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Yersinia enterocolitica Infection in Resistant and Susceptible Strains of Mice

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We investigated natural resistance in mice to *Yersinia enterocolitica*, an enteric bacterial pathogen of humans, with a view to determine host genetic factors that are important in resistance. Most mouse strains studied (C3H/HeN, BALB/c, BALB.B, DBA/2, A, Swiss, and SWR) were highly susceptible to infection (50% lethal dose [LD_{50}], 2×10^2 to 6×10^2 *Y. enterocolitica* administered intravenously [i.v.]). In contrast, C57BL/6 mice were highly resistant (LD_{50}, 2×10^5 *Y. enterocolitica* administered i.v.). Resistance to i.v. *Yersinia* infection did not appear to be related to the *Ity* locus (which codes for resistance to *Salmonella typhimurium* and other pathogens) because Ity^r mice (C3H/HeN, DBA/2, A, and SWR) were more susceptible to *Y. enterocolitica* than were Ity^s (C57BL/6) mice. In addition, because BALB.B mice (congenic to C57BL/6 mice at the *H-2* locus) were susceptible, resistance was probably not *H-2* linked. BALB/c × C57BL/6 F_1 mice were intermediate in their resistance to *Y. enterocolitica* infection (LD_{50}, 3×10^4 organisms administered i.v.), suggesting that resistance to *Y. enterocolitica* depends on a gene dosage affect or a resistance gene(s) interaction between susceptible and resistant parents. Further studies with C57BL/6 and BALB/c mice as prototype resistant and susceptible strains were undertaken. A time course study of *Y. enterocolitica* growth in various organs following i.v. infection revealed no strain difference in bacterial growth during the first 48 h of infection. Thereafter, however, C57BL/6 mice were capable of restricting *Y. enterocolitica* growth in all tissues (liver, lung, spleen, kidneys), whereas extensive bacterial proliferation occurred in BALB/c mice tissues. BALB/c mice were also more susceptible to oral *Y. enterocolitica* infection than were C57BL/6 mice, demonstrating increased mortality and greater numbers of bacteria in the Peyer's patches. Finally, whereas thymus-bearing C57BL/6 × BALB/c F_1 mice were resistant to infection, athymic (nude) C57BL/6 × BALB/c F_1 mice were susceptible. These studies provide a model to investigate natural immunity to enteric pathogens at mucosal surfaces, as well as provide the basis for clarifying the role of host genotype in *Y. enterocolitica* resistance.

Yersinia enterocolitica is a gram-negative rod of the family *Enterobacteriaceae* (1). The organism is recognized as an important human pathogen in many countries throughout the world, particularly in Europe, Scandinavia, Canada, Japan, and the United States (3, 30). *Y. enterocolitica* mainly causes enteritis with fever and diarrhea in children, whereas terminal ileitis or acute mesenteric lymphadenitis seems to predominate in adolescents and adults (14). In some instances, metastatic abscesses and septicemia may occur, leading to increased morbidity and mortality (16). Sequelae such as polyarthritis, thyroiditis, and Reiter's disease develop in some patients following *Y. enterocolitica* infection (3). In some of these patients a correlation with human leukocyte antigen B27 has been demonstrated (13, 15).

Y. enterocolitica has been recognized as a human pathogen since 1939 (27), but study of the disease has suffered from the lack of a suitable animal model. Carter et al. (10) and Carter and Collins (8) successfully produced disease in mice with the WA strain, which was isolated from the blood of a patient in upstate New York. Infection in mice closely resembles that in humans (6). Since this first description of a murine model of *Y. enterocolitica* infection, relatively little information has emerged concerning immunity to *Y. enterocolitica* in both humans and animals. On the other hand, considerable work has been done on plasmid-mediated *Y. enterocolitica* virulence factors and outer membrane proteins (2, 4, 11, 19, 21, 23, 31, 32).

We report here that host resistance to *Y. enterocolitica* in mice differs between strains. Furthermore, genetic determinants that provide *Y. enterocolitica* resistance appear to be unrelated to known genetic determinants (*Ity*) that code for immunity to *Salmonella typhimurium* which produces similar intestinal disease in humans. More importantly, the difference in *Y. enterocolitica* immunity between mouse strains can be detected at the intestinal level, suggesting that *Y. enterocolitica* can be used as a probe to study not only the role of host genotype in murine resistance to enteric pathogens but also host-parasite interactions at mucosal surfaces.

MATERIALS AND METHODS

Animals. Age-matched mice were used in all experiments. C57BL/6, BALB/cBy, SWR, DBA/2, A, BALB/cBy × C57BL/6 F_1, and BALB/cBy × C57BL/6 F_1 *nu/nu* and their thumus-bearing littermate strains were obtained from Jackson Laboratory, Bar Harbor, Maine. C3H/HeN and Swiss Webster strains were obtained from Charles River Breeding Laboratories, Inc., Wilmington, Mass., and Ace Animals, Inc., Boyertown, Pa., respectively. BALB.B (congenic to C57BL/6 mice at the *H-2* locus) breeding pairs were a gift of K. Blank (University of Pennsylvania, Philadelphia). All animals were housed in a facility accredited by the American Association for Accreditation of Laboratory Animal Care and received food and water ad libitum.

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TABLE 1. LD_{50} values of mouse strains after infection with *Y. enterocolitica* WA[a]

Mouse strain	Ity phenotype	*H-2* type	LD_{50}
C57BL/6	Ity^s	*b*	2×10^5
(BALB/c × C57BL/6)F_1	Ity^s	*b/d*	3×10^4
BALB/c	Ity^s	*d*	3×10^2
BALB.B[b]	Ity^s	*b*	2×10^2
Swiss			2×10^2
C3H/HeN	Ity^r	*k*	6×10^2
DBA/2	Ity^r	*d*	5×10^2
SWR	Ity^r	*q*	4×10^2
A	Ity^r	*a*	3×10^2

[a] Groups of 10 mice each were infected i.v. with 10-fold increasing doses of *Y. enterocolitica* and observed for a 7-week period for deaths.
[b] BALB.B mice are congenic at the *H-2* locus with C57BL/6 mice.

Bacteria. *Y. enterocolitica* WA (serotype O:8, biotype 2, Vwa^+) originally isolated from a human infection was used in all studies. The virulence of the organism was maintained by oral passage in mice. Following oral infection, *Y. enterocolitica* was isolated from infected ileal Peyer's patches (PPs) by cultivation on MacConkey agar at room temperature for 48 h (BBL Microbiology Systems, Cockeysville, Md.). Bacterial stocks were prepared by subculturing organisms from single colonies of *Y. enterocolitica* in Trypticase soy broth (BBL) at room temperature for 48 h. The stock was dispensed in 3-ml fractions in 20% glycerol and stored at −70°C. The bacterial concentration was usually 3×10^8 to 4×10^8 organisms per ml.

Animal infection. All infections were initiated with freshly thawed *Y. enterocolitica* stock. When appropriate, dilutions of freshly thawed stock were made with sterile physiological saline (0.9%) before infection. Mice were orally infected with a 19-gauge stainless steel feeding needle (Harvard Bioscience, South Natick, Mass.), after they received a 0.1-ml suspension of aluminium hydroxide-magnesium hydroxide to neutralize stomach acidity. Intravenously (i.v.) infected mice received the appropriate inoculum via the left lateral tail vein with a 25-gauge needle (in a 0.15- to 0.25-ml volume). There were always at least five mice per experimental group. In both orally and i.v. infected mice, the actual number of *Y. enterocolitica* administered was determined by plating 0.1 ml of 10-fold serial dilutions on Trypticase soy agar (BBL).

Bacterial enumeration. Mice were killed by cervical dislocation, and tissues were homogenized in sterile distilled water. Serial 10-fold dilutions of the homogenates were plated either on MacConkey or Trypticase soy agar for 24 h at 37°C. When *Y. enterocolitica* colonization of ileal mucosa and ileal PPs was compared, five terminal ileal PPs and five pieces of terminal ileal mucosa of the same PP site were used. Care was taken to remove only sections of ileal mucosa separate from ileal PPs and of approximate equal size to the ileal PP. To demonstrate murine strain differences between the number of *Y. enterocolitica* on the PP mucosal surface, in contrast to *Y. enterocolitica* in the ileal PP, the CFU of *Y. enterocolitica* recovered from the ileal mucosa from each individual mouse was subtracted from its corresponding PP CFU of *Y. enterocolitica*. This assumes that *Y. enterocolitica* adherence to ileal mucosal epithelium and PP epithelium is identical. However, this may be an inappropriate assumption, and experiments are planned to answer this question more directly. We adopted this protocol, however, in an attempt to distinguish between organisms in the PPs and those which may adhere to the PP epithelium, as has been shown for a strain of *Escherichia coli* in rabbits (5).

50% lethal dose determinations. Groups of five mice were injected i.v. with different doses of *Y. enterocolitica*. Mice were observed for a 7-week period for deaths. The 50% lethal dose (LD_{50}) was calculated by the method of Reed and Meunch (24). LD_{50} results (except those of strains DBA/2 and A) represent pooled deaths per dose from two separate experiments in which similar results were obtained, such that there were 10 mice per challenge dose per strain.

Statistical analysis. Results are expressed as mean ± 1 standard error. Differences between means were determined by the unpaired Student *t* test. Significance was determined at the $P < 0.05$ level.

RESULTS

LD_{50} (i.v.) to *Y. enterocolitica* in different mice strains. The LD_{50}s to *Y. enterocolitica* in BALB/c, BALB.B, C57BL/6, Swiss, BALB/c × C57BL/6 F_1, C3H/HeN, DBA/2, A, and SWR mice were determined (Table 1). The C57BL/6 strain was 1,000-fold more resistant to *Y. enterocolitica* compared with BALB/c, BALB.B, A, DBA/2, SWR, C3H/HeN, and Swiss strains. BALB/c × C57BL/6 F_1 mice were 100-fold more resistant (intermediately resistant) to *Y. enterocolitica* than were BALB/c mice but were more susceptible than C57BL/6 mice, indicating that there was possible gene interaction between resistant and susceptible parental strains or a gene dosage effect.

It has been suggested that *Y. enterocolitica*, similar to *S. typhimurium*, is a facultative intracellular enteric pathogen (29). One particular locus, *Ity*, has been shown to code for early resistance to *S. typhimurium* (28), and it was of interest to determine whether resistance to *Y. enterocolitica* followed the same pattern. *S. typhimurium*-resistant (Ity^r) C3H/HeN, A, DBA/2, and SWR strains were 1,000-fold more susceptible to *Y. enterocolitica* than were *S. typhimurium* susceptible (Ity^s) and *Y. enterocolitica*-resistant C57BL/6 mice. Thus, there appears to be no association between the *Ity* locus and resistance to *Y. enterocolitica*. Furthermore, there was no association with strain resistance to *Y. enterocolitica* and the *H-2* haplotype of the major histocompatibility locus. BALB.B mice congenic at the *H-2* locus with C57BL/6 mice were as susceptible to *Y. enterocolitica* as were BALB/c mice.

Effect of i.v. infection on growth of *Y. enterocolitica* in various tissues. Because it was established from the LD_{50} data that C57BL/6 mice were highly resistant to *Y. enterocolitica*, while BALB/c mice were susceptible, a kinetic study with these strains as prototypes was performed to determine in vivo where differences in bacterial proliferation occurred. Mice of both strains were infected i.v. with 8×10^4 *Y. enterocolitica*, and clearance of the organism from various tissues (spleen, liver, lung, kidney) was determined (Fig. 1).

At this i.v. infecting dose, dramatic differences in *Y. enterocolitica* restriction between the C57BL/6 and BALB/c strains occurred between days 8 and 11. During this period, there was a large increase in CFU of *Y. enterocolitica* in all organs in the susceptible strain, in contrast to the resistant strain which was able to effectively clear its liver and spleen of the organism. Differences between the C57BL/6 and BALB/c strains following other challenge doses of *Y. enterocolitica* (4×10^3 and 10^6 *Y. enterocolitica*; data not shown) also demonstrated that C57BL/6 mice were able to restrict the growth of *Y. enterocolitica* better than the BALB/c

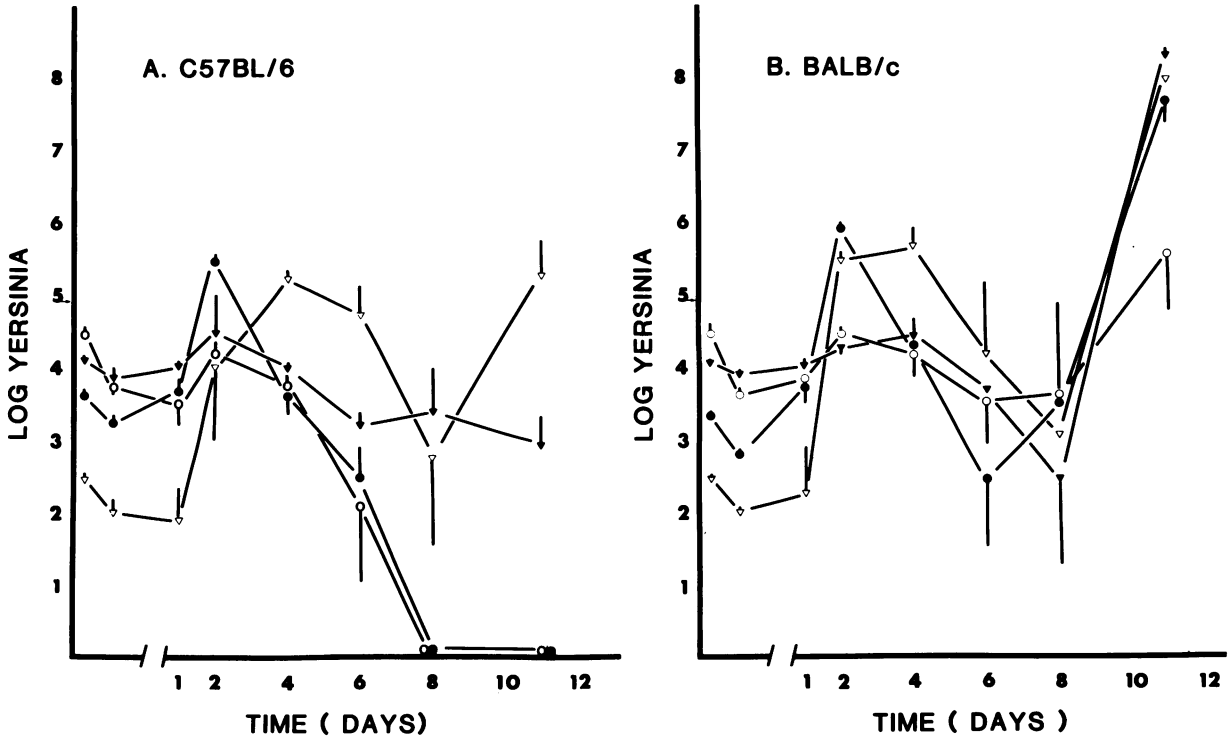

FIG. 1. Growth of *Y. enterocolitica* in spleen (●), liver (○), kidneys (▽), and lungs (▼) of C57BL/6 (A) and BALB/c (B) mice after intravenous infection with 8×10^4 organisms. Error bars represent one standard error of the mean.

strain. What is quite striking from these studies is that at no dose and in no particular organ were differences apparent between C57BL/6 and BALB/c mice during the first 24 to 48 h of infection. Thus, it is unlikely that differences in innate microbiocidal activity of fixed tissue macrophages are responsible for the differences that we observed.

Growth of *Y. enterocolitica* in athymic nude mice. The observed difference in *Y. enterocolitica* growth restriction that occurred between days 8 and 11 of infection (Fig. 1) suggests that strain differences in resistance to *Y. enterocolitica* are due to immune-mediated mechanisms. To help determine this, athymic BALB/c × C57BL/6 F_1 *nu/nu* mice and their thymus-bearing littermates were compared for their ability to restrict *Y. enterocolitica* growth (Table 2). Seven days after i.v. inoculation of *Y. enterocolitica*, nude mice had significantly greater numbers of *Y. enterocolitica* in their tissues than did their thymus-bearing littermates. These results indicate, then, that resistance of the C57BL/6 strain to *Y. enterocolitica* is at least partially determined by thymus-dependent immune mechanisms.

TABLE 2. *Y. enterocolitica* tissue growth at 7 days in athymic nude and littermate mice[a] following i.v. *Y. enterocolitica* infection

Expt	*Y. enterocolitica* infecting dose	Log_{10} *Y. enterocolitica*[b] in the following mice:	
		Nude	Littermate
1	8×10^3	5.7 ± 0.8	2.1 ± 1.0[c]
2	5×10^4	5.3 ± 0.7	2.8 ± 0.7[c]

[a] BALB/c × C57BL/6 F_1 *nu/nu* mice and their littermates were infected i.v. with *Y. enterocolitica*.
[b] Log_{10} *Y. enterocolitica* represents pooled CFU of *Y. enterocolitica* from spleen, kidney, liver, and lungs from mice infected i.v. (five mice per group).
[c] Significant difference at $P < 0.05$.

Growth of *Y. enterocolitica* in the PPs of resistant and susceptible mice. In mice orally infected with *Y. enterocolitica*, Carter (7) demonstrated that the primary site of infection was the terminal ileal PPs. Differences between C57BL/6 and BALB/c strains in *Y. enterocolitica* attachment to ileal mucosa and PPs following oral infection were thus investigated (Fig. 2). Initial colonization of *Y. enterocolitica* to terminal ileal mucosa was the same for both mouse strains (Fig. 2A). Mouse strain differences in ileal mucosal adherence were not observed until late in the infection, when BALB/c ileal PP contained approximately 10^6 CFU of *Y. enterocolitica*.

Although there were no detectable strain differences in *Y. enterocolitica* attachment to the ileal mucosa, there was a strain difference in ileal PP CFU of *Y. enterocolitica* between BALB/c and C57BL/6 strains (Fig. 2B). These differences could be observed within 24 to 48 h postinfection. This suggests that innate resistance to *Y. enterocolitica*, an enteric pathogen, can be expressed at the PP level. Furthermore, after initial PP colonization C57BL/6 mice were able to clear their infected tissue. This was in contrast to susceptible BALB/c mice in which *Y. enterocolitica* numbers rapidly increased and were maintained at a peak bacterial load of approximately 10^6 organisms (Fig. 2B). This result is in contrast to that obtained with i.v. infection, in which no differences were observed early in infection (Fig. 1).

A striking feature of the oral infection experiments was that in BALB/c mice, despite high PP levels of *Y. enterocolitica*, no organisms could be reproducibly recovered from mesenteric lymph nodes or spleen (negative data not shown). Thus, it appears that BALB/c mice are capable of restricting the infection to the intestinal wall. Despite this, after oral infection many BALB/c mice developed diarrhea and died 10 to 20 days postinfection.

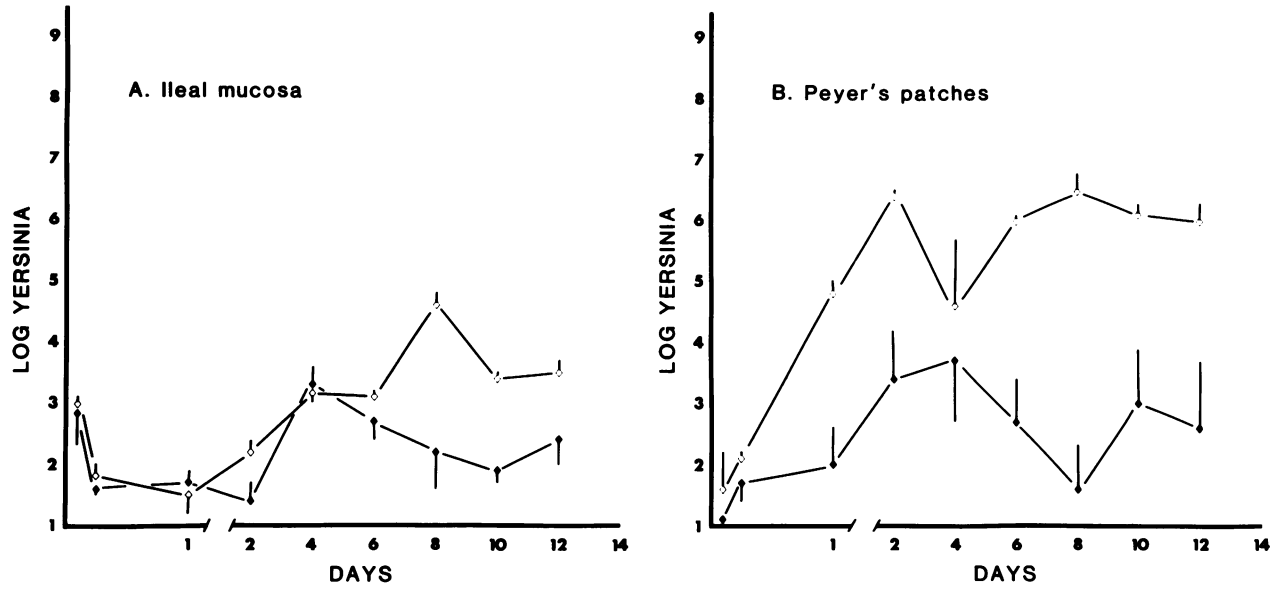

FIG. 2. *Y. enterocolitica* ileal mucosal colonization (A) and PP growth (B) in C57BL/6 (◆) and BALB/c (◇) mice after oral infection with 7×10^7 organisms. Error bars represent one standard error of the mean. Points are cumulative data from two separate experiments in which similar results were obtained.

DISCUSSION

Results of previous studies have shown that host genotype is important in resistance to a variety of infectious agents (12, 20, 22). Results of this study indicate that host genotype is also important in resistance or susceptibility to *Y. enterocolitica*. Following i.v. infection, C57BL/6 mice were 1,000-fold more resistant to *Y. enterocolitica* than were BALB/c, BALB.B, SWR, C3H/HeN, A, DBA/2, and Swiss mice (Table 1). We also determined BALB/c × C57BL/6 F_1 *Y. enterocolitica* susceptibility. Hybrid F_1 mice were intermediate in *Y. enterocolitica* susceptibility, being 100-fold more resistant than susceptible BALB/c mice. This suggests either a gene dosage effect or a possible gene interaction between susceptible BALB/c and resistant C57BL/6 mice, thus altering the effect of the dominant *Y. enterocolitica*-resistant gene(s). Studies are in progress with parental backcrosses to determine whether resistance to *Y. enterocolitica* is dictated by one gene or a group of closely linked genes, or whether *Y. enterocolitica* resistance is multigenic. Also, by utilizing recombinant inbred mouse strains derived from BALB/c and C57BL/6 progenitor strains, we are currently investigating the genetic loci associated with resistance to *Y. enterocolitica*.

Extensive tissue clearance studies in which the ability to restrict the growth of *Y. enterocolitica* following i.v. infection were compared were undertaken in susceptible BALB/c and resistant C57BL/6 strains. Following i.v. infection with 8×10^4 *Y. enterocolitica* (Fig. 1), initial restriction of *Y. enterocolitica* was similar in both susceptible BALB/c and resistant C57BL/6 strains. These results suggest that genotypic strain differences in restriction of *Y. enterocolitica* are not due to strain-restrictive differences of *Y. enterocolitica* by resident tissue phagocytes. In fact, results indicate that genetic strain differences between susceptible BALB/c and resistant C57BL/6 mice are due to strain differences in specific antiyersinia immune mechanisms which appear later in the infection because athymic nude mice were more susceptible to *Y. enterocolitica* than were their thymus-bearing littermates (Table 2). This indicates that a thymus-dependent immune response is at least partially responsible for the resistance of the C57BL/6 strain. This is under investigation. A consistent finding in our studies was that *Y. enterocolitica* in BALB/c mice often grew in the lungs. This was frequently the only site of infection (especially at a low level of infection). It thus appears that BALB/c mice are partly more susceptible to *Y. enterocolitica* because of their inability to restrict *Y. enterocolitica* growth in the lungs. Because the lung is a secretory organ, it is tempting to speculate that strain differences in lung resistance to *Y. enterocolitica* result from strain differences in anti-*Y. enterocolitica* secretory immunoglobulin A (IgA). Strain differences in resistance to *Y. enterocolitica* occurred in the gut (Fig. 2), therefore suggesting a possible role for anti-*Y. enterocolitica* secretory IgA derived from gut-associated lymphoid tissue. Furthermore, secretory IgA in the lungs is associated with bronchial-associated lymphoid tissue (26). At present, we do not know where the bacteria lodge in the lung after i.v. infection, but it is probably the lower lung parenchyma, where there is an abundant blood supply. Macroscopic lung abscesses in susceptible BALB/c mice were only observed in the alveoli, not in the bronchi, which was also demonstrated histologically by Carter (7) following i.v. infection. Therefore, mouse strain differences in lung resistance to *Y. enterocolitica* may simply be a result of i.v. inoculation, with trapping of bacteria in the lower lung parenchyma, or may represent strain differences in anti-*Y. enterocolitica* secretory IgA. At present, the answer to this question is unknown.

Because of similarities in the natural route of infection and the subsequent intestinal disease between *S. typhimurium* and *Y. enterocolitica* (7, 9), the role that *S. typhimurium* resistance genes have in controlling *Y. enterocolitica* growth was investigated. LD_{50} data (Table 1) indicate that C3H/HeN, A, DBA/2, and SWR mice, all of which were Ity^r (22, 28), were susceptible to *Y. enterocolitica*. Thus, the Ity^r gene does not appear to be important in *Y. enterocolitica* resistance. To substantiate this, we could not demonstrate

any differences in *Y. enterocolitica* tissue restriction in either Ity^r or Ity^s mice during the first 24 h postinfection (negative data not shown).

Natural infection with *Y. enterocolitica* occurs via the oral route (3). It therefore seemed appropriate to determine whether C57BL/6 mice are more resistant to *Y. enterocolitica* than are BALB/c mice following oral infection. Carter (7) demonstrated that the primary site of infection in oral-induced yersiniosis is the terminal ileal PPs. Later, MacDonald and Carter demonstrated that resident ileal PP macrophages are low in number (18), even when stimulated with macrophage-activating agents such as BCG or *Corynebacterium parvum* (17). Therefore, nonspecific macrophage-mediated resistance to an enteric pathogen at the level of the PP seems to be an unlikely event in mucosal immunity. However, genotypic strain differences in *Y. enterocolitica* resistance or susceptibility in the gut may reside in differences in initial *Y. enterocolitica* adherence to ileal PPs or mucosa. Therefore, we examined initial *Y. enterocolitica* colonization of the terminal ileum in both susceptible BALB/c and resistant C57BL/6 strains. Following oral infection with 7×10^7 *Y. enterocolitica*, initial terminal ileal colonization was similar in both mouse strains (Figure 2A). Furthermore, strain differences in ileal mucosal *Y. enterocolitica* colonization could not be detected until BALB/c PPs contained 10^6 *Y. enterocolitica*. These differences probably resulted from shedding of *Y. enterocolitica* into the ileal lumen from the PPs and their subsequent reattachment to ileal epithelial cells. Results of other studies have demonstrated that orally infected mice may shed *Y. enterocolitica* in their feces for several weeks (25). Therefore, the results suggest that strain differences in the level of PP infection between C57BL/6 and BALB/c mice do not appear to be due to differences in ileal mucosal colonization. Instead, our results suggest that strain differences in resistance to *Y. enterocolitica* occur at the PPs, either within the PPs or at the PP surface. C57BL/6 mice were able to restrict *Y. enterocolitica* growth in PPs better than BALB/c mice (Fig. 2B). A 10,000-fold difference in PP numbers could be demonstrated 8 days postinfection. Therefore, our results suggest that genotypic strain differences in natural immunity to an enteric pathogen are expressed at the level of the PPs. Previously, we demonstrated that macrophage-mediated nonspecific immunity to enteric pathogens at the PP level appears to be unlikely because of the paucity of PP macrophages (17, 18). The intriguing possibility of as yet undetected nonspecific PP effector cells that are responsible for natural antibacterial immunity offers a potential explanation for genotypic strain differences in oral-induced yersiniosis. However, perhaps other nonspecific mechanisms, i.e., genotypic strain differences in the inflammatory response or strain differences in resistance to *Y. enterocolitica* PP penetration mechanisms, are important in natural resistance to *Y. enterocolitica*. Studies are in progress to detect such strain differences.

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