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Susceptibility and Resistance to Poliovirus-Induced Paralysis of Inbred Mouse Strains

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Susceptibility to human poliovirus-induced disease in different inbred mouse strains was analyzed after intracerebral inoculation of two mouse-adapted type 2 polioviruses, the attenuated W-2 strain and the virulent Lansing strain. In contrast to inoculation with the Lansing strain, which was invariably lethal, inoculation with the W-2 strain defined three groups of mice with high, intermediate, or low disease incidence. Those in the high-disease-incidence group, the DBA/1J and DBA/2J mice, exhibited a high level of virus replication in the spinal cord by day 2 postinfection, with no detectable neutralizing-antibody response. Mice in the intermediate- and low-incidence groups had lower levels of virus replication in the spinal cord and/or produced neutralizing antibodies. No correlation was observed between *H-2* haplotype and the extent of virus replication, production of neutralizing or enzyme-linked immunosorbent assay-detectable antibodies, or T-cell-proliferative response. However, mice of the *H-2*^{k} haplotype manifested a low incidence of disease.

A genetic predisposition of humans to paralytic poliomyelitis has long been suspected (2, 26, 33); however, the nature of the putative genetic component remains unclear. Twin and pedigree studies have suggested that autosomal recessive genes are associated with susceptibility to paralytic poliomyelitis (1, 10, 30), although dominant-gene inheritance for disease susceptibility has also been noted (41). Analyses of the role of the major histocompatibility complex in paralytic-poliomyelitis susceptibility have also given variable results, with one report of a significant association with HLA-A3 and HLA-A7 (28) which was not confirmed (8, 20, 42) and a report of association of HLA-encoded genetic factors with resistance rather than susceptibility (36). Indeed, we previously reported differences between two inbred mouse strains in their cell-mediated immune responses to peripheral inoculation of the poliovirus type 2 W-2 strain (PV2/W-2) (37). However, our further investigation using 17 different mouse strains did not reveal a correlation between cell-mediated immune responses and *H-2* haplotype (38). Our present study of disease susceptibility and pathogenesis of poliovirus-induced paralysis in inbred mice of different *H-2* haplotypes indicates variation in susceptibility to the attenuated PV2/W-2 strain but not to the virulent Lansing (PV2/Lansing) strain. Susceptibility to PV2/W-2-induced paralysis did not correlate with *H-2* haplotype but appeared to correlate with the non-*H-2* genes of the DBA mouse strains, an inability to produce neutralizing antibodies, and the rapid spread and replication of virus in the central nervous system. In contrast, all three *H-2*^{k} mouse strains examined had a low incidence of disease.

To determine their susceptibility to disease, 10 strains of inbred mice were inoculated intracerebrally (i.c.) with 0.02 to 0.03 ml of either the attenuated tissue culture-derived, plaque-purified PV2/W-2 strain ($10^{7.4}$ 50% tissue culture infective doses [TCD_{50}s] (16) or the virulent, mouse brain-derived PV2/Lansing strain ($10^{4.3}$ TCD_{50}s) (14). Both virus strains were used, since PV strains of varied neurovirulence exist in nature (25, 33) and highly virulent strains can override host genetic factors and mask susceptibility or resistance (24, 32). Six-week-old, barrier-free male mice were used. A/J, AKR/J, B10.D2/J, C57BL/10J (B10), CBA/J, C3H/HeJ, DBA/1J (D1), and DBA/2J (D2) mice were purchased from the Jackson Laboratory, Bar Harbor, Maine; BALB/c mice were purchased from Cumberland View Farms, Clinton, Tenn.; and CD-1 Swiss mice were purchased from Charles River, Portage, Mich. Mice were observed daily for paralysis and death through day 30 postinfection (p.i.). The cumulative percentage of paralysis and death was calculated from the total number of mice paralyzed plus the mice that died without over paralysis (nonparalytic death). Paralysis and nonparalytic death were combined because all paralyzed mice die and less than 5% of mice die without observed paralysis (14, 16). Statistical analysis of disease incidence plus time to disease onset was determined by the life table method (27) by using the times to paralysis and to nonparalytic death as life table endpoints. Nine statistically independent comparisons (35) were made, and each was tested for significance with 1 df by using the log rank test (27). The set of comparisons was chosen on the basis of the hypothesis that a high incidence of disease would correlate with a high level of virus replication in the spinal cord and a lack of detectable neutralizing antibodies, while an intermediate or low incidence of disease would correlate with a lower level of virus replication in the spinal cord and/or the production of neutralizing antibodies. The orthogonal set of comparisons (c_i) was as follows: (c_1) D1 and D2 versus all other strains; (c_2) D1 versus D2; (c_3) A/J, B10, and BALB/c versus CD-1, B10.D2/J, AKR/J, C3H/HeJ, and

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TABLE 1. Cumulative percent paralysis and death in inbred mouse strains inoculated i.c. with PV2/W-2

Mouse strain	*H-2* type	Cumulative % paralysis and death[a]			Incidence category[b]
		Expt 1	Expt 2	Combined	
D1	q	68 (13/19)	53 (8/15)	60.5 (21/34)	High
D2	d	40 (8/20)	40 (6/15)	40.0 (14/35)	High
BALB/c	d	26 (5/19)	33 (5/15)	29.5 (10/34)	Intermediate
B10	b	29 (5/17)	27 (4/15)	28.0 (9/32)	Intermediate
A/J	a	26 (5/19)	20 (3/15)	23.5 (8/34)	Intermediate
AKR/J	k	20 (4/20)	20 (3/15)	20.0 (7/35)	Low
B10.D2/J	d	20 (4/20)	7 (1/15)	13.5 (5/35)	Low
CD-1 (Swiss)	Mixed	10 (2/20)	13 (2/15)	11.5 (4/35)	Low
C3H/HeJ	k	15 (3/20)	0 (0/15)	7.5 (3/35)	Low
CBA/J	k	5 (1/20)	7 (1/15)	6.0 (2/35)	Low

[a] Numbers in parentheses are the number of mice developing clinical disease divided by the number inoculated.
[b] Based on statistical analysis with data from this table and Fig. 1. See text for method.

CBA/J; (c_4) A/J versus B10 and BALB/c; (c_5) B10 versus BALB/c; (c_6) B10.D2/J and AKR/J versus CD-1, C3H/HeJ, and CBA/J; (c_7) B10.D2/J versus AKR/J; (c_8) C3H/HeJ versus CD-1 and CBA/J; and (c_9) CD-1 versus CBA/J.

A marked variation in susceptibility to paralysis and death in mice inoculated with PV2/W-2 was observed (Table 1, Fig. 1). The D1 and D2 mice, which share a large number of non-*H-2* genes because of their relatively recent common origin (3), had the highest incidence of paralysis and death, whereas the other strains had comparatively low to intermediate incidence rates. The D1 and D2 mice had significantly higher incidences of paralysis and death than the other mouse strains ($P < 0.005$). These two strains did not differ significantly from each other with respect to disease incidence. The values for strains with intermediate incidences of paralysis and death (A/J, B10, and BALB/c) were significantly different from those for the strains with low incidences (CD-1, B10.D2/J, AKR/J, C3H/HeJ, and CBA/J) ($P < 0.005$). All $H\text{-}2^k$ haplotype strains tested had low incidence rates. No statistically significant differences were detected among the strains with intermediate incidences or among those with low incidences of paralysis and death.

Little variation in susceptibility was seen among mice infected with the virulent PV2/Lansing strain, as all strains had a very high incidence of paralysis and death (Table 2). Because the virulent PV2/Lansing strain was invariably lethal in all mouse strains and because its pathogenesis has been previously analyzed (14, 15, 18), no further experiments were undertaken with this virus. The invariable lethality of PV2/Lansing was not unexpected since this virus spreads rapidly throughout the nervous system, presumably by fast axonal transport (18) and does not induce a neutralizing-antibody response (14, 15, 22). A previous study of disease incidence among nine mouse strains infected with

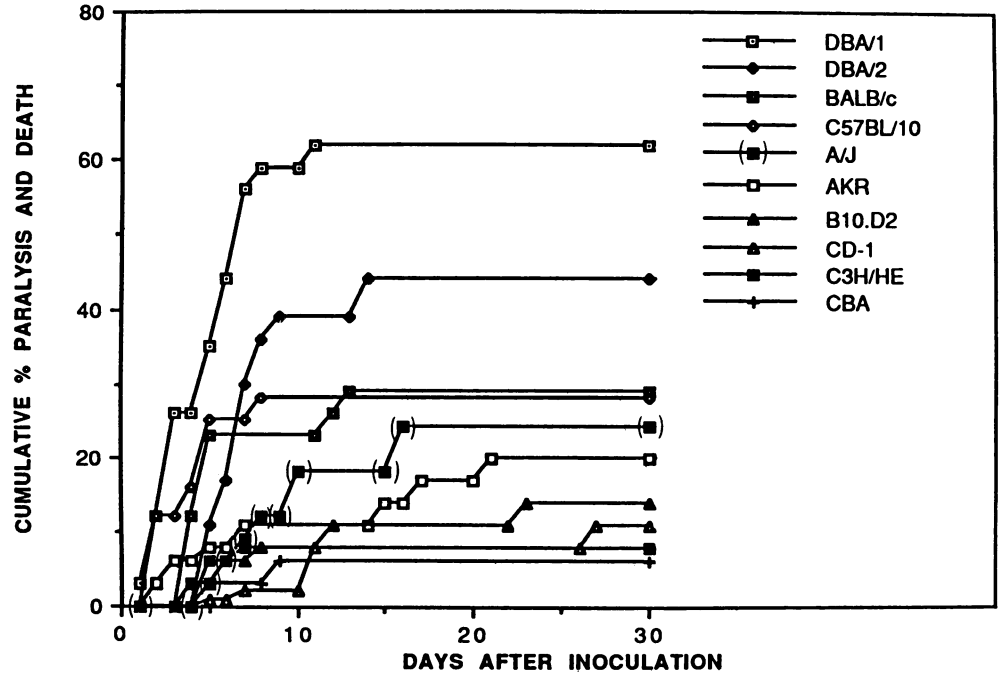

FIG. 1. Combined cumulative percent paralysis and death (from replicate experiments [Table 1]) in various inbred mouse strains after i.c. inoculation with PV2/W-2.

TABLE 2. Cumulative percent paralysis and death in inbred mouse strains inoculated i.c. with PV2/Lansing

Mouse strain	*H-2* type	Cumulative % paralysis and death[a]
D1	q	100 (15/15)
D2	d	100 (15/15)
BALB/c	d	85 (17/20)
B10	b	80 (12/15)
A/J	a	93 (14/15)
AKR/J	k	80 (12/15)
CD-1 (Swiss)	Mixed	94 (16/17)
CBA/J	k	100 (15/15)

[a] Numbers in parentheses are the number of mice that developed clinical disease divided by the number inoculated.

PV2/Lansing also found this strain to be invariably fatal (34).

To determine the basis of the observed variation in disease susceptibility to PV2/W-2, mice of each strain were inoculated i.c. with PV2/W-2 ($10^{7.4}$ TCD_{50}s) and killed at regular intervals for central nervous system virus assays and T-cell proliferation (TPRLF) assays. Other mice were bled from the retro-orbital venous plexus at periodic intervals to obtain sera for antibody assays. For virus assays, brain (brain plus brainstem) and spinal cord tissues were prepared separately as 10% homogenates and stored at −70°C until assayed. Virus replication was assayed by a microtiter method (17), and the TCD_{50} was calculated (29). Three nonparalyzed mice were assayed at each time point, and the geometric means were calculated. Paralyzed mice were not assayed, since all such mice are known to have high virus titers in the spinal cord at the onset of paralysis (17, 18). Virus replication in the brains of nonparalyzed mice rapidly peaked on day 1, 2, or 3 p.i., reaching levels of 4.5 to 6.0 $\log_{10}$ TCD_{50}s/0.02 g of tissue for all strains analyzed (Table 3). In contrast, virus replication in the spinal cords of nonparalyzed mice reached high levels (>4.0 $\log_{10}$ TCD_{50}s/0.02 g of tissue) in only four strains, D1 and D2 (high-incidence strains) and BALB/c and B10 (intermediate-incidence strains) (Table 4). In other strains, virus replication in the spinal cord was at lower levels. There was no obvious correlation between spinal cord virus replication and *H-2* haplotype.

A correlation between paralysis and death and a high level of spinal cord virus replication after i.c. PV inoculation has been previously recognized (17, 18) and might reflect a more rapid spread of virus from the brain to the cord in some mouse strains or a greater susceptibility of cells in the spinal cord to infection. If virus actually spreads more rapidly to spinal cords in susceptible mice, then several possibilities exist. Some viruses, such as the arboviruses, are thought to spread through extracellular gaps in the neuropil (4) that communicate freely with the cerebrospinal fluid compartment (5). Possibly some inbred mouse strains have larger extracellular gaps that allow virus in the cerebrospinal fluid easier access to anterior horn cells. However, our previous studies with Swiss mice gave no indication that the virulent PV2/Lansing strain spreads via the cerebrospinal fluid and extracellular gaps (18). Also, in our studies with PV2/W-2, we found no evidence of infected arachnoid or meningeal cells, which would facilitate spread through the cerebrospinal fluid (16, 17). Alternatively, virus spread might occur intracellularly via axonal transport, in which case high-disease-incidence mouse strains might have more efficient entry of PV into the transporting cells (via receptors), more efficient transport of virus, or more direct pathways to anterior horn cells. To our knowledge, no experimental evidence to support any of these possibilities exists.

Serum antibody responses were determined by both a microneutralization (13) and an indirect solid-phase enzyme-linked immunosorbent assay (ELISA) method for the total antibody response (immunoglobulin M plus immunoglobulin G) (15). The neutralizing-antibody response peaked early on day 4 in most strains and plateaued or gradually declined thereafter (Table 5). The strains with the highest incidence of paralysis and death, i.e., D1 and D2, had the lowest levels of neutralizing antibody. There was no obvious correlation between neutralizing-antibody titers and *H-2* haplotype. Thus, a second major factor apparently related to PV2/W-2-induced paralysis appears to be an impaired ability of a mouse strain to mount a neutralizing-antibody response. The importance of neutralizing antibody in preventing PV-induced disease is suggested by the observation that mice hyperimmunized to induce a serum neutralizing-antibody response to the virulent PV2/Lansing strain resist i.c. challenge with large doses of virus (14). In addition, passive administration of hyperimmune serum prevents disease after i.c. inoculation with the PV2/Lansing strain (13a). Neutralizing antibody appears to be important for clearing PV from the central nervous system and preventing disease.

Mice of all strains, including the high-disease-incidence D1 and D2 mice, were capable of producing antibodies, as

TABLE 3. Replication of PV2/W-2 in brains of inbred mouse strains after i.c. inoculation[a]

Mouse strain	Mean replication (SD) at day p.i.[b]							
	0.25	1	2	3	6	10	20	30
D1	3.2 (1.0)	**5.1** (0.4)	4.7 (0.0)	3.9 (0.5)	3.6 (0.9)	0.0 (0.0)	0.0 (0.0)	1.8 (2.0)
D2	1.2 (0.6)	**5.9** (1.4)	3.9 (2.0)	4.7 (0.1)	2.9 (0.5)	1.1 (1.0)	0.0 (0.0)	0.0 (0.0)
BALB/c	2.7 (0.7)	5.0 (0.5)	**5.3** (0.3)	4.3 (0.3)	2.6 (0.7)	2.3 (1.0)	0.7 (1.3)	3.7 (0.7)
B10	2.3 (0.5)	3.6 (0.1)	4.8 (0.9)	**5.8** (1.5)	2.7 (0.5)	0.7 (1.3)	0.0 (0.0)	0.0 (0.0)
A/J	2.1 (1.0)	5.3 (0.3)	**6.1** (1.2)	4.9 (1.4)	3.2 (0.6)	0.5 (0.8)	0.0 (0.0)	0.0 (0.0)
AKR/J	2.4 (0.2)	4.8 (0.5)	**4.9** (0.8)	3.9 (0.4)	2.9 (1.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
B10.D2/J	2.9 (1.0)	3.6 (1.5)	3.9 (0.8)	**4.8** (0.2)	2.3 (1.2)	1.1 (1.0)	0.6 (1.0)	0.0 (0.0)
CD-1	1.9 (0.6)	4.2 (0.5)	**4.5** (1.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.9 (0.8)
C3H/HeJ	2.3 (0.7)	5.0 (0.3)	5.1 (0.7)	**5.2** (0.5)	3.2 (1.6)	1.8 (0.4)	0.0 (0.0)	0.3 (0.6)
CBA/J	2.4 (0.5)	**4.8** (2.4)	3.6 (0.7)	4.6 (0.1)	3.8 (0.5)	0.6 (1.0)	0.0 (0.0)	0.0 (0.0)

[a] Inoculation with undiluted stock virus ($10^{7.4}$ TCD_{50}s).

[b] Geometric mean ($\log_{10}TCD_{50}$s) for three nonparalyzed mice. Peak virus titers are shown in boldface.

TABLE 4. Replication of PV2/W-2 in spinal cords of inbred mouse strains after i.c. inoculation[a]

Mouse strain	Mean replication (SD) at day p.i.[b]							
	0.25	1	2	3	6	10	20	30
D1	1.3 (1.4)	**4.3** (1.9)	3.8 (2.9)	1.7 (3.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
D2	0.0 (0.0)	1.8 (2.2)	**5.8** (0.6)	3.3 (2.9)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
BALB/c	0.2 (0.3)	0.0 (0.0)	**4.8** (0.6)	1.8 (3.2)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	1.2 (2.0)
B10	1.4 (2.0)	**4.0** (2.0)	1.8 (3.2)	0.2 (0.3)	1.8 (3.2)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
A/J	0.0 (0.0)	0.0 (0.0)	0.2 (0.3)	**1.8** (3.2)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
AKR/J	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
B10.D2/J	**0.9** (1.5)	0.0 (0.0)	0.7 (1.3)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.6 (1.0)	0.0 (0.0)
CD-1	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	**1.3** (2.3)	0.0 (0.0)	0.0 (0.0)
C3H/HeJ	2.8 (0.3)	2.5 (2.5)	2.0 (2.6)	1.6 (2.1)	**2.9** (2.7)	1.4 (2.4)	0.0 (0.0)	0.0 (0.0)
CBA/J	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)

[a] Inoculation with undiluted stock virus ($10^{7.4}$ TCD_{50}s).
[b] Geometric mean ($\log_{10}$ TCD_{50}s) for three nonparalyzed mice. Peak virus titers are shown in boldface.

detected by the ELISA method (Table 6). In a previous study, a prominent ELISA antibody response was observed in animals infected with PV2/Lansing, although neutralizing antibodies were not detected (15). Thus, as is the case with some other virus infections (12, 23, 39), antibodies detected by ELISA and other nonneutralizing techniques appear to be a good indication of PV infection but do not provide protection.

TPRLF responses were analyzed with suspensions of single cells of draining cervical lymph nodes pooled from three to five mice of each strain for each time point and assayed with [^{3}H]thymidine as described previously (19). Net counts per minute (cpm) were calculated as the mean cpm in wells with antigen (10 μl of inactivated, undiluted PV2/W-2 stock per well) minus the mean cpm in wells without antigen. The net cpm for control mice of each strain inoculated i.c. with virus diluent were subtracted from the experimental net cpm at each time point to control for day-to-day variation. The TPRLF responses varied considerably among the different strains (data not shown), and there was no obvious indication that a high TPRLF response was protective. These findings contrast with those of our previous study using antithymocyte serum to treat PV-infected BALB/c mice, which suggested a role for T cells in central nervous system viral clearance (19). In addition, there was no correlation of TPRLF responses with *H-2* haplotype. Still, the TPRLF responses were similar to those found in our previous study (38).

In the present investigations, we observed a marked variation in disease susceptibility (paralysis and death) in 10 inbred strains of mice inoculated with the attenuated PV2/W-2 strain. Log rank analysis defined three categories (high, intermediate, and low) of disease incidence in these mice. The disease incidences differed significantly among the three groups, and no significant differences were detected within each group. The pathogenesis studies with the PV2/W-2 strain suggest the importance of two factors as the biological bases for disease susceptibility: a high level of virus replication in the spinal cord within several days of i.c. virus inoculation and the inability of a mouse strain to mount a neutralizing-antibody response. Both factors characterized the D1 and D2 mice.

We were unable to correlate *H-2* haplotype with high disease incidence, virus replication in the brain or spinal cord, neutralizing antibody or ELISA antibody responses, or TPRLF responses. There may be a correlation between the $H\text{-}2^k$ haplotype and resistance to disease, but further analysis is needed. A variation in disease susceptibility of different mouse strains has been noted during infection with two other picornaviruses, coxsackievirus (9, 11, 40) and Theiler's virus (6, 31). In both virus infections, susceptibility has been shown to be under multigenic control by both *H-2*-associated and non-*H-2* genes (7, 21, 31, 40). The lack of a neutralizing-antibody response in the D1 and D2 mice might reflect control of this response by non-*H-2* genes, which are similar in these two strains. Further information on the genetic control of susceptibility and resistance to poliovirus-induced disease awaits analyses with congenic

TABLE 5. Serum neutralizing-antibody responses of inbred mouse strains after i.c. inoculation with PV2/W-2[a]

Mouse strain	Mean titer (SD) at day p.i.[b]			
	4	12	20	30
D1	0.4 (0.4)	0.3 (0.5)	0.0 (0.0)	0.2 (0.4)
D2	0.1 (0.3)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
BALB/c	2.6 (0.4)	2.2 (0.8)	1.8 (0.8)	1.6 (0.8)
B10	1.5 (0.4)	1.0 (0.7)	0.5 (0.4)	0.4 (0.6)
A/J	2.1 (0.3)	1.5 (0.4)	1.6 (0.4)	1.9 (0.3)
AKR/J	1.6 (0.2)	1.4 (0.5)	1.2 (0.8)	1.2 (1.0)
B10.D2/J	1.2 (0.3)	1.1 (0.7)	0.8 (0.9)	0.7 (1.0)
CD-1	1.2 (0.8)	0.7 (0.8)	0.4 (0.8)	0.7 (0.8)
C3H/HeJ	1.8 (0.5)	1.1 (0.7)	0.9 (0.6)	0.4 (0.5)
CBA/J	1.8 (0.3)	2.0 (0.4)	1.8 (0.5)	1.7 (0.5)

[a] Inoculation with undiluted stock virus ($10^{7.4}$ TCD_{50}s).
[b] Geometric mean ($\log_{10}$ of antibody titer) for five or more nonparalyzed mice. Day 0 time points showed no neutralizing antibody at the initial dilution of 1.8.

TABLE 6. Serum ELISA antibody responses of inbred mouse strains after i.c. inoculation with PV2/W-2[a]

Mouse strain	Mean titer (SD) at day p.i.[b]			
	4	12	20	30
D1	0.0 (0.0)	0.9 (1.5)	1.5 (1.4)	1.4 (1.2)
D2	0.0 (0.0)	2.4 (0.7)	3.0 (0.5)	3.1 (0.5)
BALB/c	1.4 (1.6)	3.1 (1.0)	3.0 (0.3)	3.4 (0.2)
B10	0.4 (0.9)	1.2 (1.2)	2.3 (0.0)	2.9 (0.4)
A/J	0.3 (0.8)	1.6 (1.5)	2.7 (1.6)	2.5 (1.7)
AKR/J	2.6 (0.2)	3.0 (0.2)	3.1 (0.2)	3.1 (0.2)
B10.D2/J	1.6 (0.9)	1.3 (1.2)	1.3 (1.2)	1.7 (1.0)
CD-1	0.7 (1.2)	3.0 (0.2)	3.4 (0.3)	3.7 (0.2)
C3H/HeJ	1.7 (1.0)	3.6 (0.3)	3.6 (0.2)	3.7 (0.3)
CBA/J	2.3 (0.3)	3.1 (0.5)	3.2 (0.3)	3.2 (0.5)

[a] Inoculation with undiluted stock virus ($10^{7.4}$ TCD_{50}s).
[b] Geometric mean (log_{10} of antibody titer) for five or more nonparalyzed mice. Serum was obtained from experimental mice of each strain prior to virus inoculation and assayed to establish a normal curve to which all p.i. samples were compared.

mouse strains of identical *H-2* haplotypes but different genetic backgrounds.

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