Effect of Antithymocyte Serum on Herpesvirus Hominis (type 1) Infection in Adult Mice[1] (34290)

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(Introduced by C. C. Shepard)

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Rabbit antimouse thymocyte (RAMT) serum, a potent suppressant of cell-mediated immunity (1), has been shown to affect the course of several viral infections in mice (2). The effect of RAMT serum on herpesvirus hominis (HVH) infection was considered of particular interest since certain clinical conditions associated with defects in the thymus-dependent cellular immune system, such as the Wiskott-Aldrich syndrome (3) may develop severe, even fatal, HVH infections. It was also desirable to ascertain if the effect of RAMT serum would depend on the route of HVH inoculation, since this was an important factor in the case of primary vaccinia infection in mice (4).

Materials and Methods. Virus strain. Earlier studies in adult mice demonstrated that neurovirulence of HVH strains depended on their antigenic type; HVH type 2 is more virulent than HVH type 1 whether inoculated intragenitally, intramuscularly, or intracerebrally (5, 6). Since all 28 HVH strains isolated from the brain or spinal fluid of patients, other than newborns, with herpetic meningoencephalitis and an isolate from a child with the Wiskott-Aldrich syndrome belonged to HVH type 1 (7), it was decided to study first the effect of RAMT serum on HVH type 1 infection in adult mice. The HVH type 1 virus used was the VR_3-Lennette strain, recovered from the brain of a patient with herpetic encephalitis (7). Its titer, as assayed in primary rabbit kidney tissue culture, was 10^7 $TCID_{50}$/ml.

Experimental design. Three to 4-week-old ICR mice were used in all experiments. Preparation and assay of RAMT serum have been described previously (4). Each group of at least 20 mice received intraperitoneal injections of 0.3 ml of either RAMT serum or normal rabbit serum (NRS) on days −6, −3, 0, +3, +6 and a dilution of HVH on day 0. The RAMT serum and NRS were free of anti-HVH activity by neutralization tests. Varying virus dilutions of HVH were inoculated by one of three routes: intracerebral, intraperitoneal, and intragenital. Methods for the last mode of inoculation have been reported earlier, infection being ascertained by recovery of the virus from the genitalia 3 days after inoculation (8).

Results. Groups of mice receiving either NRS or RAMT serum were inoculated intracerebrally with 10^{-4}, 10^{-5}, or 10^{-6} dilutions of HVH. At the 10^{-4} virus dilution, differences in the distribution of deaths within the two groups of 20 mice were significant (Kolmogorov–Smirnov test with $p < .01$). As shown at the top of Fig. 1, the number of days to death of 50% of the mice was 2 days earlier in the NRS group than in the RAMT serum group; by day 14, however, mortality was similar in both groups. At the 10^{-5} virus dilution, 40% of the mice in the NRS group died, but all 20 of the RAMT serum-treated mice survived (significant with $p < .01$). There were no deaths with the 10^{-6} virus dilution in either group.

Differences in mortality among the RAMT and NRS groups of 20 mice each inoculated intraperitoneally with the 10^{-1} virus dilution were not significant. Differences in mortality with the 10^{-2} virus dilution were signifi-

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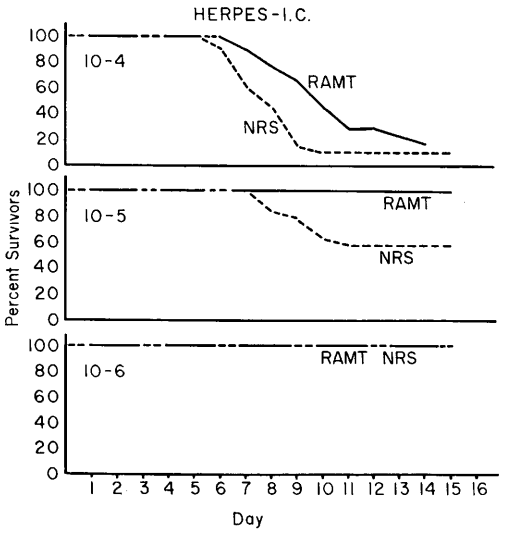

FIG. 1. Effects of rabbit antimouse thymocyte (RAMT) serum and normal rabbit serum (NRS) on *Herpesvirus hominis* (HVH) type 1 infection. Survival curve after intracerebral administration of HVH in doses of 10^{-4} to 10^{-6}.

cant; all 20 of the RAMT-treated mice died, while 10 of 20 of the NRS-treated mice survived (Fig. 2). After intragenital inoculation of undiluted virus (Fig. 3), 73% of 37 mice in the RAMT serum-treated group died, as compared to 33% of 33 mice in the NRS-treated group (significant difference at $p < .01$).

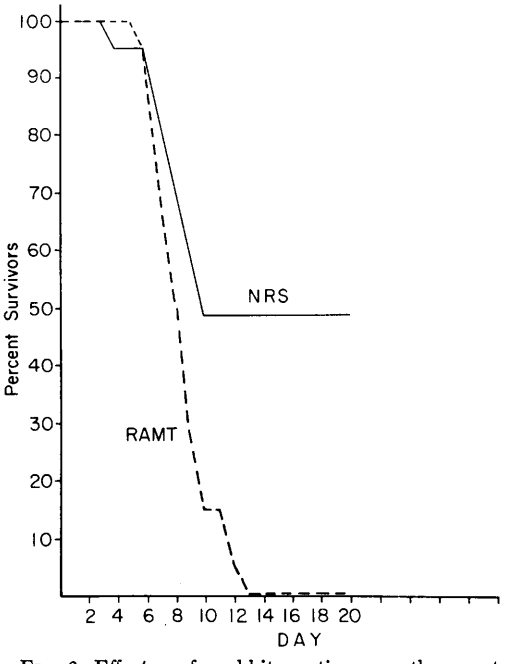

FIG. 2. Effects of rabbit antimouse thymocyte (RAMT) serum and normal rabbit serum (NRS) on *Herpesvirus hominis* (HVH) type 1 infection. Survival curve after intraperitoneal administration of HVH (10^{-2} virus dilution).

Discussion. These results suggest that cell-mediated immune mechanisms play a role in the pathogenesis of HVH infection in mice when the virus is administered intraperitoneally or intragenitally. By both these routes, the virus travels to the brain primarily via the blood (5, 9). When HVH is administered intracerebrally, mortality in the RAMT group was delayed or reduced depending on virus dose. Similar effects of RAMT in mice inoculated intracerebrally with yellow fever and lymphocytic choriomeningitis viruses (10, 11) have been observed, suggesting that inflammatory reactions play a deleterious role in the course of central nervous system infection.

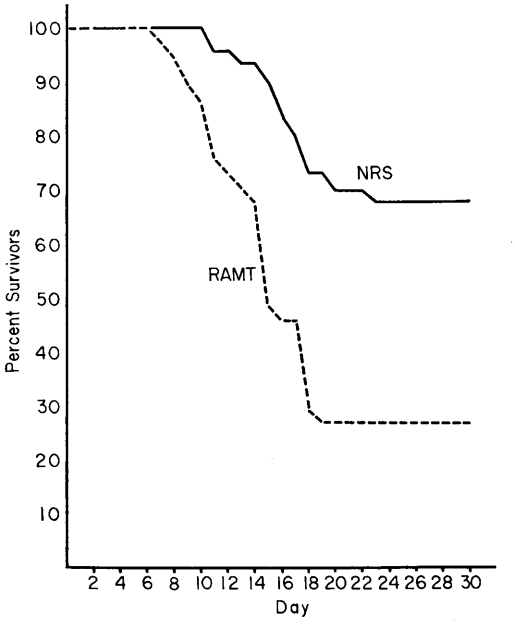

FIG. 3. Effects of rabbit antimouse thymocyte (RAMT) serum and normal rabbit serum (NRS) on *Herpesvirus hominis* (HVH) type 1 infection. Survival curve after intragenital administration of HVH (undiluted virus).

Extension of the model presented here

might provide important clues as to mechanisms for chronic or recurrent infections with HVH. These studies also argue for continued consideration of augmented severity of HVH infections in patients receiving antihuman lymphocyte serum (ALS) therapeutically for immunosuppression. Indeed, fatal HVH pneumonia in cardiac transplant recipients treated with ALS has recently been observed (12).

Also relevant is the finding that neonatally thymectomized mice are more susceptible to HVH infection, although still capable of producing neutralizing antibodies (13).

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