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Interferon and Host Resistance to Rauscher Virus-induced Leukemia[1]

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A random bred strain of mice (CD-1) was shown to develop resistance to Rauscher leukemia virus (RLV) as the animals matured. Resistant adult mice developed relatively high-serum levels of interferon (150 to 2,000 units per ml) in contrast to susceptible 21-day-old animals in which interferon levels were undetectable or low (less than 20 to 200 units per ml). A similar correlation between resistance and interferon levels was observed in comparisons between resistant CD-1 and susceptible BALB/c mice. The F_1 hybrids of CD-1 × BALB/c and BALB/c × CD-1 matings manifested an intermediate degree of susceptibility and interferon production. The difference in interferon production by CD-1 and BALB/c mice was specific for the RLV-host interaction, since both strains produced equal serum levels of interferon in response to Sindbis and Newcastle disease viruses. The mortality of CD-1 suckling mice infected with Rauscher leukemia virus was decreased by treatment with interferon. These data demonstrate an association between interferon production by the host and the observed relative resistance of the CD-1 strain of adult mice to the subsequent malignant transformation. This virus-host relationship provides an excellent model for further study of factors affecting the development of virus-induced leukemia.

In 1962, Rauscher (13) described a murine leukemogenic virus which was characterized by its capacity to induce both erythrocytopoiesis and lymphoid leukemia. In a number of strains investigated, mice of all ages were susceptible, and resistance apparently did not develop with maturation. During the course of an investigation of the effects of early experience on viral infections in mice, the CD-1 random bred strain became progressively more resistant to the Rauscher leukemia virus (RLV) as the animals matured.

This study was initiated to delineate the mechanism of host resistance. The results suggest that interferon production by the host at the time of initial infection by RLV may be one determinant of the outcome of this host-parasite relationship.

MATERIALS AND METHODS

Virus. RLV was generously supplied by Frank Rauscher of the National Institutes of Health. A 10^{-6} dilution of stock virus induced splenomegaly in 50% of recipients within 120 days. Vesicular stomatitis virus (VSV), Indiana strain, was originally obtained from the American Type Culture Collection. Stock pools were prepared and assayed in L cells. Lactic dehydrogenase (LDH) agent was provided by Abner Notkins of the National Institutes of Health. Newcastle disease virus (NDV), Herts strain, was obtained from Samuel Baron of the National Institutes of Health. The stock virus preparation, containing 3.2×10^8 plaque-forming units, was grown in embryonated hens' eggs and assayed in a continuous line of human amnion cells. Sindbis virus, originally an isolate from a Malayan mosquito pool, was obtained from Philip K. Russell at the Walter Reed Arbovirus Unit and was grown and assayed in chick embryo fibroblasts.

Interferon assay. Samples for interferon assay were acid treated and assayed as previously described by using VSV as the challenge virus (7). Titers were recorded as the reciprocal of the dilution which effected a 50% plaque reduction of the VSV challenge.

Characterization of interferon. The viral inhibitor being assayed in these experiments was characterized as interferon by the following criteria: (i) acid stability at *p*H 2; (ii) stability at 56 C for 30 min; (iii) lability at 70 C for 30 min; (iv) activity against heterologous viruses; (v) species specificity; (vi) lack of direct inhibitory activity against the challenge virus, VSV. After a reference standard was made available, the assay system for interferon in our laboratory was standardized against the reference mouse interferon provided by the National Institutes of Health.

Mice. Random-bred CD-1 mice were obtained from the Charles River Animal Farms (Wilmington,

[1] These data were partially reported at the plenary session of the Society for Pediatric Research meeting in Atlantic City, 1966.

Mass.), and BALB/c mice from the Jackson Laboratories (Bar Harbor, Maine). Animals used in these experiments were born from pregnant females shipped during the second week of gestation and housed individually with their litters until weaning. Experimental animals then were segregated by sex and housed six per cage during the study. All animals were maintained under controlled conditions of temperature with food and water ad libitum and a 12-hr lighting cycle.

RESULTS

Age and resistance. Preliminary studies suggested that CD-1 mice became progressively more resistant to RLV with maturation. The mice used in each experiment were purchased as one group, raised under the conditions described above, and inoculated with portions from a single virus pool. An inoculum of 0.01 ml of undiluted stock RLV pool per gram of body weight was used in this series of experiments.

In one experiment, groups of 17 to 20 animals were inoculated at 14, 21, 28, 35, and 42 days of age. Groups were composed of both male and female animals because no sex difference in susceptibility to RLV was observed during the course of these studies. After 8 months, only one (1/74) animal survived from the groups inoculated at 14 through 35 days of age. In contrast, 13 out of 19 animals inoculated at 42 days of age were still alive at this time. The mortality rates from this experiment after 10 months of observation are summarized in Fig. 1. No further deaths were observed during the remaining 2-month period of observation. Whenever possible, mice that died during the course of the experiment were autopsied to confirm the presence of hepatomegaly and splenomegaly, which is characteristic of the malignant transformation following RLV infection (Table 1). Spleens from normal CD-1 mice weighed less than 250 mg.

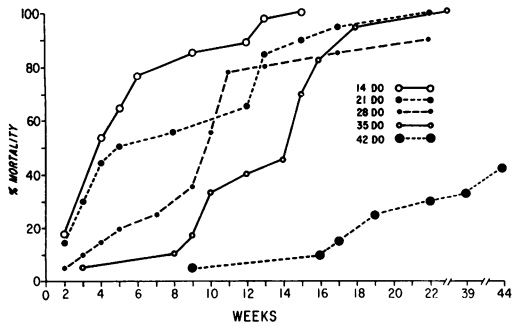

FIG. 1. *Cumulative mortality in CD-1 mice infected with Rauscher leukemia virus when 14 to 42 days old (DO).*

TABLE 1. *Mean spleen weights of mice that died following inoculation with RLV at 14 to 42 days of age*

Age at time of inoculation with RLV	No. autopsied	Spleen size mean (range)
14	17	2.15 g (0.6–4.2 g)
21	19	3.28 g (1.1–6.1 g)
28	19	3.09 g (1.1–4.5 g)
35	17	4.10 g (1.0–14.2 g)
42	6	2.70 g (0.9–6.1 g)

The development of resistance to RLV with maturation was confirmed in a series of experiments utilizing mice from 2 to 100 days of age at the time of infection. All mice were observed for 10 months, as in the previous experiment, and deaths were recorded. Up to 35 days of age, mice were consistently susceptible. A variation in susceptibility was observed in groups of 42-day-old animals inoculated with RLV, with a range of 30 to 80% final mortality in different experiments. Such variation was not found in animals inoculated at 56 to 100 days of age; animals older than 56 days at the time of inoculation consistently evidenced a mortality rate of less than 50%. The combined data from four mortality studies are summarized in Table 2.

These results indicated that resistance to the leukemogenic effect of RLV progressively increases with maturation, and provided a model which permitted an attempt to elucidate the mechanism of host resistance to this leukemogenic virus.

Age, interferon, and resistance. The production of interferon in susceptible 21-day-old CD-1 mice was compared to relatively resistant adult 63-day-old animals. Mice were inoculated intraperitoneally with 0.01 ml of undiluted RLV per gram of body weight. Groups of six to eight animals were sacrificed and bled at 8, 24, 32, and 48 hr after inoculation with RLV. The sera were pooled and assayed for interferon activity. Resistant 63-day-old adult animals produced relatively high titers of interferon following RLV infection. Detectable levels were noted at 12 to 18 hr, with a peak at 24 to 32 hr, followed by a decline and disappearance after 40 to 48 hr. In contrast, 21-day-old-susceptible animals responded to RLV infection with a limited interferon production. In a number of experiments, interferon was not demonstrable at the lowest dilution tested, usually 1:20, and in experiments in which interferon was present, the response of weanling animals was consistently 3- to 10-fold less than that of resistant adults (Table 3).

TABLE 2. *Mortality rate of mice infected with RLV at different ages*

Age	No. of dead per no. of experimental animals	Per cent
days		
2	10/10	100
7	45/46	98
14	44/46	96
21	95/100	95
28	28/29	97
35	17/17	100
42	26/43	60[a]
56–100	49/103	48

[a]Range 30 to 80%.

TABLE 3. *Serum interferon levels (units/ml) following intraperitoneal inoculation of CD-1 mice with 0.01 ml/g body weight of RLV*

Age	8 hr	24 hr	32 hr	48 hr
63 days	<40	150	130	<40
21 days	<40	<40	40	<40

To further document the impaired capacity of the more susceptible immature mouse to respond to RLV infection with the production of interferon, a similar series of experiments was carried out with both the 63-day-old and 21-day-old animals receiving an identical inoculum (0.2-ml stock RLV), rather than a dose calculated on a weight basis. Groups of five to six mice were bled and sacrificed; the pooled sera were assayed for interferon activity at 6, 15, 24, 30, 36, and 46 hr after inoculation. The results from one representative experiment are presented in Fig. 2. The interferon response of adult animals was again greater than that of susceptible weanlings, although the dose per gram of body weight in the adult animal was much smaller.

The data presented demonstrate that RLV induced a significant interferon response in adult CD-1 mice in contrast with the minimal rate of interferon production observed in the more susceptible weanling animals. This correlation between resistance and interferon production suggested a possible causal relationship.

Strain, interferon, and resistance. Rauscher's original work (13) demonstrated the susceptibility of BALB/c mice of all ages to RLV. To further establish the relationship between the interferon response and host resistance, the production of interferon was determined in susceptible adult BALB/c animals in comparison with the resistant CD-1 strain. All mice for these studies were received at 6 weeks of age, and the experiments comparing interferon production in the two strains were carried out in groups of animals that were at least 50 days old and matched for age. The pooled sera for interferon assay were obtained from groups of six to eight animals (Fig. 3). The interferon response in the susceptible BALB/c strain was below detectable levels in contrast with that of the more resistant CD-1 animals. In both strains there was variation in the level of the interferon response in different experiments, but that CD-1 mice consistently had higher levels of interferon than the BALB/c animals in this series of experiments. The peak serum interferon levels from five experiments are presented in Table 4. Although these data must be interpreted cautiously because of the variation in the levels of interferon, they clearly indicate that mature CD-1 mice produced higher levels of interferon after infection with RLV than similarly aged adult BALB/c animals.

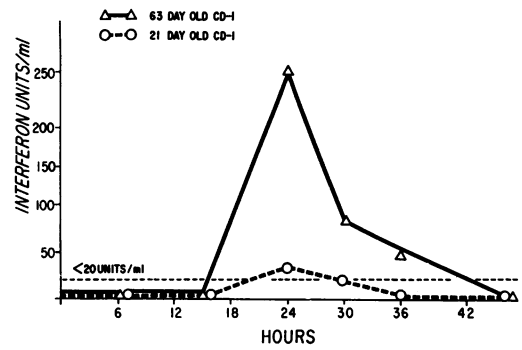

FIG. 2. *Serum interferon levels in units per milliliter in 63-day-old CD-1 and 21-day-old CD-1 mice infected with identical doses of Rauscher leukemia virus.*

Resistance to RLV and sexual maturation. The increased resistance of both male and female mice of the CD-1 strain at 6 to 8 weeks of age suggested an association with sexual maturation. To determine whether sex hormone production was a factor in host resistance in this virus-host interaction, groups of 30 to 35 female mice were ovariectomized or sham operated at 21 or 56 days of age. At the ages of 64 and 100 days, respectively (6 weeks after operation), the mice were inoculated with RLV. During the subsequent 8-month period of observation, 43% of the animals died, and there was no difference in the rate of the final mortality between either of the experimental or control groups. These results strongly suggest that sex hormone production by the ovary is not a physiological determinant of the observed relative resistance in mature female animals. These experiments were carried out only in female mice since

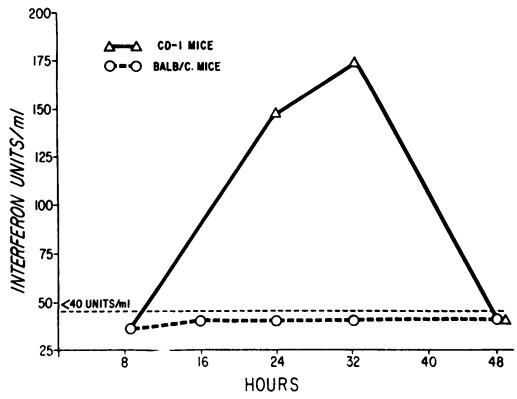

FIG. 3. *Serum interferon levels in units per milliliter in CD-1 and BALB/c mice infected with Rauscher leukemia virus.*

TABLE 4. *Serum interferon levels (units/ml) at 22 to 26 hr following RLV inoculation in CD-1 and BALB/c mice*

Expt no.	Age	CD-1	BALB/c
	days		
1	100–120	1,250	130
2	63	175	<40
3	50–56	500	130
4	60–68	180	80
5	56–60	640	70

no difference in susceptibility had been observed between males and females in either suckling or adult mice, and it seemed unlikely that castration of male mice would modify resistance to RLV.

LDH agent. LDH agent is present in many mouse colonies, and virus pools prepared in mice are frequently contaminated with this virus. Assays of our stock pool by Abner Notkins confirmed that the RLV stock preparation used in these experiments contained LDH agent. To eliminate the possibility that the interferon produced after infection with our RLV was actually in response to the contaminating LDH agent and not RLV, interferon production was determined in CD-1 and BALB/c adult mice following inoculation of a high-titered LDH virus preparation. In both strains, LDH agent induced similar low levels (approximately 20 to 25 units/ml) of interferon. In addition, a stock preparation of RLV which was passaged in rats and was shown to be free of LDH agent was found to induce serum levels of 200 to 400 units/ml of interferon in adult CD-1 mice (63 days old). These data strongly suggest that the LDH virus contaminant in the RLV pool was not contributing to the observed interferon response in adult mice.

Interferon production and strain differences. The differences in interferon production between adult CD-1 and BALB/c animals observed in these experiments was relatively specific for RLV, as demonstrated in the following experiment. Adult, 50-day-old CD-1 and 56-day-old BALB/c mice were inoculated by the intraperitoneal route with Sindbis virus, NDV, or RLV. Groups of five to seven mice were bled at the expected time of peak interferon levels for each virus, and the pooled sera were assayed for interferon activity. Samples were collected from the NDV and Sindbis groups 8 hr after inoculation, and from the RLV group 22 hr following injection (Table 5). These data show that the BALB/c strain of mice do not have a generalized deficiency in their capacity to produce interferon in response to viral infection, but rather that the limited interferon response observed in these studies appears to be relatively specific for the RLV-host relationship.

Susceptibility of offspring of CD-1 and BALB/c matings. To determine the nature of the resistance of the CD-1 strain, the susceptibility of the F_1 hybrids of CD-1 and BALB/c matings was investigated. Groups of 20 offspring of (i) CD-1 × CD-1, (ii) CD-1 × BALB/c, (iii) BALB/c × CD-1, and (iv) BALB/c × BALB/c matings were inoculated with RLV (0.01 ml/g) at approximately 56 to 60 days of age. Pooled samples of blood were obtained from each group of 20 animals for interferon assay 24 hr after inoculation. Animals were then observed for 3 months, deaths were recorded, and all survivors were sacrificed and autopsied at the termination of the experiment. The mortality rate of 49 offspring of the CD-1 and BALB/c matings was identical and was combined. Mortality data are summarized in Fig. 4. Resistance, as evidenced by only a 52% mortality rate, was observed in the F_1 hybrids compared to a 100% mortality in BALB/c animals and 35% in the CD-1 strain. Serum interferon

TABLE 5. *Serum interferon levels determined at time of expected peak value for each virus in CD-1 and BALB/c mice. (Sindbis virus and NDV at 8 hr, RLV at 22 hr)*

Strain	Infecting virus	Serum interferon level
		units/ml
CD-1	NDV	2,250
BALB/c	NDV	2,000
CD-1	RLV	500
BALB/c	RLV	130
CD-1	Sindbis	2,500
BALB/c	Sindbis	2,500

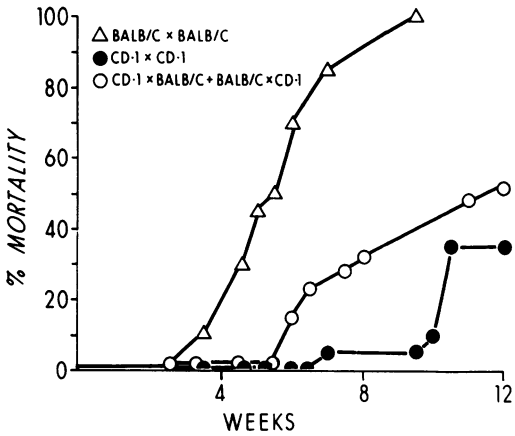

FIG. 4. *Cumulative mortality in offspring of CD-1, CD-1 to BALB/c, and BALB/c matings infected with Rauscher leukemia virus.*

levels obtained approximately 24 hr after infection with RLV are presented in Table 6.

These data confirm the resistance of CD-1 mice in comparison with the BALB/c animals. The matings of resistant CD-1 and susceptible BALB/c resulted in an intermediate degree of resistance in the F_1 hybrids. These data further support the interpretation that resistance to RLV may be associated with the capacity of the host to respond to infection with interferon production.

Effect of exogenous interferon. To further define the function of interferon in the host response to RLV, susceptible suckling CD-1 animals were treated with exogenous mouse serum interferon. A total of 47 suckling mice were inoculated with approximately 6,000-unit doses of interferon by the intraperitoneal route, following one of two protocols: (i) simultaneously with RLV, and 24 and 48 hr later, or (ii) 24 and 48 hr following RLV inoculation. The control group of 20 matched suckling mice was inoculated with a mouse serum preparation containing no interferon. The cumulative mortality of these three groups is illustrated in Fig. 5. The half-life of mouse serum interferon inoculated intravenously into recipient mice in our laboratory is 5 to 8 min. Gresser and his co-workers (8) demonstrated, however, that serum levels were maintained for longer periods following inoculation of interferon via the intraperitoneal route. This course of therapy, therefore, would be equivalent to a fraction of the natural host interferon production necessary to maintain the serum levels found to occur in resistant CD-1 mice infected with RLV (Fig. 2 and 3). Yet, the data presented in Fig. 5 suggest that the presence of interferon during the first 48 hr of infection is able to modify

TABLE 6. *Serum interferon levels at 24 hr after inoculation of Rauscher leukemia virus*

Strain	Serum interferon level
	units/ml
CD-1 × CD-1	640
BALB/c × CD-1 CD-1 × BALB/c	160
BALB/c × BALB/c	70

the mortality due to RLV during the subsequent 3-month observation period.

RLV in resistant mice. The resistant CD-1 mice survivors from one study were autopsied after an observation period of 1 year (Table 7). No gross pathology of the spleen, liver, or thymus was found, and all the spleens weighed 0.28 g or less. The peripheral white blood cell counts of these mice were in the normal range (6,600 to 10,500/mm^3). The spleen from each animal was homogenized, and 0.2 ml was inoculated as a 10% suspension into a litter of 7-day-old CD-1 mice (Table 8). These recipient litters were followed for 3 months, deaths were recorded, and, at the completion of the observation period, all animals were autopsied. Eight recipient mice from three different groups had grossly enlarged spleens (0.5 to 6.1 g) and pathological changes compatible with infections by RLV. These data strongly suggest that 3 of 10 survivors were carrying RLV, apparently in the absence of the erythrocytopoiesis or lymphocytic leukemia characteristic of the malignant transformation with this agent. Smears and bone marrow impressions from this original group of survivors were not available for more careful examination for the presence of transformations. Further investigation of this phenomenon is in progress.

DISCUSSION

The data presented demonstrate an association between interferon production in the RLV-infected host and resistance to the development of erythroblastosis and leukemia. This association was confirmed in a comparison of the interferon response in susceptible CD-1 weanlings and BALB/c adults, in contrast with relatively resistant adults of the CD-1 strain. These data suggest a causal relationship between interferon production and host resistance to this virus. They do not, however, imply that interferon is the only factor involved in the observed resistance of mature CD-1 mice to RLV, and they do not eliminate the possibility that other factors, such as antibody,

TABLE 7. *Autopsy results and spleen weights from 10 CD-1 mice which survived for a period of 1 year following inoculation of RLV at 42 days of age*

Animal	Autopsy	Spleen weight
		g
A	Normal	0.26
B	Normal	0.20
C	Normal	0.18
D	Normal	0.22
E	Normal	0.26
F	Normal	0.20
G	Normal	0.20
H	Normal	0.18
I	Normal	0.28
J	Normal	0.18

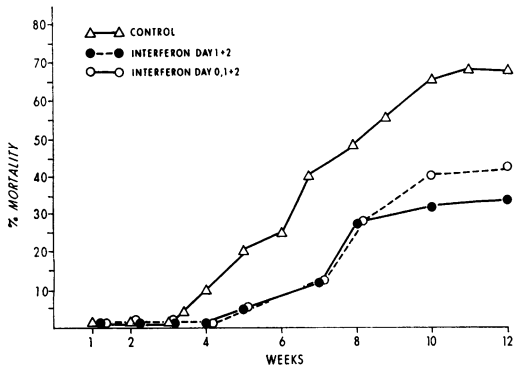

FIG. 5. *Cumulative mortality of CD-1 mice infected (at 2 to 5 days of age) with Rauscher leukemia virus and treated with interferon.*

are also determinants of host resistance in this virus-host interaction. If interferon is a determinant of host resistance in this situation, its effect most likely occurs during the first 48 hr of infection, since serum levels of interferon became undetectable after this time.

Interferon has been implicated as a critical determinant of the host defense against nontumorgenic virus (3, 6). The role of interferon in host resistance to oncogenic viruses, however, has remained more poorly defined. Exogenous interferon has been used to inhibit transformation induced by Rous sarcoma virus in vivo (1, 11), in vitro (2), and in ovo (14). The possible role of interferon as a determinant of oncogenesis has been considered by Friedman and Rabson (5), who compared a highly oncogenic variant, S, of polyoma virus with one that induced relatively few tumors, M. Infection with this low oncogenic variant was characterized by limited virus multiplication, significant interferon response by the host, and a low rate of malignant transformation. Furthermore, M variant infection protected mice against the S variant, as well as encephalomyocarditis virus, thus supporting the concept that significant levels of interferon were induced by infection with the M variant.

TABLE 8. *Mortality and spleen weight of recipient CD-1 mice inoculated at 7 days of age with a 10% suspension of spleen from each survivor*

Recipient mortality	Recipient splenomegaly
1/5	3/5 (6.1, 1.1, 0.6 g)
0/5	3/5 (0.7, 0.9, 0.5 g)
0/8	0/8
0/5	0/5
0/6	2/6 (0.48, 0.41 g)
0/8	0/8
0/5	0/5
0/9	0/9
0/8	0/8
0/8	0/8

More pertinent is the report of Todaro and Baron (15) that interferon inhibited the transformation of a mouse cell line by the oncogenic simian virus 40. In this experimental model, cellular transformation occurred in the absence of virus replication, thus indicating that interferon has the capacity to inhibit an event in the transformation process.

During the course of this study conflicting data have been reported concerning the effect of interferon on transformation with leukemogenic viruses. Gresser and his co-workers (8, 10) have demonstrated that twice daily treatment of mice infected with Friend virus inhibited the development of splenomegaly. Under similar conditions, these investigators found that treatment for only 3 days was not effective. More recently, these same investigators (9) have also prevented the development of splenomegaly with a course of interferon therapy initiated 48 hr after inoculation with Friend virus. In contrast, Vandeputte et al. (16) failed to prevent the splenomegalic response in mice to RLV. The evidence presented thus far, therefore, represents a conflicting picture of the sensitivity of leukemogenic viruses to interferon in vivo. One factor which may be of significance in the greater sensitivity of RLV to interferon in our experimental system is that these studies were carried out in the resistant CD-1 strain of mice. In contrast, the studies in which interferon failed to modify the host response to RLV utilized more susceptible strains of mice. More recently,

Wheelock and Larke (17) have confirmed the fact that interferon may affect the course of a virus-induced leukemia. In these studies, the survival time of DBA/2 mice infected with Friend virus was significantly prolonged by the daily intraperitoneal injection of interferon for 10 successive days when therapy was started as late as 31 days after infection.

In this study, BALB/c mice produced low or undetectable interferon levels following inoculation with RLV. The failure of BALB/c strain of mice to respond to RLV infection with the production of interferon also has been described by Peries (12).

Boiron and his co-workers (4) have demonstrated that C57BL/6 mice are also relatively resistant to RLV. Infection of this strain is characterized by the absence of the early erythroblastic phase, but with the subsequent occurrence of a myeloblastic leukemia. Spontaneous deaths in their C57BL/6 mice occurred at about the same rate as recorded in these experiments with CD-1 mice. The pathogenesis of RLV in the CD-1 and C57BL/6 strains may not be similar, however, since all animals dying during our studies were shown to have the splenomegaly which is characteristic of the erythroblastic phase of disease.

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