Frappier, Laval, Quebec, Canada, was grown as a pellicle on Sauton medium at 37°C for 7 days. The bacillary mass was then ground with stainless-steel balls. The BCG suspension thus obtained was diluted (60 mg/ml) in saline. This BCG preparation was subcultured twice for 7 days in Dubos Tween liquid medium. The second subculture was filtered through a membrane filter (pore size, 3 μm) to eliminate the small bacterial clumps; the dispersed suspension of bacilli thus obtained (5) was used to infect mice. The viable cell count was determined by plating serial dilutions of the dispersed bacterial suspension in triplicate onto Dubos solid medium without Tween followed by an incubation period of 18 days at 37°C.

Infection of mice. Groups of 8 to 10 mice of the different strains were inoculated into the caudal vein with 0.25 ml of one of the two doses of dispersed BCG suspensions (15.5×10^3 or 15.5×10^4 per mouse). After intravenous inoculation with such small doses of BCG, the bacilli multiply in organs, particularly in the spleen, reaching a peak 4 to 5 weeks later (4, 19, 28). Thus, 28 days after infection, the mice were weighed, ether anesthetized, and exsanguinated, and sera were collected. The degree of infection was assessed by the determination of spleen index and of spleen CFU of BCG.

Determination of spleen index. Spleens were removed aseptically, blotted dry, freed of macroscopic blood clots, and weighed. The spleen index was calculated as follows (11):

$$\text{spleen index} = \sqrt{\frac{\text{spleen weight} \times 100}{\text{whole body weight}}}$$

Groups of uninfected mice of the different strains, kept in the same conditions, were sacrificed on the same day as the test animals, and the spleen index was determined to compare with that of the experimental animals.

Determination of spleen CFU. After the spleens were weighed, they were grounded in a small sterile mortar with 90-mesh alundum in 5 ml of saline containing 0.5% bovine albumin, fraction V (Sigma Chemical Co., St. Louis, Mo.). The suspension obtained was further diluted 1:10, and culture counts for BCG were performed according to the technique previously described (14).

Assay of delayed-type hypersensitivity (DTH): footpad test. Twenty-four hours before the mice were sacrificed to assess the BCG infection, three of each group were injected in one hind footpad with 0.03 ml of saline containing 5 μg of purified protein derivative (PPD; Statens Seruminstitut, Copenhagen, Denmark). The increase in footpad thickness was measured at 24 h with dial gauge calipers. An increase of more than 0.18 mm in footpad thickness was significant at the 1% level (11).

Statistical analysis. Differences among groups were evaluated statistically by the Mann-Whitney *U* test for nonparametric data.

RESULTS

Bacterial multiplication in the spleens of various mouse strains after infection. Six inbred mouse strains that were tested fell into two sharply separated groups after intravenous injection of 15.5×10^3 CFU of BCG (Fig. 1A). For the first group of strains classified as resistant (C3H/He, A/J, and DBA/2), the mean numbers of CFU recovered from the spleens 4 weeks after infection were 7×10^2, 2.3×10^3, and 4×10^3, respectively, whereas in the second group of strains classified as sensitive (B10.A, C57BL/6, and BALB/c), the mean numbers of CFU were at least 10 times higher: 4×10^4, 4.3×10^4, and 4.5×10^4, respectively. After administration of a higher dose, 15.5×10^4 CFU of BCG (Fig. 1B), the two groups were less well distinguished: the mean number of CFU recovered from the spleens of resistant strains C3H/He and A/J was around 10 times less than that recovered from spleens of sensitive strains B10.A, C57BL/6, and BALB/c, whereas the DBA/2 strain was intermediate in its resistance, with the mean number of CFU 2.5 to 4 times less than that of the sensitive group.

When the coefficient of increase in BCG numbers expressing the multiplication of BCG in the

spleens was determined, it sharply separated the resistant and sensitive strains (Table 1). After injection of 15.5×10^3 BCG, the value of the coefficient of increase was less than 1 for the resistant strains C3H/He, A/J, and DBA/2, whereas it was higher than 2.5 for the sensitive strains B10.A, C57BL/6, and BALB/c. After injection of the larger dose of BCG (15.5×10^4), the value of the coefficient of increase was less than 1 for the six strains. However, the coefficients of the C3H/He and A/J mice were 10 times lower than those of the of B10.A, C57BL/6, and BALB/c mice. The value for the DBA/2 strain was intermediate.

Splenomegaly response. In normal mice, some variations have been noted in the whole body weight as well as in the spleen weight of different strains of similar age. In BCG-infected mice, changes also occur in total body weight and in the spleen (11). Hence, in our studies the variations in spleen weight were expressed as a root mean organ index (11) and were compared with that of uninfected mice of the different strains (Table 2). After infection with 15.5×10^3 BCG, the six strains were clearly separated into the two defined groups found when the bacterial multiplication in the spleen was assessed at the 28th day. There was no significant difference between the root mean splenic index of the three resistant strains (C3H/He, A/J, and DBA/2) in comparison with the corresponding uninjected

TABLE 1. *Multiplication of BCG in the spleens of mouse strains after intravenous infection with low doses of dispersed BCG*

Mouse strain	*H-2* haplotype	Coefficient of increase[a]	
		15.5×10^{3}[b]	15.5×10^4
C3H/HeCr	*k*	0.04	0.04
A/J	*a*	0.15	0.02
DBA/2	*d*	0.27	0.13
B10.A	*a*	2.53	0.32
C57BL/6	*b*	2.75	0.55
BALB/c	*d*	2.90	0.38

[a] Expressed as mean number of CFU of BCG recovered from the spleens at 4 weeks after infection to the number of CFU of BCG injected intravenously.
[b] BCG injected per mouse.

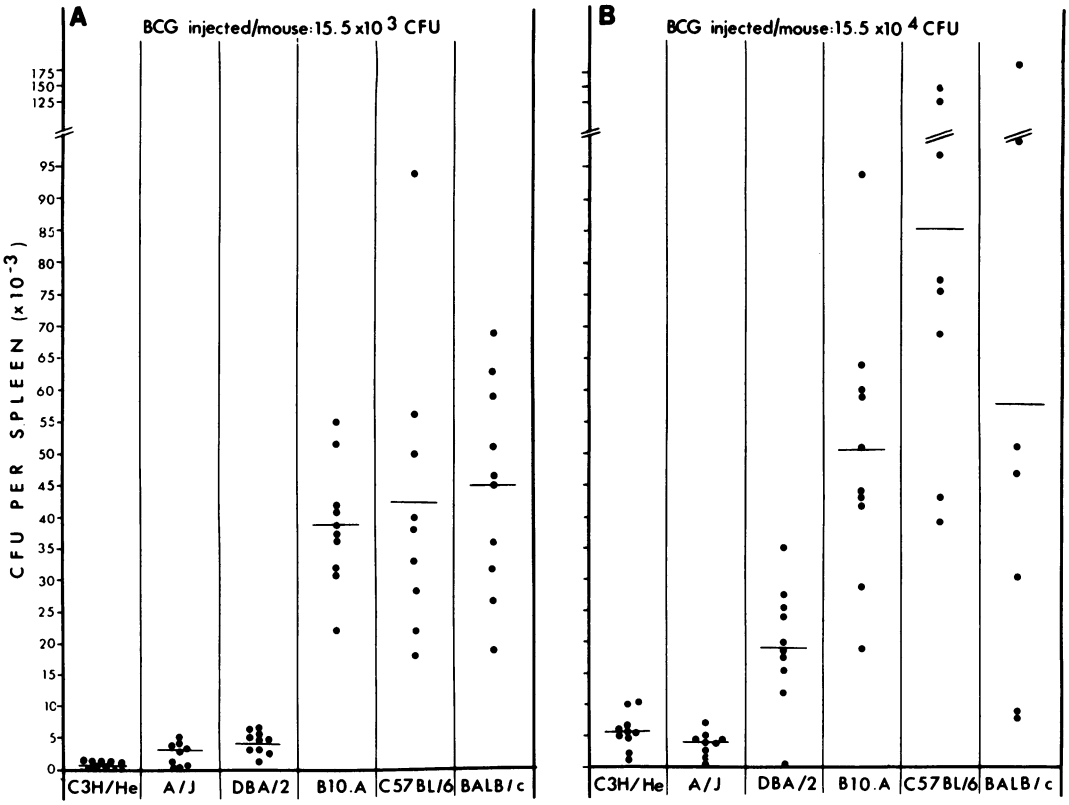

FIG. 1. *Distribution of individual numbers of CFU of BCG recovered in spleens of various strains of mice intravenously infected 28 days before with dispersed suspension of BCG. Symbol:* (——) *arithmetic mean.*

TABLE 2. *Spleen response of various inbred mice to infection with small doses of dispersed BCG*

Mouse strain	Mean spleen index values[a]				
	Control noninfected mice	15.5×10^3[b]	P[c]	15.5×10^4	P
C3H/HeCr	0.66 ± 0.05[d]	0.68 ± 0.09	NS	0.72 ± 0.06	NS
A/J	0.55 ± 0.03	0.60 ± 0.07	NS	0.68 ± 0.06	0.01
DBA/2	0.61 ± 0.01	0.61 ± 0.04	NS	0.67 ± 0.07	0.05
B10.A	0.53 ± 0.01	0.73 ± 0.03	0.001	0.86 ± 0.05	0.001
C57BL/6	0.70 ± 0.04	0.83 ± 0.02	0.001	1.02 ± 0.10	0.001
BALB/c	0.70 ± 0.06	0.84 ± 0.05	0.01	0.93 ± 0.05	0.001

[a] Expressed as shown in text; determined at 4 weeks after infection.
[b] BCG injected per mouse.
[c] Compared with uninfected controls; for each BCG dose, resistant strains versus sensitive strains, $P < 0.001$. NS, Not significant.
[d] ± Standard deviation.

strains, whereas the spleen indices of the three sensitive strains (B10.A, C57BL/6, and BALB/c) were higher ($P < 0.01$) than those of the same corresponding uninjected strains.

Footpad DTH reaction to PPD. The DTH response to PPD was assessed by a footpad technique at 27 days after infection with both doses of BCG. Footpad swelling was not observed in mice of any test strain injected with the low dose of BCG (Table 3). After infection with the larger dose (15.5×10^4), only C3H/He and BALB/c mice showed a positive footpad reaction. It should be noted that the BALB/c mice that gave a strong DTH reaction were classified as sensitive (a coefficient of bacillary multiplication higher than 2), whereas the C3H mice that also give a strong DTH reaction were classified as resistant to BCG growth.

TABLE 3. *Footpad reaction at 24 h after PPD injection in different mouse strains infected with low doses of dispersed BCG*

Mouse strain	Increase in footpad thickness (mm)[a]	
	15.5×10^3[b]	15.5×10^4
C3H/HeCr	0.10 ± 0.04	0.25 ± 0.04
A/J	0.08 ± 0.02	0.02 ± 0.003
DBA/2	0.13 ± 0.01	0.13 ± 0.005
B10.A	0.12 ± 0.05	0.11 ± 0.03
C57BL/6	0.15 ± 0.04	0.12 ± 0.03
BALB/c	0.14 ± 0.05	0.42 ± 0.05

[a] Each value is the mean of the increase in thickness of footpads of three mice ± standard error. An increase of more than 0.18 mm is significant at the 1% level.
[b] BCG injected per mouse.

DISCUSSION

In our experiments, infection of six inbred mouse strains with small doses of dispersed BCG cells separated them into resistant (C3H/He, A/J, and DBA/2) and sensitive (B10.A, C57BL/6, and BALB/c) strains as assessed by the determination of the bacterial multiplication in the spleens at 28 days and by the development of splenomegaly. The fact that mouse strains investigated by us could be separated into two distinct, nonoverlapping groups with respect to their genetic resistance to BCG (at least when the low dose was used for infection) raises the possibility that this trait is under the control of a small number of genes or even of a single polymorphic gene, similar to the situation in other bacterial and parasitic systems (7, 8, 15, 30). A formal genetic analysis on segregating hybrid and backcross populations derived from the resistant and sensitive progenitors as well as examination of BXD and BXH recombinant inbred strains (37) for resistance and sensitivity to BCG should be informative with respect to the mode of inheritance of this trait.

It seems that genetic control of the susceptibility or resistance of mice to infection with small inocula of BCG was not linked to the *H-2* locus. For example, the $H\text{-}2^a$ A/J and B10.A strains were resistant and sensitive, respectively, and the $H\text{-}2^d$ DBA/2 and BALB/c strains were resistant and sensitive, respectively, to this infection. The definite statement about the *H-2* noninvolvement in this genetic trait could, however, only be made after formal examination in congenic resistant strains. It should be noted that genetic resistance to infection with higher doses of BCG is also controlled by a gene(s) that maps away from *H-2* (23), although the distribution of resistant and sensitive strains is quite different from that described in this study, suggesting that different mechanisms are involved.

There was no correlation between the magnitude of DTH to BCG and the susceptibility to infection. At the time of sacrifice, DTH was not observed in either the sensitive or the resistant strains when the smaller dose of BCG (15.5×10^3) was used for infection. Moreover, strain BALB/c and strain C3H/He, the most sensitive and the most resistant strains, respectively, exhibited significant DTH when the higher dose of BCG (15.5×10^4) was used for immunization.

These results differ from those of Nakamura and Tokunaga (23): using a large infecting dose of BCG (2×10^7), they found the correlation between (i) the degree of resistance as assessed by the number of surviving bacteria in the spleens, (ii) the splenic index, and (iii) the degree of specific immunity as detected by the DTH reaction to PPD in their resistant (SWM/Ms) and sensitive (C3H/He) strains. They concluded that the resistance to BCG (decrease in the CFU numbers) in SWM/Ms mice was due to the establishment of cell-mediated immunity to BCG. Similarly, Collins et al. (11) concluded that splenomegaly in mice infected with 2×10^6 CFU of BCG (Montreal strain) corresponded to the period of maximal immunity being expressed by this organ. In the present study, however, an increase of the spleen index after infection with a low BCG dose was observed in sensitive strains only. With the larger dose of BCG used (15×10^4), increases in the spleen index of the resistant strains were significantly lower than those of sensitive strains ($P < 0.001$). In other words, splenomegaly corresponded to BCG susceptibility rather than to resistance and was probably a reflection of the severity of infection rather than of the immunity to infection. The discrepancy among the interpretations of Nakamura and Tokunaga, Collins et al., and ourselves could certainly be attributed to differences in the sizes of the infective inocula ($\leq 10^4$ versus $>10^6$ CFU) and suggests that mechanisms of resistance are different in these two situations. The fact that the size of inoculum is critical and must be considered in determining genetic susceptibility or resistance has been noted in another infection as well: Araujo et al. (3), having demonstrated differences in susceptibility to *Toxoplasma gondii* infection among inbred strains of mice, observed that whereas BALB/c was the least susceptible strain to a low dose of toxoplasma (5×10^3), it was the most susceptible when a larger inoculum (10^5) was used.

The inverse relationship between the dose of inoculum and the growth of BCG in the spleen that we obtained agrees with that noted by other investigators (4, 19) when intermediate doses of BCG (about 10^3 and 10^4) were used to infect mice intravenously. Lefford (19) suggested that this inoculum effect was related to a progressive reduction of the latent period before the induction of immunity (as assessed by the resistance to *Listeria monocytogenes*). If one assumes that a positive footpad test to BCG is a probe of the establishment of cell-mediated immunity, at least at a local level (25), it seems unlikely that the conclusions of Lefford are applicable to our observations: the DTH reaction to BCG was observed in the highly resistant C3H/He as well as in the highly sensitive BALB/c strains. On the other hand, other strains (both resistant and sensitive ones) did not exhibit a DTH reaction when tested at 28 days after infection. Development of DTH to BCG could, therefore, be dissociated from resistance in this model.

In conclusion, this study reports a new observation, namely, that inbred mouse strains differ markedly in their ability to inhibit multiplication of BCG. This phenomenon was most clearly demonstrable with a low infective dose of BCG (15×10^3 CFU), so low that no reaction to tuberculin in the footpad test was demonstrable at the time when the degree of resistance or sensitivity was determined. This phenomenon now requires more detailed analysis, both at the genetic level and with respect to kinetic and dose-response studies dealing with the phenotypic expression of the described trait. We can only postulate at the moment that genetic variations at the level of natural (nonimmune or noninduced) resistance or at the level of suppressor activity of specific anti-BCG responses are involved.

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LITERATURE CITED

1. **Adelman, N., S. Cohen, and T. Yoshida.** 1978. Strain variations in murine MIF production. J. Immunol. **121:** 209–212.
2. **Allen, E. M., V. L. Moore, and J. O. Stevens.** 1977. Strain variation in BCG-induced chronic pulmonary inflammation in mice. I. Basic model and possible genetic control by non H-2 genes. J. Immunol. **119:**343–347.
3. **Araujo, F. G., D. M. Williams, F. C. Grumet, and J. S. Remington.** 1976. Strain-dependent differences in murine susceptibility to toxoplasma. Infect. Immun. **13:** 1528–1530.
4. **Benoit, J. C., and M. Panisset.** 1963. Survie et multiplication du BCG et du bacille tuberculeux chez la souris. IV. Survie et multiplication de souches-filles du BCG en fonction du temps et de la dose. Acta Tuberc. Pneumol. Scand. **43:**125–136.
5. **Benoit, J. C., M. Quevillon, and M. Panisset.** 1963. Obtention par filtration de bacilles isolés, de suspensions contenant des agrégats bacillaires. Mise au point d'une méthode quantitative. Rev. Can. Biol. **22:**437–445.
6. **Bradley, D. J., and J. Kirkley.** 1977. Regulation of Leishmania populations within the host. I. The variable course of *Leishmania donovani* infections in mice. Clin. Exp. Immunol. **30:**119–129.
7. **Bradley, D. J., B. A. Taylor, J. Blackwell, E. P. Evans, and J. Freeman.** 1979. Regulation of Leishmania populations within the host. III. Mapping of the locus controlling susceptibility to visceral leishmaniasis in the mouse. Clin. Exp. Immunol. **37:**7–14.
8. **Cheers, C., and I. F. C. McKenzie.** 1978. Resistance and susceptibility of mice to bacterial infection: genetics of listeriosis. Infect. Immun. **19:**775–762.
9. **Civil, R. H., and A. A. F. Mahmond.** 1978. Genetic

differences in BCG-induced resistance to Schistosoma mansoni are not controlled by genes within the major histocompatibility complex of the mouse. J. Immunol. **120**:1070–1072.

10. **Closs, O., and O. A. Hangen.** 1973. Experimental murine leprosy. I. Clinical and histological evidence for varying susceptibility of mice infection with *Mycobacterium lepraemurium*. Acta Pathol. Microbiol. Scand. Sect. A **81**:401–410.
11. **Collins, F. M., C. C. Congdon, and N. E. Morrison.** 1975. Growth of *Mycobacterium bovis* (BCG) in T lymphocyte-depleted mice. Infect. Immun. **11**:57–64.
12. **Collins, F. M., and G. B. MacKaness.** 1970. The relationship of delayed hypersensitivity to acquired antituberculous immunity. I. Tuberculin sensitivity and resistance to re-infection in BCG-vaccinated mice. Cell. Immunol. **1**:253–265.
13. **Collins, F. M., and T. E. Miller.** 1969. Growth of drug-resistant strain of *Mycobacterium bovis* (BCG) in normal and immunized mice. J. Infect. Dis. **120**:517–533.
14. **Forget, A., R. Turcotte, J. C. Benoit, and A. G. Borduas.** 1978. Enhancing effect of passive immunization with mycobacterial antibodies on humoral and cellular immunity in BCG-infected mice. Ann. Immunol. (Paris) **129C**:255–265.
15. **Groves, M. G., and J. V. Osterman.** 1978. Host defenses in experimental scrub typhus: genetics of natural resistance to infection. Infect. Immun. **19**:583–588.
16. **Holt, P. G., P. J. Fimmel, L. M. Roberts, and D. Koats.** 1977. Modification by soluble antigen of the immune response to mycobacterial infection. Infect. Immun. **16**: 904–909.
17. **Hormaeche, C. E.** 1979. Natural resistance to *Salmonella typhimurium* in different inbred mouse strains. Immunology **37**:311–327.
18. **Klesius, P. H., and S. E. Hinds.** 1979. Strain-dependent differences in murine susceptibility to coccidia. Infect. Immun. **26**:1111–1115.
19. **Lefford, M. J.** 1970. The effect of inoculum size on the immune response to BCG infection in mice. Immunology **21**:369–381.
20. **MacKaness, G. B., N. Smith, and A. W. Wells.** 1954. The growth of intracellular tubercle bacilli in relation to their virulence. Am. Rev. Tuberc. Pneumol. **69**:479–494.
21. **Medina, S., S. I. Vas, and H. O. Robson.** 1975. Effect of nonspecific stimulation on the defense mechanisms of inbred mice. J. Immunol. **114**:1720–1725.
22. **Morrison, W. I., G. E. Roelants, K. S. Mayor-Withey, and M. Murray.** 1978. Susceptibility of inbred strains of mice to *Trypanosoma congolense*: correlation with changes in spleen lymphocyte populations. Clin. Exp. Immunol. **32**:25–40.
23. **Nakamura, R. M., and T. Tokunaga.** 1979. Strain difference of delayed-type hypersensitivity to BCG and its genetic control in mice. Infect. Immun. **22**:657–664.
24. **Neta, R., and S. B. Salvin.** 1980. In vivo release of lymphokines in different strains of mice. Cell. Immunol. **51**:173–178.
25. **Patel, P. J.** 1980. Expression of antibacterial resistance at the site of a delayed hypersensitivity reaction. Infect. Immun. **29**:59–65.
26. **Pierce, C., R. J. Dubos, and G. Middlebrook.** 1947. Infection of mice with mammalian tubercle bacilli grown in tween-albumin liquid medium. J. Exp. Med. **86**:159–173.
27. **Pierce, C. H., R. J. Dubos, and W. B. Schaefer.** 1953. Multiplication and survival of tubercle bacilli in the organs of mice. J. Exp. Med. **97**:189–205.
28. **Pierce-Chase, C. H., R. M. Fauve, and R. Dubos.** 1964. Corynebacterial pseudotuberculosis in mice. I. Comparative susceptibility of mouse strains to experimental infection with *Corynebacterium kutscheri*. J. Exp. Med. **120**:267–281.
29. **Plant, J., and A. A. Glynn.** 1974. Natural resistance to Salmonella infection, delayed hypersensitivity and Ir genes in different strains of mice. Nature (London) **248**: 345–347.
30. **Plant, J., and A. A. Glynn.** 1979. Locating salmonella resistance gene on mouse chromosome. Clin. Exp. Immunol. **37**:1–6.
31. **Robson, H. G., and S. I. Vas.** 1972. Resistance of inbred mice to *Salmonella typhimurium*. J. Infect. Dis. **126**: 378–386.
32. **Sever, J. L., and G. P. Youmans.** 1957. The enumeration of nonpathogenic viable tubercle bacilli from the organs of mice. Ann. Rev. Tuberc. **75**:280–294.
33. **Sher, N. A., S. I. Chaparas, J. Pearson, and M. Chirigos.** 1973. Virulence of six strains of *Mycobacterium bovis* (BCG) in mice. Infect. Immun. **8**:736–742.
34. **Skamene, E., P. A. L. Kongshavn, and D. H. Sachs.** 1979. Resistance to *Listeria monocytogenes* in mice is genetically controlled by genes which are not linked to the H-2 complex. J. Infect. Dis. **139**:228–231.
35. **Stiffel, C., D. Mouton, Y. Bouthillier, C. Detreusefond, and G. Biozzi.** 1970. Réponse du SRE au *Mycobacterium tuberculosis* (BCG) et au *Corynebacterium parvum* chez des souris de différentes lignées. RES J. Reticuloendothel. Soc. **7**:280–293.
36. **Sultzer, B. M.** 1978. Infection with bacillus Calmette-Guerin activates murine thymus-independent (B) lymphocytes. J. Immunol. **120**:254–261.
37. **Taylor, B. A.** 1978. Recombinant inbred strains: use in gene mapping, p. 423–428. *In* H. Morse (ed.), Origins of inbred mice. Academic Press, Inc., New York.
38. **Tokunaga, T., S. Yamamoto, R. M. Nakamura, A. Kurosawa, and T. Murohashi.** 1978. Mouse-strain difference in immunoprophylactic and immunotherapeutic effects of BCG on carcinogen-induced autochthonous tumors. Jpn. J. Med. Sci. Biol. **31**:143–154.
39. **Turcotte, R., L. Lafleur, and M. Labreche.** 1978. Opposite effects of BCG on spleen and lymph node cells: lymphocyte proliferation and immunoglobulin synthesis. Infect. Immun. **21**:696–704.
40. **Vogel, S. V., R. N. Moore, J. D. Sipe, and D. L. Rosenstreich.** 1980. BCG-induced enhancement of endotoxin sensitivity in C3H/HeJ mice. J. Immunol. **124**:2004–2009.
41. **Youmans, G. P., A. S. Youmans, and K. Kanai.** 1959. The difference in response of four strains of mice to immunization against tuberculous infection. Am. Rev. Respir. Dis. **80**:753–756.