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Mouse Genetic Locus *Lps* Influences Susceptibility to *Neisseria meningitidis* Infection

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We surveyed a number of inbred mouse strains for susceptibility to meningococcemia. Mice of all strains became bacteremic after intraperitoneal injection of a serogroup C, serotype 2a human disease isolate, but the strains differed in levels of bacteremia, indicating influences of the host genome on susceptibility. There was no significant correlation between level of bacteremia and differences at major histocompatibility or immunoglobulin loci; the *Salmonella* susceptibility locus, *Ity*; the complement C5 locus, *Hc*; the antibody response locus, *xid*; or the transferrin locus, *Trf*. However, the *Lps* locus, which influences a range of host cellular responses to endotoxin and affects susceptibility to *Salmonella typhimurium*, did influence susceptibility to meningococcemia. There were significant differences in levels of bacteremia between C3H/HeJ (Lps^d) mice and each of the other strains (all Lps^n). We confirmed the association of the Lps^d genotype with susceptibility by using coisogenic strains from two widely separated mouse lineages: C3H and B10. Lps^d mice experienced a 1,000-fold proliferation of bacteria and were bacteremic for days before clearing the infection. In contrast, Lps^n mice cleared the bacteremia in less than 1 day. There was no difference in meningococcal growth in vitro in serum from C3H/HeJ and coisogenic C3H/HeN (Lps^n) mice, suggesting that the *Lps*-related difference in susceptibility may involve a cellular response.

Neisseria meningitidis is a gram-negative diplococcus that is responsible for significant human disease. It is a leading cause of bacterial meningitis in infants, young adults, and closed populations such as military recruits, and it causes frequent, severe epidemics in some parts of the world (4, 9). Although the incidence of meningococcal disease in the general population is low, the rapid course of the disease and the significant morbidity and mortality associated with it make it a public health hazard (4). In humans, the main identified host susceptibility factor is deficient humoral immunity. The presence of bactericidal antibodies in serum is associated with a low incidence of meningococcal disease (4, 8, 9). People with hereditary deficiencies of complement or immunoglobulin and infants with physiologic hypoimmunoglobulinemia are at relatively greater risk for the disease (4, 9, 24).

Mice have previously been used in the study of pathogenesis of and immunity to meningococcal disease (4, 13). After intraperitoneal (i.p.) injection with virulent strains, mice develop peritonitis and a transient bacteremia (4). Mouse infection models have been used in immunoprotection studies (31) and in assessing the relative virulence of different strains of meningococci (14), but consideration has seldom been given to host factors contributing to susceptibility to murine meningococcal infection. Host factors such as genotype influence the susceptibility of mice to a number of pathogens (26). For example, the Lps^d allele of C3H/HeJ mice is associated with increased susceptibility to infection with *Salmonella typhimurium* (21) and *Escherichia coli* (12). The Lps^d allele is also associated with decreased susceptibility to endotoxin lethality and numerous defective responses of macrophages, B and T lymphocytes, and fibroblasts to stimulation with bacterial lipopolysaccharide (LPS) (10, 20).

To determine whether host genotype influences the susceptibility of mice to meningococcal infection and to try to identify specific host variables influencing susceptibility, we surveyed a number of inbred mouse strains and found that significant differences in susceptibility were associated with the *Lps* genotype of the host.

MATERIALS AND METHODS

Mice. All mice were obtained from Jackson Laboratory, Bar Harbor, Maine, except for strains C3H/HeN (Charles River Laboratories, Raleigh, N.C.) and C57BL/10Sc (designated B10Sc) (Harlan/Sprague-Dawley Laboratory, Indianapolis, Ind.). The panel (Table 1) included strains of disparate genotypes, and, in particular, strains varying at the major histocompatibility locus, *H-2*; the immunoglobulin heavy-chain locus, *Igh-1*; the *Salmonella* susceptibility locus, *Ity*; the complement C5 locus, *Hc*; the X-linked immunodeficiency locus, *xid*; the transferrin locus, *Trf*; and the LPS response locus, *Lps* (10). Strains CBA/J and CBA/NJ are coisogenic, differing at the *xid* locus (10). Strains C3HeB/FeJ, C3H/HeN, and C3H/HeJ are essentially coisogenic, differing at the *Lps* locus (7, 10), as are strains C57BL/10 (designated B10) and B10Sc (10). The *Lps* type (Lps^n denoting normal response and Lps^d denoting defective response) of each of the C3H and B10 strains was confirmed by endotoxin toxicity testing (19) (data not shown).

Female mice were used at 6 to 13 weeks of age. Mice used in individual experiments were within 2 weeks of the same age and generally had been kept in our animal facility for 1 to 2 weeks. All mice except strain B10Sc were specific pathogen free. In general, 4 to 10 mice of a strain and two or three different mouse strains were used in each experiment. Mice were housed in autoclaved, filtered cages and fed autoclaved mouse chow, specially supplemented for autoclaving (Ralston Purina Co., St. Louis, Mo.), and sterile water ad libitum.

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TABLE 1. Inbred mouse strains used and alleles at selected loci[a]

Mouse strain	Alleles at following locus:						
	H-2	*Igh-1*	*Ity*	*Hc*	*xid*	*Trf*	*Lps*
A/J	*a*	*e*	*r*	0			
AKR/J	*k*	*d*	*r*	0			
BALB/cJ	*d*	*a*	*s*	1			
BUB/BnJ	*q*	*a*		1			
CBA/J	*k*	*j*	*r*	1		a^b	
CBA/NJ	*k*	*j*	*r*	1	+[c]	a^b	
C3H/HeJ	*k*	*j*	*r*	1			d^d
C3HeB/FeJ	*k*	*j*	*r*	1			
C3H/HeN	*k*	*j*	*r*	1			
C57BL/6J (B6)	*b*	*b*	*s*	1			
C57BL/10SnJ (B10)	*b*	*b*	*s*	1			
C57BL/10ScCr (B10Sc)	*b*	*b*	*s*	1			d^d
DBA/2J	*d*	*c*	*r*	0			

[a] *H-2* is the major histocompatibility locus (10). *Igh-1* is the immunoglobulin heavy-chain locus (10). *Ity* is a locus affecting susceptibility to *S. typhimurium* and other pathogens (16). *Hc* is the locus for complement component C5 production (6). *xid* is the X-linked immunodeficiency locus (23). *Trf* is the transferrin locus (10). *Lps* is a locus affecting responses to bacterial LPS (10, 20).

[b] Other strains are Trf^b.

[c] Other strains lack the *xid* genotype.

[d] Other strains are Lps^n.

Bacteria. The human disease isolate *N. meningitidis* FAM18 (serogroup C, serotype 2a) was used.

Infection experiments. The methods for growing meningococci, intraperitoneal (i.p.) infection, and tail bleeding have been described previously (31). Mice were injected with 1×10^2 to 6×10^2 CFU of log-phase meningococci in 500 μl of phosphate-buffered saline (PBS), and levels of bacteremia at various times after injection were determined by culturing blood samples. In this way the course of the bacteremia in individual mice could be monitored. The lower limit of detection was 10^2 CFU/ml of blood. In initial experiments, blood was cultured at 4, 8, and 12 h after injection. In other experiments, blood was cultured at 4, 12, and 24 h after injection and then at 24-h intervals until at least two consecutive negative blood cultures were obtained, after which blood samples were no longer taken from that mouse for culture. On rare occasions, mice were bacteremic after a single negative blood culture.

Statistical methods. For each time point in the initial experiments (4-, 8-, and 12-h bleedings), an analysis of variance was performed to compare the average bacteremia levels ($\log_{10}$ CFU/ml of blood) of each strain. Tukey's studentized range test (27) with a simultaneous significance level of 0.01 was used in comparing each pair of strain averages. Thus, if in fact there is no difference, the probability of at least one comparison showing significance is 0.01 for the entire set of pairwise comparisons. In addition, a linear contrast was used to compare the bacteremia levels of all complement-sufficient (Hc^1) mice with those of the C5-deficient (Hc^0) mice. For these comparisons and for determination of the mean and standard error in the initial experiments, the infrequent sterile blood cultures were assigned a value equal to the lower limit of detection (2.0). In Fig. 1 and 2, the graphs of mean bacteremia level represent the data only for mice that were bacteremic at a sampling time.

Meningococcal strain verification. Colonies from cultures of C3H/HeJ mouse blood after a 9-day bacteremia were shown by colony blot radioimmunoassay (3) to express the common pathogenic *Neisseria* H.8 antigen (3) and the two class 5 outer membrane proteins of strain FAM18 (15) (data not shown). Slide agglutination with *N. meningitidis* group C antiserum (Difco Laboratories, Detroit, Mich.) confirmed the expression of the capsular antigen of strain FAM18 by the 9-day isolates. Using Western blot radioimmunoassay (3), we detected immunoglobulin G antibodies against strain FAM18 in a serum sample from a C3H/HeJ mouse after a 16-day bacteremia (data not shown).

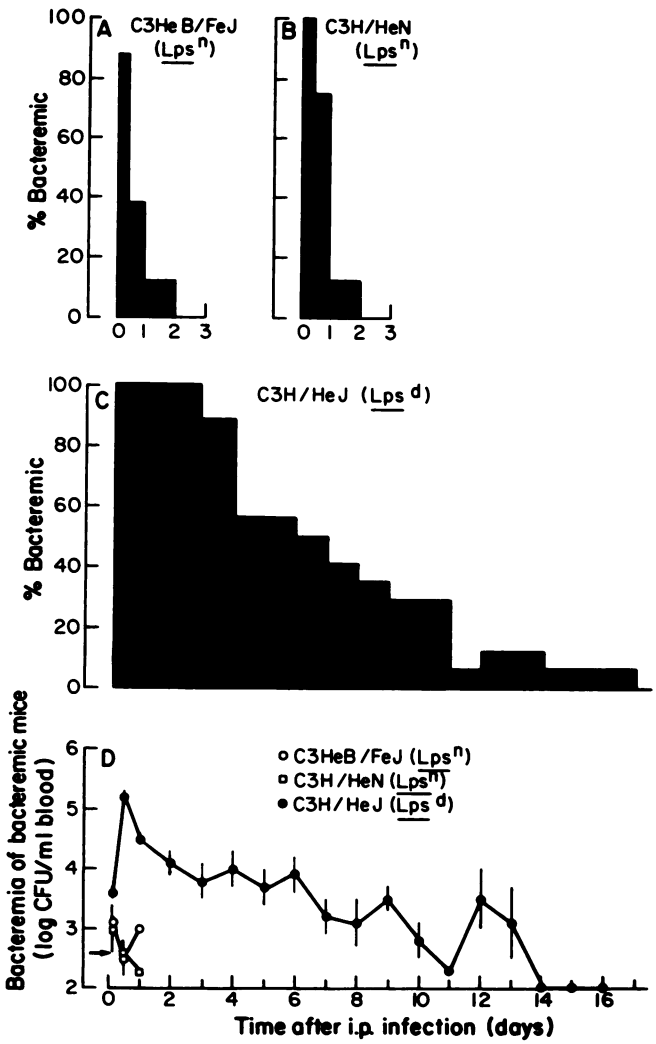

FIG. 1. Meningococcemia in C3H mouse strains. (A to C) Percentage of mice of strain C3HeB/FeJ (8 mice, panel A), C3H/HeN (8 mice, panel B), and C3H/HeJ (18 mice, panel C) bacteremic at various times after i.p. infection with strain FAM18. The level of detection was 10^2 bacteria per ml of blood. (D) Mean bacteremia of bacteremic mice of the three strains at each of the time points, with bars representing the standard error of the mean. The approximate inoculum size is indicated by an arrow on the ordinate.

Meningococcal growth in mouse serum. Log-phase meningococci in GC broth (31) were mixed with an equal volume of fresh mouse serum, incubated for 45 min with agitation at 37°C in a 5% CO_2 atmosphere, and then plated on GC medium base agar (Difco) for viable counts. Infant-rabbit serum, which is not bactericidal for meningococci (32), was used as a control.

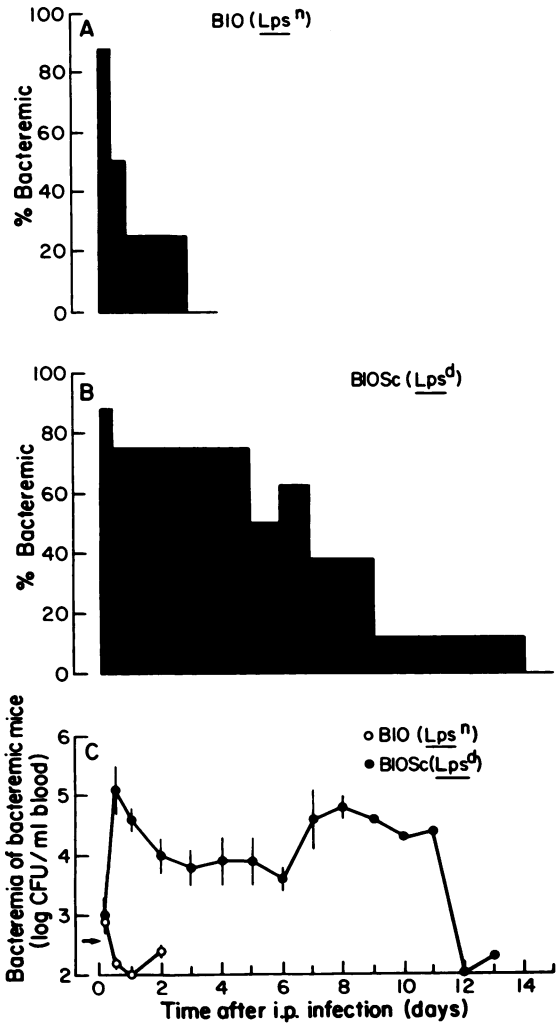

FIG. 2. Meningococcemia in B10 mouse strains. (A and B) Percentage of mice of strain B10 (8 mice, panel A) and B10Sc (8 mice, panel B) bacteremic at various times after i.p. infection with strain FAM18. The level of detection was 10^2 bacteria per ml of blood. (C) Mean bacteremia of bacteremic mice of the two strains at each of the time points, with bars representing the standard error of the mean. The approximate inoculum size is indicated by an arrow on the ordinate.

RESULTS

Meningococcemia in 10 inbred mouse strains. We chose 10 mouse strains representing different lineages with extensive genotypic differences (Tables 1 and 2). A total of 8 to 19 mice of each strain were infected i.p. with meningococcal strain FAM18 and bled 4, 8, and 12 h later. The mean $\log_{10}$ levels of bacteremia are listed in Table 2. All mice of all strains were bacteremic at one or more of the sampling times, except for 4 of the 19 C57BL/6 (designated B6) mice. Each strain showed a maximum bacteremia at the 4- or 8-h sampling times, except for strain C3H/HeJ, which showed a maximum at 12 h. There was considerable variation in levels of bacteremia in the different mouse strains at the three time points. At the 4-h sampling time, 14 pairwise comparisons of strains showed significant differences ($P < 0.01$) (Table 3). However, none of these pairs of strains was significantly different at both the 8- and 12-h sampling times, except for the comparisons of strain C3H/HeJ with strains C3HeB/FeJ and B6. Although several pairwise comparisons showed significant differences at one of the three time points, there was no readily apparent correlation between greater susceptibility in this model with any of the loci shown in Table 1 at the 4- and 8-h sampling times. However, there were significant differences, of 1.4 to 2.7 orders of magnitude, between strain C3H/HeJ (*Lps*^{d}) and each of the other nine strains (all *Lps*^{n}) at the 12-h sampling time. The coisogenic strains C3H/HeJ (*Lps*^{d}) and C3HeB/FeJ (*Lps*^{n}) differed significantly at each of the sampling times: $P = 0.01$ at 4 h, $P = 0.02$ at 8 h, and $P = 0.0001$ at 12 h. C3H/HeJ mice also differed significantly ($P < 0.01$) from B6 mice at each of the sampling times. In all of these cases, C3H/HeJ mice experienced a higher level of bacteremia than the other strains did. In contrast, comparison of mice differing at the complement C5 locus *Hc* revealed a significant difference only at 4 h ($P = 0.01$, compared with $P = 0.48$ at 8 h and $P = 0.32$ at 12 h).

TABLE 2. Level of bacteremia in mice of different strains at 4, 8, and 12 h after i.p. injection of meningococci

Mouse strain	No. of mice	Mean bacteremia ($\log_{10}$ CFU/ml of blood)[a,b] at following times after i.p. injection[c]:		
		4 h	8 h	12 h
A/J	8	3.9	3.2	3.3
AKR/J	8	2.7	2.6	2.4
BALB/cJ	8	3.3	3.8	2.4
BUB/BnJ	8	2.6	3.4	2.7
CBA/J	8	3.1	2.9	2.0
CBA/NJ	8	3.7	3.9	2.4
C3H/HeJ	18	3.6	3.5	4.7
C3HeB/FeJ	8	3.0	2.9	2.2
B6	19	2.5	2.5	2.6
DBA/2J	11	3.6	3.9	2.2

[a] The standard error of the mean was ≤0.3 for each value.
[b] Sterile blood cultures were assigned a value of 2.0, equal to the lower limit of detection.
[c] Meningococci were injected at 1×10^2 to 6×10^2 ($10^{2.0}$ to $10^{2.8}$) CFU (strain FAM18 was used).

Meningococcemia in *Lps* coisogenic strains. In the initial experiments, C3H/HeJ mice displayed a marked proliferation of bacteria in the blood at 12 h after infection. We repeated the experiments, but continued to culture the blood until mice were no longer bacteremic. We used three coisogenic strains differing at the *Lps* locus: C3H/HeJ (*Lps*^{d}), C3HeB/FeJ (*Lps*^{n}), and C3H/HeN (*Lps*^{n}). After i.p. inoculation, most mice of each strain became bacteremic, but there were significant differences in the extent and duration of bacteremia, which correlated with *Lps* type (Fig. 1). Meningococci multiplied severalfold in mice of both *Lps*^{n} strains by 4 h after infection, but the mice were clearing the bacteremia by 12 h and none was bacteremic at 2 days. The mean and median durations of bacteremia for both *Lps*^{n} strains were <1 day. In contrast, greater meningococcal proliferation (of approximately 3 orders of magnitude) occurred in *Lps*^{d} C3H/HeJ mice by 12 h. In addition, the *Lps*^{d} mice remained bacteremic for longer than the *Lps*^{n} mice did before eventually clearing the infection. All C3H/HeJ mice were bacteremic at 48 h, the mean and median durations of bacteremia were both 6 days, and one mouse had a positive blood culture at 16 days.

We tested whether the association of the *Lps*^{d} genotype with susceptibility to prolonged, significant meningococcemia could also be detected in a different host genetic background by using coisogenic B10 (*Lps*^{n}) and B10Sc

TABLE 3. Pairwise comparison of levels of bacteremia of 10 mouse strains at three sampling times[a]

Mouse strain	Comparison with strain:								
	A	AKR	BALB/c	BUB/Bn	CBA	CBA/N	C3H/HeJ	C3HeB/FeJ	B6
A									
AKR	1								
BALB/c									
BUB/Bn	1								
CBA	3								
CBA/N		1, 2		1					
C3H/HeJ	3	1, 3	3	1, 3	3	3			
C3HeB/FeJ	1						3[b]		
B6	1		1, 2			1, 2	1, 2, 3		
DBA/2	3	1		1			3		1, 2

[a] The presence of a number in the table indicates that there was a statistically significant difference ($P < 0.01$) between two strains at a particular sampling time: 1, 4 h; 2, 8 h; 3, 12 h.
[b] $P = 0.01$ at 4 h; $P = 0.02$ at 8 h; $P = 0.001$ at 12 h.

(*Lps*^{d}) mice. The results (Fig. 2) were essentially identical to those for the C3H strains. *Lps*^{n} mice were clearing the bacteremia by 12 h after infection, and the mean and median durations of bacteremia were both <1 day. *Lps*^{d} mice experienced a 1,000-fold-higher bacteremia level at 12 h, and the mean and median durations of bacteremia were both 6 days, with one mouse remaining bacteremic for 13 days. All mice survived the infection.

Meningococcal growth in mouse serum. We wanted to determine whether the difference in meningococcal growth in vivo in *Lps* coisogenic mice was related to differences in serum factors such as bactericidal antibody and complement or transferrin. There was no detectable difference in growth of strain FAM18 in vitro in serum from C3H/HeJ and C3H/HeN mice (the doubling time was less than 45 min in 50% serum from both strains), indicating that serum factors alone did not account for the different susceptibilities of *Lps* coisogenic mice.

DISCUSSION

Inbred mouse strains provide a valuable tool in understanding how genetically determined host factors influence susceptibility to infectious diseases caused by a wide variety of pathogens (26). Although mice have been used in the study of *N. meningitidis* infection (4), there has been little consideration of the possible effects of the differing host genotypes used by different investigators. The mouse strains we used in this study represented disparate genotypes and varied at a number of loci known to influence susceptibility to other pathogens, including the *Ity* locus (16), the *xid* antibody production locus (23), and the complement C5 locus *Hc* (6). The mouse strains also varied at loci that could be hypothesized to influence meningococcal infection. These included *Hc*, since complement-mediated bactericidal activity is associated with immunity against meningococcal disease in humans (4, 8, 9, 24), and the transferrin locus, *Trf*, since transferrin-mediated iron turnover has been implicated as important in meningococcal infection in mice (13).

There were differences between some mouse strains in the level of meningococcemia displayed after i.p. infection, indicating that the host genotype influenced susceptibility. These differences may indicate that susceptibility in this model is polygenic, although minor differences in inoculum size or metabolic state of the bacteria, as well as other host or pathogen factors, could contribute to the differences we observed. There was no significant correlation between the level of meningococcemia in this model and particular alleles at any of the loci described above or with major histocompatibility or immunoglobulin alleles.

In contrast, there were significant differences in susceptibility associated with the *Lps* locus. *Lps*^{d} mice experienced a longer duration of bacteremia than *Lps*^{n} mice, as well as a greater bacteremia level at 12 h. Although both C3HeB/FeJ and C3H/HeN mice are frequently used as coisogenic relatives of C3H/HeJ mice (7, 12, 19, 21), these strains have been separated for years, and there is at least one other locus unrelated to *Lps* that varies between the strains, which is responsible for *Salmonella* susceptibility in C3HeB/FeJ mice (22). For this reason, we also confirmed our results by using coisogenic strains from the B10 lineage. Susceptibility to meningococcal infection completely correlated with the *Lps* genotype in all the coisogenic mouse strains. More rigorous proof of the role of the *Lps* locus in determining susceptibility or resistance to meningococcemia will require either backcross linkage analysis or infection studies with appropriate recombinant inbred mice.

The *Lps* locus influences susceptibility to *S. typhimurium* (21) and *E. coli* (12). *Lps*^{d}-mediated susceptibility to *S. typhimurium* is caused by proliferation of the bacteria in the reticuloendothelial system of the host as a result of diminished antibacterial activity of macrophages (21). Meningococcal disease, which is typically rapid and fulminant and against which humoral defenses are considered of primary importance (4, 9), is very different from typhoid fever, which is generally a more prolonged intracellular infection in which cellular defenses are clearly important (21). Although the evidence is not complete, the meningococcus is generally considered an extracellular pathogen, unable to survive in host immune cells (9, 25). We do not know whether *Lps* determines the host response to pathogens that exploit the host by very different mechanisms or whether a common intracellular site of action influences the survival of meningococci as well as salmonellae.

Virtually all of the reported effects of the *Lps* locus involve cellular responses (10, 20). Macrophages of *Lps*^{d} mice show multiple defects, including decreased activation in response to endotoxin (10, 20) and defective anti-*Salmonella* activity (21). *Lps*^{d} macrophages are deficient in the release of tumor necrosis factor and interferon in response to LPS stimulation and are defective in tumoricidal activity and in their response to macrophage migration inhibiting factor (1, 10). The kinetics of polymorphonuclear leucocyte and macrophage influx into the peritoneal cavity following the injection of LPS is influenced by the *Lps* locus (19). B

lymphocytes of Lps^d mice show reduced mitogenic stimulation, polyclonal activation, and maturation in response to LPS (10, 30).

Thus, it is likely that a cellular response to meningococcal infection was influenced by the mouse locus *Lps*. Defects in one or more of the above cell types could account for the significant, prolonged meningococcemia we observed in Lps^d mice. Although cell-mediated immunity in meningococcal disease has not been as extensively studied as humoral immunity, there is evidence for interactions between some of these cell types and meningococci in human disease and murine infection. Mononuclear cells are thought to play a role in clearance and killing of circulating meningococci (5, 17). Meningococci cause a pyogenic infection, and polymorphonuclear leukocytes kill meningococci in vitro (25). Also, some lymphocytes are meningococcidal (17), and meningococci and immunization with meningococcal antigens impair the function of B and T lymphocytes (11, 18, 28, 29).

The defect we observed in Lps^d mice is unlikely to be mediated by a difference in specific acquired antibody response, since differences between *Lps* variant strains occurred early (12 h) after infection, before any acquired antibody response was detectable. The observation that strain FAM18 meningococci grew equally well in serum from Lps^n and Lps^d mice also argues, albeit indirectly, that the increased susceptibility of Lps^d mice to meningococcal infection was not due to natural differences in serum factors such as antibody, complement, or iron.

Lps^d-associated susceptibility to meningococcemia is not unique to infection with strain FAM18, since some other strains caused a bacteremia of even greater duration in C3H/HeJ mice than that caused by strain FAM18 (our unpublished data). However, some strains of meningococci were cleared relatively rapidly in C3H/HeJ mice (our unpublished data), indicating that there may be differences in the ability of different meningococci to exploit the Lps^d genotype. We are currently investigating possible differences in meningococcal surface components that correlate with differences in growth in C3H/HeJ mice. In murine typhoid fever, there is also variation in the ability of different *S. typhimurium* strains to exploit the Ity^s genotype (2).

Host susceptibility loci can have pleiomorphic effects. For example, the murine locus *Ity* influences the killing of a number of pathogens, including both procaryotes and eucaryotes and both intra- and extracellular pathogens (16). We have shown that the murine locus *Lps*, which influences cellular responses to endotoxin and susceptibility to *S. typhimurium*, also affects susceptibility to *N. meningitidis* infection. Coisogenic mice differing at the *Lps* locus may provide a useful, well-defined genetic background with which to study some aspects of resistance to meningococci that have not been as well characterized as humoral immunity.

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