GENETIC CONTROL OF RESISTANCE TO STREET RABIES VIRUS IN MICE

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It is well known that not all animals manifesting clinical signs of street rabies virus (SRV)\(^1\) infection die. These observations have been made in natural (1–4) and experimental infections (5–12). In one study, it was shown that 16% of outbred Swiss Webster mice inoculated intraperitoneally (i.p.) with SRV survived after developing signs of illness and that recovery was associated with high levels of rabies virus-neutralizing antibody in the brain (5). In contrast, Baer and associates (12) have shown that little, if any, SRV-neutralizing antibody was present in brains of Swiss ICR mice that survived with sequelae of infection after peripheral inoculation of SRV. The importance of virus-neutralizing antibody in brains of mice in one model of sickness with recovery, but not the other, is perplexing. This difference might be explained by the genetic constitution of the host in that it has been shown that immunized substrains of outbred Swiss mice vary in their resistance to rabies virus (13, 14). Furthermore, greater vaccine protection has been obtained in Swiss than non-Swiss mice (15).

To more adequately define parameters responsible for resistance/susceptibility to SRV infection, and for recovery from infection after onset of clinical signs, it is important to study a host in which all members behave identically. Thus, several inbred mouse strains were tested in the anticipation that strains would be identified that responded differently to SRV. It is shown that there was a marked variation in strain susceptibility to i.p. inoculated SRV and that resistance was genetically controlled. Furthermore, clinical signs were apparent only occasionally in mice of some resistant strains. Mice of other resistant strains developed these signs, but disease failed to progress and they survived.

Materials and Methods

Mice. SJL/J, CBA/J, DBA/2J, A/J, B10.ASlSnJ, C57BL/6J, A.SW/SnJ, and A/WySnJ mice were purchased from The Jackson Laboratory, Bar Harbor, ME. C57BL/10ScN mice were obtained from the National Institutes of Health, Bethesda, MD, and BALB/cAnNhApBr mice were purchased from Harlan-Sprague Dawley, Madison, WI. All mice were maintained as inbred stocks at the Rocky Mountain Laboratories (RML). Athymic nude mice, produced by successive cross-intercrossing onto a BALB/c background, were purchased from Harlan-Sprague Dawley and maintained as outbreds at the RML.

\(^1\)Abbreviations used in this paper: CNS, central nervous system; CVS, challenge virus standard; i.c., intracerebral; MEM-BSA, minimal essential medium-bovine serum albumin; MICLD\(_{50}\), mouse intracerebral 50% lethal dose; RML, Rocky Mountain Laboratories; SRV, street rabies virus; SW, Swiss-Webster.
F₁ hybrids and backcross mice were produced in our laboratory. All mice used were 8–15 wk of age. 21-d-old outbred Swiss-Webster (SW) mice raised at the RML were used to prepare and to titrate stock viral pools and individual brain suspensions for virus.

Rabies Viruses. Unless stated otherwise, mice were inoculated with a wild-type SRV that had been isolated from an adult bat (*Eptesicus fuscus*) and then passaged six times by intracerebral (i.c.) inoculation in SW mice. The brain suspension titer was $10^{6.5}$ mouse intracerebral 50% lethal doses (MICLD₅₀)/0.03 ml as calculated by the method of Reed and Muench (16). SRV that had been isolated from cat, dog, sheep, skunk, or another bat were kindly provided by Ms. Bernie Kraft, Montana Veterinary Diagnostic Laboratory, Bozeman, MT. These viruses had been passaged two to three times i.c. in SW mice, and their brain suspension titers ranged from $10^{6.0}$ to $10^{6.9}$ MICLD₅₀/0.03 ml. The laboratory-adapted challenge virus standard (CVS) rabies virus was obtained from John Moore of the RML. The brain suspension titer was $10^{6.5}$ MICLD₅₀/0.03 ml.

All stock viral pools were prepared as 10% mouse brain suspensions and stored at −70°C in minimal essential medium (Flow Laboratories, McLean, VA) containing 2% bovine serum albumin (Miles Laboratories, Elkhart, IN), 100 U of penicillin G (Eli Lilly and Co., Indianapolis, IN) per ml and 1 µg of amphotericin B (E. R. Squibb and Sons, Inc., Princeton, NJ) per ml (MEM-BSA). Virus titrations were done by i.c. inoculation of 0.03 ml of serial 10-fold viral dilutions in MEM-BSA into six SW mice per dilution.

Experimental Design. In most instances, mice were inoculated i.p. with 0.5 ml of 10% mouse brain suspension containing $5 \times 10^7$ MICLD₅₀ of SRV. Mice were held in glass jars in which watering bottle stems were less than 0.5 inch from the bedding surface. The close proximity of water to the bedding allowed paralyzed mice to drink, preventing deaths due to dehydration. Each day mice were observed for deaths and clinical signs of illness such as ruffled fur and spasticity and/or paralysis of the legs. 21 d after inoculation, survivors were killed and serum, brain, and cerebrospinal fluid were harvested and stored at −70°C. Animals that died were considered susceptible. Animals that survived were considered resistant, and those resistant mice that survived after onset of clinical signs were judged to have recovered from disease.

Statistical Analysis. Analysis of statistical significance of data was performed by the $\chi^2$ test for a 2 × 2 contingency table.

Results

Resistance of Inbred Mouse Strains to SRV. 10 inbred strains of mice were inoculated i.p. with $5 \times 10^7$ MICLD₅₀ of virus. The data presented in Table I show that female SJL, CBA, BALB/c, and DBA/2 mice were highly resistant to clinical disease (≥90% survivors). A similar resistance also was noted in male SJL and CBA, but was not as apparent in male BALB/c and DBA/2 mice. The males in the latter two strains were, however, greater than nine times more resistant than male mice of the susceptible strains (see below).

In contrast to these strains, male and female A.SW/Sn and A/WySn mice were highly susceptible to i.p. inoculated virus (≤8% survivors, Table I). C57BL/10, A, B10.A(SnR)J, C57BL/6, and outbred athymic nude mice were of moderate and variable susceptibilities. Female mice of two substrains, A and A/WySn, differed substantially in their susceptibility to clinical disease (41% vs. 3% resistant, respectively), and athymic nudes were somewhat more resistant than highly susceptible A.SW/Sn and A/WySn mice (Table I). Additional experiments have shown that $1.7 \times 10^6$ MICLD₅₀ of i.p. inoculated SRV failed to kill any of the inbred mice, indicating that a threshold of resistance was present in all strains. The extent of this marked resistance in SJL and CBA mice was substantiated by their 100% resistance to $>1 \times 10^5$ MICLD₅₀ of virus (data not shown). These data also indicated that resistance to SRV was not controlled solely by the major histocompatibility locus (H-2) because susceptible A.SW/Sn and resistant SJL mice have the same H-2b haplotype.
Table I

Resistance of Inbred Mouse Strains to SRV *

| Strain          | H-2 | Survivors/total (%) |
|-----------------|-----|---------------------|
|                 |     | Female | Male |
| SJL/J s         | z   | 74/74 (100) | 62/62 (100) |
| CBA/J k         | k   | 56/56 (100) | 32/34 (94)  |
| BALB/cAnN d     | d   | 51/52 (98)  | 29/50 (58)  |
| DBA/2J d        | d   | 36/40 (90)  | 5/9 (56)    |
| C57BL/10ScN b   | b   | 46/93 (50)  | 7/42 (17)   |
| A/J a           | a   | 9/22 (41)   | ND        |
| B10.A/SgSnJ a   | a   | 13/35 (37)  | 8/16 (50)  |
| C57BL/6J b      | b   | 18/66 (27)  | 3/19 (16)  |
| A.SW/SnJ s      | s   | 3/37 (8)    | 2/35 (6)   |
| A/WySnJ a       | a   | 2/62 (3)    | 1/51 (2)   |
| Athymic on BALB/cAnN background | d | 4/21 (19) | 2/19 (11) |

* 8- to 15-wk-old mice were inoculated i.p. with 5 × 10⁷ MICLD₉₀ of SRV. 21 d postinoculation, the experiment was terminated. 

Table II

Susceptibility of Inbred Strains of Mice to i.c. Inoculation of SRV *

| Mouse strain | Concentration of virus (MICLD₉₀) |
|--------------|----------------------------------|
|              | 1,000 | 100 | 10 |
|              | survivors/total |
| SJL          | 0/5   | 0/5 | 0/5 |
| CBA          | 0/5   | 0/5 | 0/5 |
| A/WySn       | 0/5   | 0/5 | 0/5 |
| A.SW/Sn      | 0/5   | 0/5 | 0/5 |

* 12-wk-old female mice were inoculated i.c. with various concentrations of SRV. All mice were dead 14 d after inoculation.

Susceptibility of Inbred Strains of Mice to Intracerebral Inoculation of SRV. The experiments described above have shown that strains of mice varied markedly in their susceptibility to i.p. inoculated SRV. This observation raised the question of whether similar results would be obtained if virus were inoculated directly into the target organ. The results presented in Table II show that 1,000, 100, or 10 LD₉₀ of i.c. inoculated virus was lethal for all mice tested. It also was determined that i.c. inoculated virus replicated equally well in brains of mice that differed in their susceptibility to i.p. inoculated virus (Table III). Thus, genetic control of resistance to rabies virus was not apparent when virus was inoculated i.c.

Resistance of SJL and A.SW/Sn Mice to Different SRV Isolates. The data in Table I show a marked variation in the susceptibility of inbred strains of mice to a SRV that had been isolated from a bat. To determine whether these differences in susceptibility were unique to one virus isolate, resistant SJL and susceptible A.SW/Sn mice were inoculated i.p. with one of six different SRV isolates. It is shown in Table IV that all isolates were lethal for A.SW/Sn mice and that none killed SJL mice. Thus, variation in mouse strain susceptibility was not affected by the source of SRV. In contrast, i.p.
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### TABLE III

*Replication of SRV in Brains of SJL and A/WySn Mice after i.c. Inoculation*

| Mouse strain | 24  | 48  | 72  | 96  | 120 |
|--------------|-----|-----|-----|-----|-----|
| SJL          | <0.7, 0.75 | 0.7, 0.7, 0.7 | 1.4, 1.8, 2.5 | 3.6, 4.0, 4.2 | 3.5, 4.0, 4.3 |
| A/WySn       | 0.7, 0.75, 1.0 | 0.75, 1.0, 1.5 | 1.4, 1.5, 1.5 | 2.5, 3.8, 4.3 | 3.3, 4.1, 4.5 |

* 12-wk-old female mice were inoculated i.c. with 1,000 LD₅₀ of SRV. At the indicated intervals, brains were removed and titrated for infectious virus by i.c. inoculation of 21-d-old SW mice. Values represent individual titers of three mice per strain per test interval.

### TABLE IV

*Resistance of SJL and A.SW/Sn Mice to Various SRV Isolates*

| Virus isolated from | MICLD₅₀ | Survivors/total (%) |
|---------------------|--------|---------------------|
| Dog                 | 1.7 × 10⁷ | 0/5 (0) | 5/5 (100) |
| Sheep               | 5.0 × 10⁷ | 1/5 (20) | 5/5 (100) |
| Bat                 | 5.0 × 10⁷ | 0/5 (0) | 5/5 (100) |
| Cat                 | 6.7 × 10⁷ | 1/5 (20) | 5/5 (100) |
| Skunk               | 1.1 × 10⁸ | 0/5 (0) | 5/5 (100) |
| Bat                 | 1.3 × 10⁸ | 0/5 (0) | 5/5 (100) |

* 8- to 15-wk-old female mice were inoculated i.p. with rabies viruses isolated from six different animals. The experiment was terminated 21 d after inoculation.

† Concentration of virus inoculated i.p. as determined by i.c. inoculation of 21-d-old SW mice.

inoculation of 5 × 10⁷ MICLD₅₀ of highly pathogenic laboratory-adapted CVS rabies virus, which has been propagated by serial i.c. passages in laboratory animals and is characterized by a rapidly fatal disease course after i.c. inoculation, produced a markedly different result: all SJL, CBA, A/WySn, and A.SW/Sn mice died (data not shown). Thus, virulence factor(s) of CVS virus overcame the genetic resistance of SJL and CBA mice to i.p. inoculated SRV.

Resistance of F₁ Hybrids and Backcross Mice to SRV. F₁ hybrids produced by crossing resistant strains with moderately and highly susceptible strains of mice were inoculated i.p. with SRV to determine the dominant phenotype. The data presented in Table V show that all female and most male F₁ hybrids produced by 16 different crosses were highly resistant to infection (≥86% survivors). In three instances, however, male hybrids produced from crosses involving DBA/2 mice were ≤60% resistant, whereas females of these same crosses were 100% resistant. It also has been shown that F₁ hybrids produced by crossing resistant mice (SJL × CBA) were 100% resistant, and crosses of susceptible mice (A/WySn × A.SW/Sn) were only 4% resistant (data not shown). These data indicate that resistance was dominant, that gene complementation did not influence resistance of F₁ hybrids produced from susceptible strains, and that if a sex factor was important it was obscured in 97% (724/747) of the F₁ hybrids.

The number of genes controlling susceptibility was determined by inoculating backcross mice produced by mating F₁ hybrids with susceptible parents (Table VI). The data from all four backcrosses indicated one and/or two genes controlled
TABLE V
Resistance of F1 Hybrids to SRV*

| F1 Hybrid (female × male) | Survivors/total |  |
|---------------------------|-----------------|---|
|                           | Female          | Male |
|                            | %               |     |
| (SJL × A/WySn)            | 48/49 (98)      | 59/59 (100) |
| (A/WySn × SJL)            | 18/18 (100)     | 42/42 (100) |
| (SJL × A.SW)              | 31/33 (94)      | 40/41 (96) |
| (A.SW × SJL)              | 6/7 (86)        | 6/7 (86) |
| (CBA × A/WySn)            | 8/8 (100)       | 13/13 (100) |
| (A/WySn × CBA)            | 46/47 (98)      | 52/57 (91) |
| (CBA × A.SW)              | 18/19 (95)      | 16/18 (89) |
| (A.SW × CBA)              | 20/20 (100)     | 22/24 (92) |
| (A/WySn × DBA/2)          | 6/7 (100)       | 6/10 (60) |
| (SJL × C57BL/6)           | 8/8 (100)       | 7/8 (88) |
| (SJL × C57BL/10)          | 31/31 (100)     | 35/35 (100) |
| (C57BL/10 × SJL)          | 43/44 (98)      | 33/34 (97) |
| (B10.A × SJL)             | 14/14 (100)     | 13/13 (100) |
| (B10.A × CBA)             | 25/29 (86)      | 16/17 (94) |
| (B10.A × DBA/2)           | 18/18 (100)     | 2/8 (25) |
| (DBA/2 × C57BL/6)         | 3/3 (100)       | 3/6 (50) |

*8- to 15-wk-old F1 hybrids were inoculated i.p. with 5 × 10^7 MICLDₙ₀ of SRV. The experiment was terminated 21 d after inoculation. Control resistant SJL and susceptible A/WySn mice were included in all experiments.

TABLE VI
Resistance to SRV of Backcross Mice Produced by Mating F1 Hybrids with Susceptible Parents *

| Backcross (female × male) | Survivors/total |  |
|---------------------------|-----------------|---|
|                           | Female          | Male |
|                            | %               |     |
| (A/WySn × SJL)F₁ × A/WySn | 74/128 (59) ‡‡ | 68/121 (56) ‡‡ |
| (A/WySn × (A/WySn × SJL)F₁) | 24/38 (63) ‡§ | 19/33 (58) ‡§ |
| (SJL × A/WySn)F₁ × A/WySn  | 53/95 (56) ‡‡ | 35/83 (42) ‡‡ |
| (SJL × A.SW/Sn)F₁ × A.SW/Sn | 60/75 (80) ‡§ | 40/64 (63) ‡§ |

*8- to 15-wk-old backcross mice were inoculated i.p. with 5 × 10^7 MICLDₙ₀ of SRV. The experiments were terminated 21 d after inoculation. Control resistant SJL and susceptible A/WySn mice were included in all experiments.
‡‡ Results are statistically significant for one gene controlling susceptibility.
§§ Results are statistically significant for one or two genes controlling susceptibility.
†† Results are statistically significant for two genes controlling susceptibility.

susceptibility in both male and female progeny. Interestingly, the percentage of survival appeared to be somewhat greater in female than male mice. The ostensible enhanced resistance of females in these backcrosses may be due to a sex-linked factor that was not apparent until the dominant resistant gene(s) was diluted.

Additional evidence that susceptibility was inherited as one gene in the (A/WySn × SJL)F₁ × A/WySn backcross progeny was shown with F₂ hybrids; 42/52 (80%) of the progeny in an (A/WySn × SJL)F₁ × (A/WySn × SJL)F₁ cross survived (data not
Table VII

| Strain | H-2 | Survivors/total | Recovered survivors/total survivors |
|--------|-----|----------------|-----------------------------------|
| SJL    | s   | 136/136 (100)  | 11/136 (8)                        |
| CBA    | k   | 86/88 (98)     | 21/86 (24)                        |
| DBA/2  | d   | 41/49 (84)     | 28/41 (68)                        |
| BALB/c | d   | 80/102 (78)    | 72/80 (90)                        |

*8- to 15-wk-old male and female mice were inoculated i.p. with $5 \times 10^7$ MICLD_{50} of SRV. 21d postinoculation, the experiment was terminated. Mice that survived after onset of clinical symptoms were judged to have recovered from disease.

Comparison of Clinical Responses in Mouse Strains Resistant to SRV. It is shown in Table VII that two distinctly different clinical responses occurred in resistant mouse strains inoculated i.p. with SRV. Few SJL and CBA mice developed signs of clinical illness such as ruffled fur and spasticity and/or paralysis of the legs. A high percentage of DBA/2 and BALB/c mice did develop these signs, but disease failed to progress and they survived. The severity of paresis in the latter group also was more extensive than that which occasionally occurred in SJL and CBA mice. Even though SRV was isolated from the spinal cord and brain of resistant SJL mice that did not develop signs of illness, they never became unconscious. In contrast, susceptible mice that contained high levels of SRV in brain and spinal cord became unconscious before death (data not shown). These data indicate that the sensory neurons of mice that died were affected, whereas those of the survivors were not.

All survivors tested were resistant to 100 LD_{50} of i.c. inoculated SRV, which killed 100% of control mice of similar age (data not shown). Thus, even though there were no clinical signs of infection of the central nervous system (CNS) in many mice, they had developed resistance to a subsequent lethal i.c. challenge of SRV.

Discussion

In this study of the genetic control of resistance to i.p. inoculated SRV in mice, it was found that (a) there were marked differences in resistance among inbred strains of mice, (b) female mice in two of four resistant strains were more resistant than males, (c) clinical signs with either minimal CNS implications or marked paralysis occurred in resistant strains and were strain specific, (d) resistance was dominant and not controlled solely by the H-2 complex, (e) susceptibility appeared to segregate as one and/or two genes, (f) the difference in strain susceptibility was not dependent on the SRV isolate, and (g) all strains were susceptible to i.c. inoculated SRV.

The evidence for genetic control of resistance was obtained using inbred mouse strains, F1 and F2 hybrids, and progeny produced by backcrossing F1 hybrids to susceptible parents. It appeared that susceptibility segregated as one and/or two genes. These results were dependent on the strain and/or sex of the susceptible parent used to produce backcross progeny. In the two instances in which the susceptible parent was an A/WySn male, one gene controlled susceptibility. If, however, the
susceptible parent was an A.SW or a female A/WySn, one or two genes appeared to control susceptibility. The reason for this variation is unknown and somewhat vexatious. Experiments in progress to explain these differences, wherein second backcross progeny produced from first backcross rabies-resistant males crossed with susceptible females are challenged i.p. with SRV, should confirm if one and/or two genes for susceptibility breed true.

Several examples of the greater resistance of female mice to i.p. inoculated SRV as compared with males were detected in this study. The most obvious illustration was BALB/c and DBA/2 mice and F1 hybrids produced with DBA/2 mice. Also, female backcross progeny consistently were more resistant than their male counterparts. Enhanced resistance to various viral and bacterial pathogens of female as compared with male mice has been well documented (17-22). It also has been shown in immunized outbred Swiss mice challenged i.c. with rabies virus (13). Differences in sex chromosomes and/or sex hormones have been suggested as possible influences in the enhanced resistance of female mice (23). The findings presented herein suggest that another defense mechanism, which is masked in some strains, exists in female mice. In strains such as SJL, this component appeared to be hidden by a more dominant factor, but as dilution occurred with backcrossing, it became apparent. Conversely, in BALB/c and DBA/2 mice, the dominant factor appeared to be weaker and consequently sex-linked differences in resistance were immediately apparent in inbreds and F1 hybrids. Experiments in progress, wherein highly resistant SJL and CBA mice, which show no sex difference in susceptibility, are crossed with resistant BALB/c and DBA/2 mice should help to elucidate this sex-linked factor.

During these experiments, two entirely different clinical responses occurred in resistant mice, depending on whether they were inbreds, F1 or F2 hybrids, or backcross progeny: (a) no or only minimal clinical signs of disease and (b) obvious illness with paralysis. Even though many SJL mice remained asymptomatic with regard to spinal cord infection, i.e., they showed no leg paralysis, preliminary data have shown that SRV was present in their spinal cords and brains 5-7 d after i.p. inoculation. These data indicate that their motor neurons were not involved in the course of infection or that the extent of infection was inadequate to cause motor dysfunction. Why SRV, which invaded the CNS, did not cause signs of disease and why virus was not detected in spinal cords and brains of SJL mice ≥10 d postinoculation is unknown (data not shown). It is conceivable that this is partly due to the resistance of mice that survived after i.p. inoculation of SRV. It is likely that resistance was not associated with SRV replication in the brain in that (a) low concentrations of i.c. inoculated SRV killed susceptible and resistant strains (Table II) and (b) similarly inoculated virus replicated with equal efficiency in brains of mice of different susceptibilities (Table III). Thus, physiological (24), virological (25-28), nonimmune (29-34), or immune (35-42) factors alone or in combination must be considered as mechanisms of resistance. At present, neutralizing antibody appears to be important in that preliminary data have indicated that the first detectable serum-neutralizing antibody titers of mice inoculated i.p. with SRV were threefold higher in SJL and CBA than in A/WySn and A.SW mice. These titers consistently remained 5- to 10-fold higher in resistant mice. Moreover, it recently has been shown that mice which produce high rabies virus serum-neutralizing antibody titers are more resistant to rabies infection than mice that do not (38). The importance of neutralizing antibody in resistance is further
emphasized by our previous studies (5) and by investigations of Wiktor and Koprowski (43) who showed that mice inoculated subcutaneously with hybridoma cells producing anti-rabies antibody were protected against i.c. rabies virus challenge. It also has been noted in this laboratory that passive i.p. transfer of mouse anti-rabies immune serum protected mice against i.c. challenge with 100 ICLD$_{50}$ of SRV (data not shown).

It has been shown for the first time that there is genetic control of resistance to SRV in mice. Resistance was dominant and susceptibility appeared to segregate as one and/or two genes. In some resistant strains, female mice were more resistant than males. Furthermore, resistant strains were identified that usually remained either asymptomatic or, in contrast, developed signs of clinical disease but survived. This model of SRV infection in mice provides promising probes for the investigation of resistance mechanisms, male-female differences in resistance, and survival after onset of clinical disease.

**Summary**

Resistance to intraperitoneally inoculated street rabies virus (SRV) in mice was shown to be under genetic control. SJL/J, CBA/J, DBA/2J, and BALB/cAn mice were resistant, whereas A/WySn/J and A.SW/SnJ mice were susceptible. In addition, female mice of the resistant BALB/cAn and DBA/2J strains were more resistant than their male counterparts. Resistance was not controlled solely by the major histocompatibility locus because susceptible A.SW/SnJ and resistant SJL/J mice have the same $H-2^b$ haplotype. Challenge of F$_1$ hybrids produced by crossing resistant and susceptible strains indicated resistance was dominant (97% survivors). Inoculation of backcross mice produced by mating F$_1$ hybrids with susceptible parents showed that one and/or two genes controlled susceptibility. Furthermore, inoculation of SRV obtained from six different animals indicated that differences in strain susceptibilities were not dependent on the SRV isolate. Genetic control of resistance to SRV was, however, abrogated by intracerebral inoculation of virus. Resistant strains of mice were detected that either remained asymptomatic or, in contrast, developed signs of clinical disease, but disease failed to progress and they survived. The recognition of resistant and susceptible strains of mice, differences in female-male resistance within the same resistant strain, as well as dissimilar clinical responses in different resistant mouse strains to intraperitoneally inoculated SRV provide promising probes for investigation of host resistance and mechanisms for survival after onset of clinical rabies.

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