0019-9567/78/0019-0123$02.00/0
INFECTION AND IMMUNITY, Jan. 1978, p. 123-130
Vol. 19, No. 1

Printed in U.S.A.

Susceptibility of Inbred and Outbred Mouse Strains to Sendai Virus and Prevalence of Infection in Laboratory Rodents

JOHN C. PARKER,[1]* MARY D. WHITEMAN,[1] AND CONRAD B. RICHTER[2]

Microbiological Associates, Inc., Walkersville, Maryland 21793,[1] and Oak Ridge Associated Universities, Inc., Oak Ridge, Tennessee 37830[2]

Received for publication 30 June 1977

Sendai virus is one of the more prevalent and serious virus infections of rodents. Infection was found in 66% of the mouse, 63% of the rat, 83% of the hamster, and 44% of the guinea pig colonies examined. Twenty-four inbred and outbred strains of mice were tested for their sensitivity to lethal Sendai virus infection. The 129/J mice tested were approximately 25,000-fold more sensitive than SJL/J mice; however, both mouse strains were similarly permissive in support of viral replication in their lung tissues. Histopathological studies revealed that whereas lesions in both sensitive and resistant mice were qualitatively similar, the lesions in the more sensitive 129/J mice appeared earlier, were much more extensive, and persisted longer than in the resistant SJL/J mice. These results suggest that the observed variance in sensitivity is not the result of a genetic restriction on virus infection and replication but rather is the result of a physiological factor(s) possibly related to some aberration or strain difference in the humoral or cell-mediated immune response.

Sendai virus infection of mice was first detected in Japan by Fukumi et al. (13) in 1954 and later, in 1964, was found to be widespread in the United States (22). Infections occur in mouse, hamster, rat, and guinea pig colonies throughout the world, but disease and death are well documented only for mice (13, 19, 22, 24, 25, 32). Originally, Sendai virus was thought to produce only subclinical enzootic and occasional epizootic infections in mice (15, 21, 32). It was not until a few years later that the full potential of Sendai virus as a respiratory pathogen was recognized (5, 26, 33, 34; J. M. Ward, M. J. Collins, Jr., and J. C. Parker, Abstr. 27th Annu. Meet. Am. Assoc. Lab. Anim. Sci., Abstr. no. 42, 1976). It is now believed that Sendai virus is the leading cause of pneumonia in mice and, together with the mouse hepatitis viruses, is the most prevalent and important of the naturally occurring virus infections of mice (J. C. Parker, unpublished data).

Sendai virus infection in mouse colonies may manifest itself in several distinct ways. Infection may be enzootic or epizootic, may or may not persist as a chronic infection, and may or may not be associated with clinical disease and mortality (5, 21, 33, 34). The factors determining these types of infection patterns are not understood completely.

In the present study, the occurrence of clinical disease and mortality in mice was found to be directly related to the extreme range of sensitivity of different mouse strains. Whereas both sensitive 129/J mice and resistant SJL/J mice were similarly permissive to viral infection and replication, the 129/J mice were 25,000-fold more sensitive than the SJL/J mice to lethal infection. Also, the present study reports the sensitivity of 22 other mouse strains and additional studies performed in an attempt to explain the variance in sensitivity.

MATERIALS AND METHODS

Animals. Inbred 129/ReJ, 129/J, DBA/1J, DBA/2J, A/HeJ, A/J, SWR/J, C57L/J, C3Heb/FeJ, BALB/cJ, C58/J, AKR/J, C57BL/6J, C57BL/10Sn, RF/J, and SJL/J mice 4 to 6 weeks old were obtained from Jackson Laboratories, Bar Harbor, Maine; C3H/Bi, DBA/2, and C57BL/6 mice 4 to 6 weeks old were obtained from Microbiological Associates, Inc., Walkersville, Md.; and outbred Swiss mice 4 to 6 weeks old were obtained from Microbiological Associates, Inc.; National Laboratory Animal Co., Creve Coeur, Mo.; Life Sciences, St. Petersburg, Fla.; and the National Institutes of Health, Bethesda, Md. Nude Swiss mice were reared in germfree isolators in our laboratory. These mouse colonies were free of Sendai virus infection; however, pneumonia virus of mice was indigenous in both colonies (Jackson Laboratories, Microbiological Associaties, Inc.) that supplied inbred mice. Usually, male mice were tested. Mice were housed in plastic, disposable filter-topped cages containing sterilized bedding and diet. Apples were used as the water source.

For antibody surveillance studies, rats, hamsters, guinea pigs, gerbils, and mice were obtained from a

variety of commercial or institutional colonies. Usually, 20 to 50 animals of mixed sexes, 4 months or more in age, were tested from each colony.

Virus. The P3193 strain of Sendai virus was isolated in 129/J mice from a lung suspension of a naturally infected 129/J mouse that had been sent to the Microbiological Associates, Inc., Diagnostic Laboratory. All passages of P3193 were made in 129/J mice. Homogenates of infected lungs (10% suspension [wt/vol] in basal medium [Eagle] with antibiotics clarified at 1,700 × *g* for 30 min at 5°C) were inoculated by intranasal (i.n.) instillation of 0.05 ml of undiluted or diluted 10% infected mouse lung suspension. Lungs of mice were harvested 5 to 6 days after inoculation. P3193 virus was tested by the mouse antibody production test (11) and found not to contain other murine virus contaminants.

Serology. Sera and plasma were heated at 56°C for 30 min and tested by the microtiter technique (31). The hemagglutination inhibition (HI) test employed 8 units of antigen and human or guinea pig erythrocytes (23). The complement fixation (CF) test employed the optimal dilution of antigen and 5 50% hemolytic complement units of complement (10). Sendai virus strain 52 was used in the serology antigen (21). Titers of 1:10 or greater were considered positive.

Virus titration and quantitation. (i) Tissue culture. Clarified 10% suspensions of infected lung tissues were diluted 10-fold, and 0.1 ml was inoculated into each of three tubes of primary rhesus monkey kidney cells (Microbiological Associates, Inc.). Cells were observed for cytopathic effects daily for 10 to 14 days, and end-point titers were calculated by the method of Kärber (18).

(ii) Mice. Usually three or more different mouse strains were included in a single titration experiment, and 129/J mice were always included as a control. Four mice were inoculated i.n. with 0.05 ml of each 10-fold virus dilution (10^{-1} to 10^{-8}). The same person (M.D.W.) made all inoculations throughout the titration experiments. Infected mice were observed for disease and death through day 14 or longer. Virus titers are expressed as the number of tissue culture infective doses ($TCID_{50}$) required to produce a lethal infection (LD_{50}), $TCID_{50}/1$ LD_{50}. Thus, the $TCID_{50}$ titer (in tissue culture) minus the LD_{50} titer (in mice) equals 1 lethal dose (LD_{50}) in mice expressed in $TCID_{50}$. This provided an adjusted basis for direct comparison of sensitivity between mouse strains.

Histology. Lungs of mice were perfused with neutral buffered Formalin, embedded in paraffin, sectioned at 5 μm, and stained with hematoxylin and eosin (American Histology Laboratory, Wheaton, Md.).

RESULTS

Prevalence of Sendai virus infection. Over the past 13 years, colonies of mice, rats, hamsters, guinea pigs, and gerbils have been tested by the HI or CF test for antibody to Sendai virus. More than one-half of all mouse, rat, and hamster colonies were infected (Table 1). Of the four uninfected hamster colonies tested, three are no longer functioning and one has since become infected with Sendai virus. The prevalence of infection within infected colonies was high. In 60% or more of the colonies tested (except guinea pigs), more than one-half of the animals in each colony had been infected as determined by seroconversion.

Comparative sensitivity of the HI and CF test. The CF test replaced the HI test after a study showed that the CF test was more sensitive (Fig. 1). Twenty Swiss mice were infected i.n. with 0.05 ml of $10^{4.0}$ $TCID_{50}$ of Sendai virus (strain P1656B; isolated from a naturally infected C3H/Bi mouse), and 7 days later, another 20 uninfected Swiss mice were placed in contact (the same cage) with the infected mice. A total of 18 of the 20 uninfected mice became infected, and all mice were followed serologically for 38 weeks. Both inoculated and contact-infected an-

TABLE 1. *Prevalence of Sendai virus infection in rodent colonies*

Rodent colony	No. of colonies infected/no. tested[a]	Colonies infected (%)	No. of infected colonies in which >50% of the animals were positive for antibody[b]
Mice	47/71	66	30 (64)[c]
Rats	15/24	63	9 (60)
Hamsters	20/24	83	14 (70)
Guinea pigs	7/16	44	1 (14)
Gerbils	0/5	0	0

[a] Twenty or more animals were tested from each colony, except guinea pig colonies, from which 10 to 15 animals were tested.

[b] HI or CF.

[c] Numbers in parentheses indicate percentages.

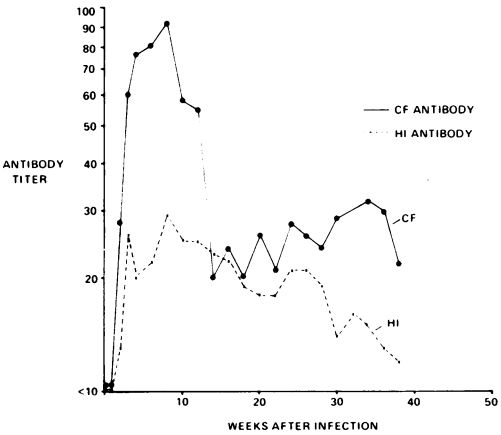

FIG. 1. *CF and HI antibody responses in Swiss mice naturally infected by contact with other inoculated-infected Swiss mice. A total of 18 mice per time point were repeatedly bled through 38 weeks. Antibody titer is the reciprocal geometric mean CF or HI titer.*

imals responded in a similar manner except that the antibody (CF and HI) titers were approximately twofold higher in inoculated mice after recovery from the infection.

In mice infected by contact (Fig. 1), 67% had a detectable CF antibody (mean titer, 1:28) by day 14, whereas only 33% (mean titer, 1:13) had a detectable HI antibody. Both the CF and HI antibodies increased to their highest titers by week 8; however, the CF titers were threefold higher than the HI titers (1:92 CF versus 1:29 HI). The CF antibody titer decreased sharply thereafter and persisted at approximately the same and later at a higher titer than the HI antibody.

Susceptibility of mouse strains. A difference in the susceptibility of different strains of mice was suspected when a colony of approximately 4,000 aging mice (originally free of Sendai virus infection) containing six inbred strains was accidentally exposed to Sendai virus. The infection spread throughout the colony, and within 4 months 43% of the mice had died. There were large variances in the mortality rates among the different mouse strains. A combined total of 66% of the 129/J, Snell, and C3H/Bi mice died, whereas only 29% of the C57L and C57BL/6 mice died (AKR mouse deaths were equivocal since they also had advanced lymphoma).

To determine whether the differences in mortality rates were strain dependent, Sendai virus was titrated simultaneously in 129/J and Swiss mice. The LD_{50} titers were $10^{6.5}$/0.05 ml and $10^{2.8}$/0.05 ml, respectively. In addition, two contact-infection experiments were performed in an attempt to mimic a natural situation in which Sendai virus is inadvertently introduced (Table 2) into a colony. In a single cage (18 by 18 inches [ca. 45.7 by 45.7 cm]), 10 each of 129/J, Swiss C3H/HeJ, and SJL/J mice were exposed to 10 129/J mice that had each been infected with Sendai virus ($10^{6.8}$ $TCID_{50}$/0.05 ml i.n.) 4 days previously. The second experiment used 129/J, 129/ReJ, C3H/Bi, and C57BL/6 mice. All of the inoculated 129/J mice died, and all surviving mice in both experiments seroconverted. The 129/J, 129/ReJ, and C3H/Bi contact-infected mice began to show clinical illness by day 5, and all subsequently died, whereas only one (10%) Swiss and none of the C3H/HeJ, SJL/J, or C57BL/6 mice died or became visibly sick.

To further investigate this apparent variation in sensitivity of mouse strains, 24 different inbred and outbred strains of mice were titrated with Sendai virus (Table 3). The 129/ReJ strain was 32,000-fold and the 129/J strain was 25,000-fold more sensitive to lethal infection than was the most resistant SJL/J strain. The most susceptible strains of mice were 129/ReJ, 129/J, nude Swiss, DBA/1J, C3H/Bi, DBA/2J, and DBA/2. Interestingly, C3Heb/FeJ was 25 times more resistant than C3H/Bi. LD_{50} titers of DBA/2 from colonies from Jackson Laboratories and Microbiological Associates, Inc., were

TABLE 2. *Course of Sendai virus infection in seven mouse strains placed in contact with acutely infected 129/J mice*

Expt no.	Mouse strain	No. of mice	Mortality (%, by day)	Infectivity (% survivors with antibody)	Antibody[a] titer	
					CF	HI
1	129/J	11	100, 13	—[b]	—	—
	Swiss[c]	10	10	100	188	26
	C3H/HeJ	9	0	100	93	15
	SJL/J	11	0	100	182	46
2	129/J	10	100, 14	—	—	—
	129/ReJ	10	100, 13	—	—	—
	C3H/Bi	10	100, 20	—	—	—
	C57BL/6	10	0	100	97	32

[a] Geometric mean antibody titers of mice 21 days postinfection.
[b] — indicates no survivors.
[c] Microbiological Associates, Inc.

TABLE 3. *Susceptibility of inbred and outbred strains of mice to Sendai virus infection*

Mouse strain	No. of replicate titrations	LD_{50} ± SE[a] (log_{10})
129/ReJ	1	0.5
129/J	4	0.6 ± 0.4
Nude (Swiss)	1	0.7
DBA/1J	3	1.3 ± 0.4
C3H/Bi	1	1.4
DBA/2J	3	1.6 ± 0.3
DBA/2	1	2.0
A/HeJ	3	2.5 ± 0.1
A/J	2	2.5 ± 1.0
SWR/J	1	2.7
Swiss[b]	1	2.7
C57L/J	2	2.7 ± 0.5
C57BL/10Sn	2	2.8 ± 0.6
C3Heb/FeJ	2	2.8 ± 0.1
Balb/CJ	1	3.0
C57BL/6	1	3.0
Swiss[c]	1	3.1
C58/J	1	3.2
AKR/J	3	3.4 ± 0.2
Swiss[d]	1	3.4
Swiss[e]	4	4.4 ± 0.0
C57BL/6J	1	4.4
RF/J	2	5.0 ± 0.5
SJL/J	3	5.0 ± 0.4

[a] $TCID_{50}/LD_{50}$. SE, Standard error.
[b] National Institutes of Health.
[c] Life Sciences.
[d] National Laboratory Animal Co.
[e] Microbiological Associates, Inc.

$10^{1.6}$ and $10^{2.0}$ $TCID_{50}/LD_{50}$, respectively, indicating no significant difference between the same strain reared in different locations. Also, no differences in mortality were noted between male and female 129/J mice.

Two strains of Sendai virus, P3193 and P2184 (isolated from a naturally infected C3H/Bi mouse), were titrated simultaneously in 129/J and SJL/J mice to determine whether the virus strain had any effect on mouse-strain sensitivity. For 129/J mice the $TCID_{50}/LD_{50}$ was 10^0 for P2184 virus and 10^1 for P3193 virus, and for SJL/J mice it was $10^{5.4}$ for P2184 virus and $10^{5.9}$ for P3193 virus. The differences were not thought to be significant.

It is noteworthy that the infectivity titers (infective dose [ID_{50}] by seroconversion) in mice of all strains were nearly identical regardless of their sensitivity to lethal infection. Likewise, $TCID_{50}$ and ID_{50} in mice were similar. Thus, 129/J mice and SJL/J mice that differed in their lethal dose by 25,000-fold had similar $TCID_{50}$/mouse ID_{50} titers ($10^{0.1}$ and $10^{0.6}$, respectively).

There was no correlation of CF antibody titers between sensitive and resistant mice that received the same virus dose. Whereas antibody titers varied widely between the mouse strains (1:20 to 1:300), the antibody titers in 129/J mice, for example, were usually 1:40 to 1:80, and those in SJL/J mice were usually 1:40 to 1:320. There was, on the other hand, what appeared to be a general tendency for the resistant and intermediate strains to have slightly higher CF antibody titers than the surviving mice of the sensitive strains. However, these data are inconclusive, and additional studies will be necessary to evaluate the immune response.

Course of infection in sensitive 129/J and DBA/2J and resistant SJL/J and RF/J mice. (i) Virus growth curve. Virus growth curves in the lungs of mice were determined to examine what factor(s) might be operative in the observed strain-sensitivity variance. Twelve 129/J and 12 SJL/J mice were inoculated i.n. with a high dose ($10^{6.2}$ $TCID_{50}$/0.05 ml) of Sendai virus, and on days 1, 3, 5, and 7 the lungs from three mice of each strain (except on day 7, one mouse each) were removed, weighed, and titrated in cell culture (Fig. 2). Control mice were sham inoculated, and the lungs of one mouse of each strain at each time point was harvested, weighed, and assayed for virus. Control mice were always free of Sendai virus. The high virus dose was lethal for both strains, and two mice of each strain died before day 7. Although the virus titers in the lungs of 129/J mice were slightly higher than those of SJL/J mice, the nearness of the titers was surprising in view of the wide difference in the LD_{50} (Table 3).

A comparable experiment was performed by using a low dose of virus ($10^{1.7}$ $TCID_{50}$/0.05 ml) to approximate a dose thought to be equivalent to a natural infective dose. In two experiments, the course of infection was followed in 18 129/J and SJL/J mice and in 18 DBA/2J and RF/J mice, respectively (Fig. 3 and 4). Although lung weights of all infected mice increased after infection, those of 129/J mice were always heavier. By day 5, 129/J lungs from three mice weighed 0.381 ± 0.303 g, and SJL/J lungs from three mice weighed 0.233 ± 0.077 g, a difference in weight of 0.148 g or 64% heavier in 129/J mice (controls were 0.138 ± 0.017 and 0.170 ± 0.005 g, respectively). Virus titers in both resistant

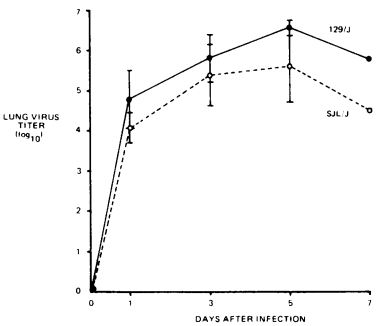

FIG. 2. *Sendai virus growth curve in the lungs of 129/J and SJL/J mice inoculated with $10^{6.2}$ $TCID_{50}$ of Sendai virus. Each point represents the mean titer of three mice, except day 7, which is that of one mouse.*

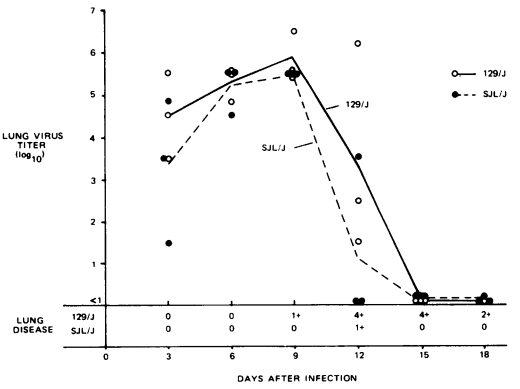

FIG. 3. *Sendai virus infection in sensitive 129/J and resistant SJL/J mice inoculated with a low virus dose ($10^{1.7}$ $TCID_{50}$/0.05 ml). Symbols are individual lung virus titers (log_{10} per 0.1 ml of 10% lung tissue suspension), and the lines are mean titers. Lung disease is expressed as gross lung consolidation graded from normal (0) to >75% consolidation (4+).*

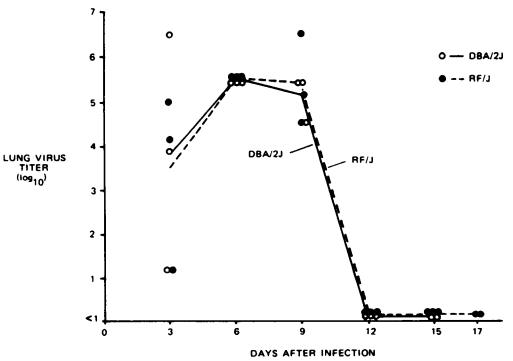

FIG. 4. *Sendai virus infection in sensitive DBA/2J and resistant RF/J mice inoculated with a low virus dose ($10^{1.7}$ $TCID_{50}$/0.05 ml). Symbols are individual lung virus titers (log_{10} per 0.1 ml of 10% lung tissue suspension), and the lines are mean titers.*

and sensitive mice increased rapidly to the maximum between days 6 and 9. Thereafter, titers declined and no virus was detectable after day 12. All of the DBA/2J and 129/J mice showed clinical signs of pneumonia and several died during the experiment, whereas RF/J and SJL/J mice appeared normal and none died. It may be noteworthy that virus was not isolated from the 129/J mice on day 15 or 18, whereas the animals were severely ill and their lungs showed extensive consolidation (Fig. 3).

(ii) Histopathology. Twenty-two 129/J and 20 SJL/J mice were inoculated i.n. with 10 or 50 $TCID_{50}$ of Sendai virus, and two mice per strain plus one sham-inoculated and one uninfected control mouse per strain were sacrificed on days 3, 6, 9, 13, 15, 17, 24, and 37. All of the 129/J mice were sick by day 9, whereas SJL/J remained normal. Six 129/J mice died of viral pneumonia during the experiment.

Qualitatively, the histopathological reaction to the infection was basically the same in both strains; however, there were several important quantitative, as well as chronological, differences in various responses. Neither strain showed detectable pathological changes on day 3, but by day 6 acute inflammatory response was present at the bronchiolar and alveolar levels in the 129/J mice. The SJL/J mice showed only bronchial epithelial hypertrophy, without significant inflammatory reaction.

Damage in the lungs of the 129/J mice was severe by day 9 and was characterized by loss of alveolar architecture due to cellular infiltration and necrosis. The appearance of the bronchial epithelium ranged from massive sloughing of necrotic cells in some bronchi to typical virus-induced cell hypertrophy in others. At this time, the lesions in SJL/J mice appeared similar to those in 129/J mice; however, they were quantitatively not as severe, and some bronchial re-epithelialization was already in progress. By day 13, re-epithelialization was almost complete in the SJL/J mice, and alveolar lesions were well into the reparative stage. Conversely, active bronchial infection still persisted in the 129/J mice in some bronchial segments while simultaneously re-epithelialization progressed in other segments that had sloughed earlier. Alveolar lesions were severe and much more widespread in the 129/J mice and exhibited little in the way of healing tendencies. Both strains exhibited cuffs of mixed mononuclear cells (lymphocytes, histiocytes, and plasma cells) in peribronchiolar and perivascular spaces at this time.

Although there appeared to be some evidence of early repair in alveolar lesions in the 129/J mice on day 15, re-epithelialization of denuded bronchial basement membranes was not complete; as a practical matter, mice infected with 50 $TCID_{50}$ did not survive past day 15. Thus, the damage in the lungs of this strain was severe. The SJL/J mice at this time showed only isolated foci of mononuclear cells, bronchial epithelial hyperbasophilia, and residual focal alveolar lesions in lungs that appeared otherwise normal.

For the remainder of the pathology time studies, the 10 $TCID_{50}$-infected mice were used for both strains and 50 $TCID_{50}$-infected mice were used for the SJL/J strain only. The 50-$TCID_{50}$ pathology in the SJL/J mice will be mentioned only as a comparison to the 10-$TCID_{50}$ pathology in this strain.

By day 17, repair of alveolar damage in the SJL/J mice at both doses had progressed still further, and few recognizable residual effects were present in the bronchi. The 129/J mice still had no completed bronchial re-epithelialization, and alveolar architecture over broad areas remained badly deranged. Squamoid metaplastic epithelium was common in damaged parenchyma as well as in reparative bronchioles, assuming the typical appearance of carcinoma in situ or metastatic carcinoma. The appearance of 129/J lungs at day 24 was not significantly different from that at day 17, although several large abscesses were observed at this time, reaffirming the severity of the underlying damage. The 10- and 50-$TCID_{50}$ lungs from the SJL/J mice were similar in appearance both revealing small residual alveolar scars and follicular collections of mononuclear cells in perivascular peribronchiolar spaces, but otherwise resembling control lungs in appearance.

Although definite healing was in progress in the 129/J mice by day 37, the extensive lung damage remaining was in dramatic contrast to

the largely normal SJL/J mice (both doses). Large, residual alveolar lesions characterized by thickened septae, cellular infiltrates, atelectasis, and so-called "bronchiolization" remained, although fairly well circumscribed by this time. Polypoid clusters of metaplastic squamoid epithelium persisted in the alveoli and adhered to the bronchial walls in some places. It was obvious from these sections that scarring would have been extensive in 129/J lungs. Mononuclear cell cuffs and follicles were present around vessels and bronchi and, occasionally, in the parenchyma in both strains, but they were only slightly above background levels in the SJL/J mice.

The heightened clinical sensitivity of the 129/J strain to Sendai infection is a manifestation of the more extensive damage to the lungs that the infection causes in this strain. Histopathologically, lesions in the 129/J group appeared earlier, were much more extensive, and lasted longer than those in the cohort SJL/J group.

DISCUSSION

Sendai virus infection is the most serious and disruptive of the naturally occurring viruses of mice. Since 1973, the Murine Virus Diagnostic Laboratory at Microbiological Associates has been directly (in laboratory studies) or indirectly (through consulting or referral) involved in sixty-six documented epizootics of Sendai virus in mice. The proportion of epizootics that result in clinical (morbidity and mortality), as compared with subclinical (seroconversion and pulmonary histopathology), infection is difficult to assess largely because of the inability of some investigators to recognize Sendai virus infection and because of variables such as age, strain, and immunological status, which profoundly affect the course of the infection. However, based on our experience, we estimate that more than one-half of all epizootics have some clinical manifestation.

Inbred strains of mice show wide variation in their sensitivity to infection with Sendai virus. A lethal infection in 129/ReJ mice was induced with only 3 $TCID_{50}$, whereas 100,000 $TCID_{50}$ were required to produce lethal infections in SJL/J mice. The other 22 mouse strains tested had $TCID_{50}/LD_{50}$ titers that ranged between 129/ReJ and SJL/J. These data corroborate information received by the Murine Virus Diagnostic Laboratory in that mouse strains most frequently reported with Sendai virus-induced clinical disease were the same strains found to be the most sensitive in the present study.

The genetics of natural resistance and susceptibility to viral infections are complex and include such factors as the cellular and humoral immune responses, interferon, presence or lack of cell receptors, intracellular blocks of viral replication, and macrophage susceptibility (12). While Robinson et al. (27) suggested that interferon was mainly responsible for the elimination of Sendai virus from lungs, Blandford et al. (7) demonstrated local antibody in cells of the respiratory submucosa as early as day 2 after infection. Also, high concentrations of interferon present in the lungs of mice fail to block Sendai virus replication (28). The immune response, however, is of prime importance in terminating Sendai virus infection (1, 6, 8, 9, 27, 28). Immunoglobulin-containing cells are detectable in the lung tissues of Swiss mice at 3 days after infection, and free antibody is detectable after 5 days (8, 9). Cyclophosphamide treatment, which suppresses several antiviral mechanisms, results in the failure to limit or eradicate virus and is associated with a delay in the appearance of local antibody, reduction of pathology to basement membrane and mucosal cells of the lung, and a delay in the mononuclear infiltration of the lungs (6, 28). Blandford (6) showed that local antibody is associated with virus eradication and lung tissue damage and suggested that the cell-mediated immunity plays no part in the infection. However, Anderson et al. (1) recently reported that a detectable cell-mediated response did occur after Sendai virus infection of mice and that cytotoxic activity appeared in 4 days and peaked at 6 days. It is not known, however, how the systemic, local, and cell-mediated responses interrelate and what, if any, effects the strain of mouse may have on the quantitative or qualitative host response to Sendai virus infection.

It may be significant, however, that in preliminary studies Blandford (6) showed that C3H mice developed more glomerular Sendai immunoglobulin deposits than did C57BL mice and that F1 (C3H × C57BL) hybrids were intermediate. Also, C57BL/6 mice that are more resistant to Sendai virus infection also are highly resistant to tumor induction by polyoma virus (17) and to mouse poxvirus infection (29, 30), and in both latter cases the resistance is due likely to either an aggressive humoral or cellular immune response (3, 29, 30). In addition, Sendai virus-sensitive DBA/2 mice are more susceptible than Sendai virus-resistant C57BL mice to induction of polyoma tumors (16), which is thought to result from earlier development of cellular immune response in C57BL mice (17).

In the present study it may be significant that the sensitivity of immune-deficient, T-cell-depleted athymic nude (Swiss) mice was essentially identical to that of 129/ReJ and 129/J

mice. However, the courses of clinical disease in the nude and the 129/ReJ and 129/J mice were dissimilar. Nude Swiss mice developed a chronic wasting disease similar to that described by Ward et al. (34) and died after a prolonged infection (7 to 28 days), whereas 129/J mice died of acute disease usually within 6 to 14 days after infection.

Macrophages are responsible for differences in mouse strain sensitivity to mouse hepatitis virus infection (4). Mouse hepatitis virus resistance can be reversed by treatment of the mice with cyclophosphamide (36) or cortisone (14), but the conversion is not due to inhibited antibody production (36). Macrophages, sensitive to Sendai virus infection, also might provide a possible partial explanation for our findings because Sendai virus has been shown to infect macrophages of mice (20), and infected macrophages may elude the immune system and thus enhance infectivity rather than restrict it (35) by providing a continual source of virus to perpetuate and enhance the lung pathology and lethality of sensitive mice.

Indeed, differences in the histopathological response of the sensitive 129/J and resistant SJL/J mice might suggest a macrophage peculiarity and/or an aberration of the immune response. The qualitative histopathology of Sendai virus-induced lung disease has been described in detail elsewhere (2, 27) and in general was confirmed in the present study. The differences observed in the present study between infected 129/J and SJL/J mice were: (i) the severity of the reaction, (ii) the chronological sequence of events, (iii) the degree of metaplastic epithelial changes (26), and (iv) the amount of persistent chronic lung damage. Damage to the lungs of the 129/J mice was much more extensive, particularly at the alveolar level where extensive cellular infiltration and parenchymal necrosis obliterated normal architecture to the degree that only after 37 days was there significant evidence of repair, i.e., removal of necrotic debris by macrophages and restoration of most basic architectural patterns, if not normal tissue. With the exception of small focal scars and residual macrophages, restoration of normal architecture in the SJL/J mice was nearly complete by day 15.

The possible persistence of active virus replication, as manifested by markedly hypertrophic bronchial epithelium (26), through day 13 in 129/J mice was significantly different from that in SJL/J mice. Also, re-epithelialization of bronchi after virus-induced epithelial sloughing was still not complete by day 24 in the 129/J mice, but nearly completed by day 13 in the SJL/J mice. This long delay in re-epithelialization, which may be a consequence of lengthy active virus infection, may in turn be responsible for the greater degree of squamoid metaplastic epithelial changes seen in the reparative stages of 129/J lungs. These changes possess a striking resemblance to carcinoma in situ or metastatic carcinoma in the lungs in some instances (26; R. P. Custer, personal communication).

It is tempting to speculate that some of the observed acute pathology could result from antibody complexing with virus budding from the bronchial epithelial cells (8). Although the present study has quantitatively and qualitatively documented the wide degree of variance observed in the sensitivity of different strains of mice to Sendai virus infection, further studies will be necessary to determine the factors that are operative and how they interact to explain the observed difference in the sensitivity of mouse strains to Sendai virus infection.

ACKNOWLEDGMENTS

The excellent technical assistance of Sue Cross and Pamela Howton is gratefully acknowledged. We also thank Robert Peters for providing data collected during a Sendai virus epizootic in mice, and Wallace Rowe for reviewing the manuscript.

This research was supported by Public Health Service contract NO1-CP-33288 within the Virus Cancer Program of the National Cancer Institute.

LITERATURE CITED

1. **Anderson, M. J., D. R. Bainbridge, J. R. Pattison, and R. B. Heath.** 1977. Cell-mediated immunity to Sendai virus infection in mice. Infect. Immun. **15**:239–244.
2. **Appell, L. H., R. M. Kovatch, J. M. Reddeclift, and P. J. Gerone.** 1971. Pathogenesis of Sendai virus infection in mice. Am. J. Vet. Res. **32**:1835–1841.
3. **Argyris, B. F.** 1965. Maturation of immunological responsiveness to transplantation antigens. Transplantation **3**:618–626.
4. **Bang, F. B., and A. Warwick.** 1960. Mouse macrophages as host cells for the mouse hepatitis virus and the genetic basis of their susceptibility. Proc. Natl. Acad. Sci. U.S.A. **66**:329–336.
5. **Bhatt, P. N., and A. M. Jonas.** 1974. An epizootic of Sendai infection with mortality in a barrier-maintained mouse colony. Am. J. Epidemiol. **100**:222–229.
6. **Blandford, G.** 1975. Studies on the immune response and pathogenesis of Sendai virus infection of mice. III. The effects of cyclophosphamide. Immunology **28**:871–883.
7. **Blandford, G., R. J. R. Cureton, and R. B. Heath.** 1971. Studies on the immune response in Sendai virus infection of mice. J. Med. Microbiol. **4**:351–355.
8. **Blandford, G., and R. B. Heath.** 1972. Studies on the immune response and pathogenesis of Sendai virus infection in mice. I. The fate of viral antigens. Immunology **22**:637–649.
9. **Blandford, G., and R. B. Heath.** 1974. Studies on the immune response and pathogenesis of Sendai virus infection in mice. II. The immunoglobulin class of plasma cells in the bronchial sub-mucosa. Immunology **26**:667–671.
10. **Center for Disease Control.** 1974. Laboratory branch

complement fixation test. Center for Disease Control, Atlanta, Ga.
11. **Collins, M. J., Jr., and J. C. Parker.** 1972. Murine virus contaminants of leukemia viruses and transplantable tumors. J. Natl. Cancer Inst. **49**:1139–1143.
12. **Fenner, F.** 1972. Genetic aspects of viral diseases of animals. Prog. Med. Genet. **8**:1–60.
13. **Fukumi, H., F. Nishikawa, and T. A. Kitayama.** 1954. A pneumotropic virus from mice causing hemagglutination. Jpn. J. Med. Sci. Biol. **7**:345–363.
14. **Gallily, R. A., A. Warwick, and F. B. Bang.** 1964. Effect of cortisone on genetic resistance to mouse hepatitis virus in vivo and in vitro. Proc. Natl. Acad. Sci. U.S.A. **51**:1158–1164.
15. **Grunert, R. R.** 1967. Isolation of Sendai virus as a latent respiratory virus in mice. Lab. Anim. Care **17**:164–171.
16. **Jahkola, M.** 1965. Nature and inheritance of the resistance of inbred mice to tumor induction by polyoma virus. Acta Pathol. Microbiol. Scand. Suppl. **173**:1–69.
17. **Law, L. W., and R. C. Ting.** 1965. Immunologic competence and induction of neoplasmas by polyoma virus. Proc. Soc. Exp. Biol. Med. **119**:823–830.
18. **Lennette, E. H., and N. J. Schmidt (ed.).** 1969. Diagnostic procedures for viral and rickettsial infections, 4th ed., p. 49. American Public Health Association, Inc., New York.
19. **Makino, S., S. Seko, H. Nakao, and K. Mikazuki.** 1973. An epizootic of Sendai virus infection in a rat colony. Exp. Anim. (Tokyo) **22**:275–280.
20. **Mims, C. A., and F. A. Murphy.** 1973. Parainfluenza virus Sendai infection in macrophages, ependyma, choroid plexus, vascular endothelium and respiratory tract in mice. Am. J. Pathol. **70**:315–328.
21. **Parker, J. C., and R. K. Reynolds.** 1968. Natural history of Sendai virus infection in mice. Am. J. Epidemiol. **88**:112–125.
22. **Parker, J. C., R. W. Tennant, T. G. Ward, and W. P. Rowe.** 1964. Enzootic Sendai virus infections in mouse breeder colonies within the United States. Science **146**:936–938.
23. **Parker, J. C., R. W. Tennant, T. G. Ward, and W. P. Rowe.** 1965. Virus studies with germfree mice. I. Preparation of serologic diagnostic reagents and survey of germfree and monocontaminated mice for indigenous murine viruses. J. Natl. Cancer Inst. **34**:371–380.
24. **Profeta, M. L., F. S. Lief, and S. A. Plotkin.** 1969. Enzootic Sendai infection in laboratory hamsters. Am. J. Epidemiol. **89**:316–324.
25. **Reed, J. M., L. J. Schiff, A. M. Shefner, and M. C. Henry.** 1974. Antibody levels to murine viruses in Syrian hamsters. Lab. Anim. Sci. **24**:33–38.
26. **Richter, C. B.** 1970. Application of infectious agents to the study of lung cancer: studies on the etiology and morphogenesis of metaplastic lung lesions in mice, p. 365–382. *In* Paul Nettesheim, M. G. Hanna, Jr., and J. W. Deatherage, Jr. (ed.), Morphology of experimental respiratory carcinogenesis. U.S.A.E.C. Symposium Series 21. U.S. Atomic Energy Commission, Division of Technical Information Extension, Oak Ridge, Tenn.
27. **Robinson, T. W. E., R. J. R. Cureton, and R. B. Heath.** 1968. The pathogenesis of Sendai virus infection in the mouse lung. J. Med. Microbiol. **1**:89–95.
28. **Robinson, T. W. E., R. J. R. Cureton, and R. B. Heath.** 1969. The effect of cyclophosphamide on Sendai virus infection of mice. J. Med. Microbiol. **2**:137–145.
29. **Schell, K.** 1960. Studies on the innate resistance of mice to infection with mousepox. I. Resistance and antibody production. Aust. J. Exp. Biol. Med. Sci. **38**:271–288.
30. **Schell, K.** 1960. Studies on the innate resistance of mice to infection with mousepox. II. Route of inoculation and resistance; and some observations on the inheritance of resistance. Aust. J. Exp. Biol. Med. Sci. **38**:289–300.
31. **Sever, J. L.** 1952. Application of a microtechnique to viral serological investigations. J. Immunol. **88**:320–329.
32. **Tennant, R. W., J. C. Parker, and T. G. Ward.** 1966. Prevalence of viruses in mouse colonies. Natl. Cancer Inst. Monogr. **20**:25–36.
33. **Ward, J. M.** 1974. Naturally occurring Sendai virus disease of mice. Lab. Anim. Sci. **24**:938–942.
34. **Ward, J. M., D. P. Houchens, M. J. Collins, Jr., D. M. Young, and R. L. Reagan.** 1976. Naturally occurring Sendai virus infection of athymic nude mice. Vet. Pathol. **13**:36–46.
35. **Waters, D. J., H. Koprowski, and L. J. Lewandowski.** 1975. The potential role of phagocytically active cells in establishing chronic parainfluenza 1 virus infection in human brain. J. Neurol. Sci. **25**:491–498.
36. **Willenborg, D. O., K. V. Shah, and F. B. Bang.** 1973. Effect of cyclophosphamide on the genetic resistance of C3H mice to mouse hepatitis virus. Proc. Soc. Exp. Biol. Med. **142**:762–766.