Susceptibility to Tuberculosis: Clues from Studies with Inbred and Outbred New Zealand White Rabbits

Susan E. Dorman,1 Christine L. Hatem,1 Sandeep Tyagi,1 Katherine Aird,1 Javier Lopez-Molina,1 M. Louise M. Pitt,2 Bernard C. Zook,3 Arthur M. Dannenberg, Jr.,4,5,6,7 William R. Bishai,1,5,8 and Yukari C. Manabe1,5,8,*

Departments of Medicine1 and Pathology,2 School of Medicine, and Departments of Environmental Health Sciences,5 Molecular Microbiology and Immunology,6 International Health,3 and Epidemiology,2 Bloomberg School of Public Health, The Johns Hopkins University, Baltimore, and Department of Aerobiology and Product Evaluation, U.S. Army Medical Research Institute of Infectious Diseases, Fort Detrick, Frederick,7 Maryland, and Department of Pathology, George Washington University Medical Center, Washington, D.C.8

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The rabbit model of tuberculosis (TB) is important because rabbits develop a disease that is similar to TB in humans, namely, granulomas with caseous necrosis, liquefaction, and cavities. We describe here a comparison of inbred and outbred New Zealand White rabbits infected by aerosol with either Mycobacterium tuberculosis Erdman or H37Rv strain. Five weeks after infection with either bacillary strain, the inbred rabbits had significantly larger pulmonary tubercles than did outbred rabbits (2.7 versus 1.4 mm in diameter; P < 0.01). After infection with H37Rv, the inbred rabbits had significantly more pulmonary tubercles than did the outbred rabbits (98 ± 12 versus 33 ± 13; P < 0.01), with more mycobacterial CFU per tubercle (809 ± 210 versus 215 ± 115; P = 0.027) (means ± standard errors of the means). Compared with histologic examination of lung granulomas from outbred rabbits, histologic examination of those from inbred rabbits showed more caseous necrosis, more visible bacilli, and fewer mature epitheloid cells. The delayed-type hypersensitivity (DTH) responses to intradermal tuberculin were significantly lower, and peritoneal macrophages from uninfected inbred rabbits produced significantly less tumor necrosis factor alpha after lipopolysaccharide (LPS) stimulation in vitro than those from the outbred rabbits (2,413 ± 1,154 versus 8,879 ± 966 pg/ml). We conclude that these inbred rabbits were more susceptible to TB than their outbred counterparts and had an impaired ability to contain disease, resulting in more grossly visible tubercles that were larger than those observed in outbred rabbits. Preliminary evidence is presented for a cell-mediated immune defect with lower DTH responses and macrophages that have a decreased ability to respond to in vitro stimulation with LPS or M. tuberculosis infection.

Mycobacterium tuberculosis infects one-third of the world’s population, yet only a minority of infected persons fail to control the infection and develop clinical tuberculosis (TB) disease. Human immunodeficiency virus infection and other disorders of cell-mediated immunity are risk factors for development of TB disease after infection. Most TB patients lack identifiable risk factors for progression to TB, however. Several lines of evidence support a role for genetic factors in human susceptibility to TB. These include higher TB disease concordance rates in monozygotic twins than in dizygotic twins (7, 14, 31) and different responses (ranging from no disease to death) among children who have inadvertently ingested virulent M. tuberculosis instead of BCG (2, 27). Population-based studies of genetic determinants of susceptibility have identified several polymorphisms that may be associated with an increased risk for TB, although many have been population specific and may not be generalizable (5, 6, 29, 30, 35).

The murine model of experimental M. tuberculosis infection has been used extensively to study TB pathogenesis and host determinants of TB susceptibility (17). Mice are relatively inexpensive, and immunologic reagents are plentiful. Different inbred strains of mice are often used to model genetic susceptibility to TB, although all mice infected with virulent M. tuberculosis eventually die of a progressive granulomatous disease. The rabbit model of TB is attractive because of its similarities to human TB. Outbred rabbits are known to be relatively resistant to intravenous and aerosol infection with M. tuberculosis and usually recover from infection in 4 to 6 months (13, 18, 21), just as most humans arrest their infection. In addition, after experimental aerosol infection with M. tuberculosis, rabbits develop pulmonary granulomas and occasionally cavities that are histologically similar to those found in humans. In the mid-20th century, Lurie and colleagues inbred strains of rabbits with different susceptibilities to experimental infection with virulent tubercle bacilli (19, 21). These rabbits became infertile and no longer exist. We describe here an inbred strain of New Zealand White (NZW) rabbits that is uniformly more susceptible than outbred NZW rabbits to infection with M. tuberculosis.

MATERIALS AND METHODS

Microorganisms. Cultures for aerosol infection were prepared by thawing frozen stock aliquots of M. tuberculosis Erdman strain (a kind gift of the late
Frank M. Collins from the Trudeau Collection) and H37Rv luciferase (a kind gift of Clifton E. Barry III). Bacilli were grown to log phase in Middlebrook 7H9 medium supplemented with oleic acid-albumin-dextrose-catalase enrichment medium (OADC; Becton Dickinson, Sparks, Md.) and 0.05% Tween 80. Clumps were allowed to settle for 2 to 3 h and were then suspended in a 10% dilution of oleic albumin complex (Becton Dickinson Bioscience, Sparks, Md.) in 0.9% NaCl.

*M. tuberculosis* Erdman, H37Rv luciferase, and CDC1551 were each used to infect rabbit peritoneal macrophages. Bacteria were grown on 7H10 agar supplemented with OADC. On the day of infection, log-phase bacteria in colonies were scraped from the plate and placed in a vial containing Hanks’ balanced salt solution (HBSS) and 0.1-mm-diameter zirconia-silica beads (BioSpec Products, Bartlesville, Okla.). Vials were shaken by hand for 30 s and then centrifuged at 200 × g for 2 min. Supernatants were withdrawn, adjusted to an optical density of 0.16, and then diluted with an equal volume of complete RPMI 1640 plus 10% fetal bovine serum.

Animals and infection. Pathogen-free NZW rabbits (2.5 to 3 kg) were used for more than 20 generations by the late J. Thorbecke, New York University, and available from Covance Research Products, Inc. (Denver, Pa.), and market NZW rabbits (Covance Research Products, Inc.) were maintained in standard cages under biosafety-level-3 conditions and were fed commercial rabbit chow and water ad libitum. All animals were maintained in accordance with protocols approved by the Institutional Animal Care and Use Committee of Johns Hopkins University, George Washington University, and the U.S. Army Medical Research Institute of Infectious Diseases. Phlebotomy and aerosol exposure were performed as previously described (8). Four weeks after infection, a 1:30 dilution of 4× Old Tuberculin concentrate (Wyeth Lederle, Pearl River, N.Y.) was injected intradermally, and 2 days later, the resulting skin reactions were measured with calipers. Old Tuberculin is used because standard purified protein derivative does not elicit a measurable skin test response in commercial rabbits. Delayed-type hypersensitivity (DTH) responses were quantitated by measuring the double-skin thickness of the indurated skin minus the double-skin thickness of normal unaffected skin and then multiplying the difference by the width and length of the indurated area and a factor of 0.52 (10). At 5 weeks after infection, the rabbits were euthanized with an intravenous pentobarbital preparation (Euthasol; NLS Animal Health, Baltimore, Md.). The grossly visible pulmonary tubercles were counted, and their diameters were measured (11, 21). Spleen, hilar lymph nodes, and lung lobes were homogenized, and aliquots were plated on 7H10 agar supplemented with OADC. CFU were enumerated at day 21. Lung histopathology was assessed independently by two pathologists (A. M. Dannenberg, Jr., and B. C. Zook). Zook scored the slides with rabbit identifiers removed. Tissue was fixed with formalin and then embedded in paraffin. Standard histologic sections were cut and then stained with either hematoxylin and eosin or an acid-fast stain. Tissue sections were evaluated for the mean area of granulomas, the percentage of granulomas with caseous necrosis, the mean area of caseous necrosis, the percentage of mature versus immature epithelioid macrophages, and the mean number of acid-fast bacilli. The degree of neutrophil infiltration, lymphocyte and plasma cell infiltration, fibroblast accumulation, and perigranulomatous pneumonitis were graded on a scale from 1 to 4 (11): 1+, slight response; 2+, moderate response; 3+, marked response; 4+, severe response.

Elicitation and isolation of peritoneal macrophages. Peritoneal macrophages were elicited from uninfected adult rabbits by intraperitoneal injection of 200 ml of sterile Brewer’s thioglycolate medium (Becton Dickinson) freshly prepared according to the manufacturer’s instructions. After 72 h, the rabbits were euthanized as described above. The peritoneal cavity was opened, and 250 ml of cold, sterile HBSS was instilled, allowed to remain for 1 min, and collected by aspiration. The aspirates were filtered through sterile gauze to remove debris and then centrifuged at 10 min at 750 × g at 4°C to pellet the cells. Peritoneal macrophages were purified by centrifugation through a density gradient (Lympohyte-Mammal; Cedarlane Labs, Hornby, Ontario, Canada) and washed with HBSS. The red blood cells were lysed with ACK lysis buffer (BioSource International, Camarillo, Calif.). The macrophages were washed three times with HBSS, resuspended in complete RPMI 1640 (Gibco, Carlsbad, Calif.) containing 10% fetal bovine serum (Gibco), and distributed onto tissue culture plates (Corning Costar, Acton, Mass.) at a density of 10⁵ cells/ml. After overnight incubation at 37°C with 5% CO₂, nonadherent cells were removed by aspiration and the adherent cells were washed twice with HBSS. The adherent cells were collected using a cell scraper, washed, counted, and resuspended in complete RPMI 1640 containing 10% fetal bovine serum at a density of 10⁶ cells/ml. 1-ml aliquots were placed in wells of 24-well Falcon tissue culture plates (Becton Dickinson Labware, Lincoln Park, N.J.) and incubated overnight prior to stimulation or infection.

Infection and stimulation of peritoneal macrophages. Aliquots (500 µl) of mycobacterial inocula or media were added to the wells containing monolayers of adherent peritoneal macrophages and incubated at 37°C for 2 h (multiplicity of infection, 5 viable bacilli per macrophage). Macrophages were then washed three times using HBSS, and 1 ml of complete RPMI 1640 containing 10% fetal bovine serum was added to each well. *Escherichia coli* lipopolysaccharide (LPS) (200 ng/ml; Sigma, St. Louis, Mo.) was added to selected uninfected wells. At 24 and 48 h after infection, supernatants from selected wells were removed and frozen at −70°C. Both at 2 h and 24 h after infection, the extracellular bacilli were removed by washing, and the adherent cells were lysed by addition of phosphate-buffered saline (PBS) containing 0.016% digitonin (Sigma) and 0.25% Tween 80 (Sigma) followed by incubation for 10 min at 37°C. The lysates were plated on solid Middlebrook 7H10-OADC medium, and the bacterial CFU were enumerated after 21 days.

Cytokine detection. The cytokine tumor necrosis factor alpha (TNF-α) was detected in cell culture supernatants using enzyme-linked immunosorbent assays. Flat-bottom 96-well plates (Nalge Nunc International, Rochester, N.Y.) were coated with anti-rabbit TNF-α polyclonal antibody (8 µg/ml; Becton Dickinson, San Diego, Calif.). Cell culture supernatants or TNF-α standards (Becton Dickinson) were added and incubated for 2 h, followed by three washes with 0.05% Tween 20 in PBS. Biotinylated anti-TNF-α (1 µg/ml; Becton Dickinson) was added and incubated for 2 h, followed by three washes with 0.05% Tween 20 in PBS. Avidin-horseradish peroxidase conjugate (Becton Dickinson) was then added, the plates were incubated for 30 min, and ABTS substrate solution (Kirkegaard & Perry Laboratories, Gaithersburg, Md.) was added. Absorbance at 405 nm was determined for each well, and cytokine concentrations were determined by linear regression analysis. All incubations were at room temperature, and samples were analyzed in duplicate.

<table>
<thead>
<tr>
<th>Rabbit group</th>
<th>No. of rabbits</th>
<th>No. of tubercles (mean ± SE)</th>
<th>Avg diam (mean ± SE) (mm)</th>
<th>OT_TA (mean ± SE) (mm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inbred</td>
<td>6</td>
<td>351 ± 41</td>
<td>3.80 ± 0.30</td>
<td>471 ± 68</td>
</tr>
<tr>
<td>Outbred</td>
<td>6</td>
<td>305 ± 107</td>
<td>2.13 ± 0.22</td>
<td>1,342 ± 488</td>
</tr>
</tbody>
</table>

P 0.170 0.044 0.055

a OT, 2-day reaction to the intradermal injection of Old Tuberculin.
RESULTS

Phenotype. In appearance, the inbred rabbits had several features that distinguished them from outbred rabbits. The inbred rabbits had smaller, closer-set eyes, had more-rounded stunted facies, and often were lop-eared (Fig. 1). Behaviorally, the inbred animals were more sedentary, had poor grooming habits, and were more excitable than their outbred counterparts. Inbred rabbits also had smaller litters than outbred rabbits and often failed to care for their young.

Pulmonary TB in inbred and outbred NZW rabbits. In the first experiment, the pulmonary tubercles in six outbred rabbits were compared with those in six inbred rabbits 5 weeks after aerosol infection with *M. tuberculosis* Erdman (Table 1). Impinger samples obtained at the time of the aerosol contained $(6.6 \pm 1.8) \times 10^8$ CFU/ml of impinger fluid. Although the number of tubercles was similar, the average tubercle diameter was significantly smaller in the outbred rabbits.

In the second experiment, the pulmonary tubercles in 12 inbred rabbits were compared with those in 6 outbred rabbits (Fig. 2) 5 weeks after aerosol infection with *M. tuberculosis* H37Rv luciferase. In spite of a bacterial inoculum similar to that used in the previous Erdman experiment (H37Rv concentration in impinger sample [mean ± standard error of the mean], $[7.4 \pm 3.1] \times 10^3$ CFU/ml of impinger fluid), the total number of tubercles was one-third of the number after aerosol infection with Erdman strain, confirming previous observations that Erdman strain results in more tubercles after the same inhaled dose than does the H37Rv strain (25). The increased pathogenicity of Erdman strain may account for the smaller difference in the number of grossly visible tubercles between inbred and outbred rabbits, since strains with greater virulence such as *M. bovis* have previously been shown to result in less difference in tubercle counts between susceptible and resistant rabbit strains (1). After infection with H37Rv, inbred rabbits had significantly more tubercles with larger mean diameters than did outbred rabbits (Table 2). Bacillary cultures of homogenized hilar lymph nodes, spleens, lungs, and individual lung granulomas were performed in order to determine the extent of disease. Nine of eleven (82%) inbred animals had culture-positive hilar lymph nodes, compared with only two of six (33%) outbreds, with a significant difference in their bacillary content ($P < 0.01$). Spleens from both inbred and outbred rabbits had few cultivatable bacilli. When the entire right upper lung lobes were homogenized in 5 ml of PBS, the inbred rabbits had 10-fold more CFU per right upper lung lobe than did the outbred rabbits ($P < 0.01$). From 5 to 10 individual granulomas per lung were homogenized in 1 ml of PBS and plated to determine the number of CFU per granuloma. The inbred rabbits had significantly more bacilli per granuloma than did the outbred rabbits (809 ± 210 CFU versus 215 ± 115 CFU [mean ± standard deviation]; $P = 0.027$). As predicted, there was not a linear relationship between the size of the granuloma and the number of bacilli.

After experimental infection with either *M. tuberculosis* strain, DTH skin responses were significantly lower in the inbreds than in the outbreds (Tables 1 and 2).

Histopathologic analysis of inbred and outbred pulmonary TB. Only the tissue sections of lung granulomas produced by *M. tuberculosis* Erdman were evaluated histologically, because in outbred rabbits our experiments with H37Rv luciferase produced too few lesions for valid comparisons with those in inbred rabbits. The pulmonary lesions caused by the Erdman strain in the inbred rabbits were larger, with more frequent caseous necrotic centers, which often contained visible acid-fast bacilli (Table 3). In addition, perigranulomatous pneumonitis was more likely to be present (Table 3). The lesions caused by the Erdman strain in the outbred rabbits were smaller, with less caseation and infrequent visible bacilli. Their lesions contained more mature epithelioid macrophages and more lymphocytes and plasma cells (Fig. 3 and Table 3).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Inbred</th>
<th>Outbred</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of rabbits</td>
<td>12</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>No. of tubercles (mean ± SE)</td>
<td>98 ± 12</td>
<td>33 ± 13</td>
<td>0.007</td>
</tr>
<tr>
<td>Avg diam of tubercles (mean ± SE) (mm)</td>
<td>2.73 ± 0.13</td>
<td>1.43 ± 0.09</td>
<td>0.001</td>
</tr>
<tr>
<td>Tuberculin reaction (mm)$^1$</td>
<td>289 ± 35</td>
<td>1,152 ± 348</td>
<td>0.009</td>
</tr>
<tr>
<td>Mean no. of CFU/SE (no. of rabbits) in:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymph node$^a$</td>
<td>697 ± 192 (9 of 11)</td>
<td>26 ± 20 (2 of 6)</td>
<td>0.004</td>
</tr>
<tr>
<td>Granuloma$^b$</td>
<td>809 ± 210 (12 of 12)</td>
<td>215 ± 115 (5 of 6)</td>
<td>0.027</td>
</tr>
<tr>
<td>Right upper lung lobe</td>
<td>11,475 ± 9,448 (11)</td>
<td>1,154 ± 986 (6)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

$^a$ Bacillary CFU in both right and left hilar lymph nodes.

$^b$ Bacillary CFU in typical granuloma from each rabbit.
Cytokine responses in peritoneal macrophages. Purified thioglycolate-elicited peritoneal macrophages from three inbred rabbits and three outbred rabbits showed a consistent and statistically significant difference in the production of TNF-α when incubated for 24 h with LPS or when infected with M. tuberculosis H37Rv. Infection with M. tuberculosis CDC1551 and Erdman strains resulted in a similarly diminished production of TNF-α that trended towards statistical significance (Fig. 4). The inbred-rabbit macrophages also had lower TNF-α production after a 48-h stimulation (data not shown). There were no differences in intracellular bacillary counts immediately after infection or at 24 h after infection to account for the differences in TNF-α.

DISCUSSION

In this study, we describe an inbred NZW rabbit strain that is more susceptible than outbred NZW rabbits to an aerosol M. tuberculosis infection. At 5 weeks after experimental infection, this susceptibility is characterized by larger grossly visible primary pulmonary tubercles, with more caseous necrosis and greater numbers of bacilli. Similar susceptible inbred rabbits were propagated by Lurie in the mid-1940s but became extinct (20). Lurie’s susceptible strain C rabbits developed 10 times more grossly visible tubercles with a significantly higher bacillary burden per gram of tissue than the strain III resistant rabbits. In addition, the strain C rabbits cleared bacilli in the draining hilar lymph nodes more slowly and developed a variable and often extensive chronic disease with secondary pulmonary lesions, just as the inbred rabbits described herein (19, 21, 22). Reestablishment of an inbred susceptible rabbit strain provides the opportunity to study the immunopathogenesis of TB with current scientific technology in an animal model in which the disease course and pathology are similar to those found in humans. The emergence of immunological reagents and sequencing of the rabbit genome will facilitate future studies.

The exact immunologic and genetic defects in the inbred rabbits described here remain to be elucidated. However, the

![FIG. 4. Mean TNF-α production by thioglycolate-elicited peritoneal macrophages from outbred (black bars; n = 3) and inbred (grey bars; n = 3) rabbits, after a 24-h incubation with LPS or each of the three strains of virulent M. tuberculosis. Bars represent standard error. P values of <0.05 are marked by an asterisk.](https://iai.asm.org/)
results provide some clues. To probe for an immunologic defect, we evaluated macrophage TNF-α production after in vitro stimulation, since macrophage function is important for host defense against M. tuberculosis and antibodies directed against rabbit TNF-α (but not most other cytokines) were available. We found that cultured peritoneal macrophages from uninfected inbred rabbits produced less TNF-α when incubated with LPS or any of three strains of M. tuberculosis than did those from uninfected outbred rabbits. This diminished TNF-α production by inbred-rabbit peritoneal macrophages may reflect a broad defect in macrophage activation or a defect that is limited to TNF-α production. Interestingly, peripheral blood mononuclear cells from healthy persons with a history of prior extrapulmonary TB had lower LPS-stimulated TNF-α production than did peripheral blood mononuclear cells from healthy persons with latent M. tuberculosis infection as indicated by a positive tuberculin skin test (32).

In M. tuberculosis-infected inbred rabbits, diminished macrophage function, and diminished macrophage TNF-α production in particular, may explain the more-severe TB disease and pulmonary histopathology. TNF-α is unambiguously important in host defense against M. tuberculosis in humans and mice. It has multiple immunoregulatory functions, including early induction of chemokines leading to leukocyte recruitment. TNF-α also participates in the development of functional granulomas that help to control mycobacterial disease (26, 28). In patients treated with anti-TNF-α monoclonal antibodies for rheumatoid arthritis or Crohn’s disease, the high incidence of reactivation TB, the high proportion of patients with disseminated TB, and the typically short time between initiation of anti-TNF-α treatment and onset of TB symptoms support a critical role for TNF-α in immunologic control of this disease (15, 23). Studies using TNF receptor 1−/− mice, wild-type mice treated with neutralizing anti-TNF antibody, or TNF-α−/− mice have demonstrated the importance of TNF-α in controlling acute and chronic tuberculous infection (3, 12, 16). In one study, both wild-type and knockout mice had similar T-cell profiles in lungs, but TNF-α−/− mice had increased pulmonary neutrophils associated with increased necrosis (3). Our histopathologic findings for inbred rabbits are similar to those for TNF-α−/− mice. Our inbred rabbits had larger pulmonary tubercles, with increased caseous necrosis containing a significantly higher number of bacilli.

On the other hand, Kaplan and colleagues have published a series of papers on studies of both rabbit and mouse that underscore the critical importance of cytokine balance in TB pathogenesis (4, 33, 34). They have developed a rabbit model of mycobacterial meningitis that very closely mirrors TB meningitis in human patients. This model has been valuable for studying the immunopathogenesis of mycobacterial meningitis and for evaluation of novel pharmacological therapies for mycobacterial meningitis (33, 34). An important finding emerging from these studies is that higher levels of TNF-α produced during mycobacterial central nervous system infection was correlated, at least in part, with more severe disease, and in this sense, TNF-α is a double-edged sword with respect to TB pathogenesis.

In our studies, the inbred rabbits had a significantly decreased DTH response to tuberculin, in spite of the greater number of bacilli present. This is consistent with the previously described susceptible (strain C) and resistant (strain III) rabbits of Lurie. TB strain C rabbits had lower DTH responses to both tuberculin and dead bacilli (19, 21), a finding which may be due to less bacillary killing and lower concentrations of bacillary antigens. The observed macrophage defect in TNF-α production that we found in currently available inbred rabbits may explain, in part, their lower tuberculin responses. Diminished TNF-α production at the site of tuberculin injection may reduce the local production of chemokines and affect vascular endothelial function, both of which are required for cell infiltration in tuberculin reactions. However, DTH responses are the result of an intricate cytokine cascade in which TNF-α is just one component (3, 9). Additional studies are warranted to better understand the relationship between DTH and effective host defense against M. tuberculosis.

One limitation of our work is that we did not perform immunohistochemical studies for TNF-α in pulmonary or DTH lesions. In addition, we did not evaluate the in vitro function of freshly isolated pulmonary alveolar macrophages. In mice, in vivo macrophage differentiation in a particular anatomical microenvironment may influence macrophage-mycobacterium interactions (24), and responses of pulmonary alveolar macrophages may be different from those of peritoneal macrophages. Nevertheless, the more severe disease in M. tuberculosis-infected inbred rabbits had characteristics similar to those found in TNF-α-deficient mice experimentally challenged with M. tuberculosis and those found in humans with TB following treatment with TNF-α inhibitors, which supports an association in these rabbits between their diminished macrophage TNF-α production and their susceptibility to M. tuberculosis.

The rabbit is an attractive model in which to study TB immunopathogenesis as rabbits have disease manifestations and pathology similar to those found in humans. The reestablishment of an inbred rabbit strain that is less resistant to M. tuberculosis than its outbred counterpart allows an important opportunity to investigate the mechanisms underlying susceptibility to TB.

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REFERENCES


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ERRATUM

Susceptibility to Tuberculosis: Clues from Studies with Inbred and Outbred New Zealand White Rabbits


Departments of Medicine and Pathology, School of Medicine, and Departments of Environmental Health Sciences, Molecular Microbiology and Immunology, International Health, and Epidemiology, Bloomberg School of Public Health, The Johns Hopkins University, Baltimore, and Department of Aerobiology and Product Evaluation, U.S. Army Medical Research Institute of Infectious Diseases, Fort Detrick, Frederick, Maryland, and Department of Pathology, George Washington University Medical Center, Washington, D.C.

Volume 72, no. 3, p. 1700–1705, 2004. Page 1703: Figure 3 should appear as shown below.