Vesicular Stomatitis Virus Causes Abortion and Neonatal Death in Ferrets

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Vesicular stomatitis virus caused transplacental infection in ferrets, resulting in infant death. No clinically significant illness was observed in the adult, despite histological changes in the uterus, liver, and spleen.

Vesicular stomatitis virus serotype Indiana (VSV) is a large membrane-bounded ribonucleic acid rhabdovirus. It is a natural pathogen of cattle, swine, and horses but can induce experimental infection in many laboratory animals (3, 11). Partially because of the ease with which it can be grown in a large number of vertebrate and invertebrate cell cultures, as well as its usefulness for interferon assays, VSV is used in many laboratories and has infected at least 40 laboratory workers (6). In humans, VSV is reported to cause a self-limited disease characterized by myalgia, fever, and intermittent chills. The entire course of the illness is typically 1 week (2). A similar benign illness is usual for the adults of many other species (10). However, immunological immaturity and possibly other non-immunological host factors have been shown to increase dramatically the central nervous system lesions caused by VSV in mice (5, 8). We now show that infection of a pregnant ferret (Mustela furo) any time during the second half of its 42-day gestation period results in a mild clinical illness of the adult; however, there is infection of the fetus and placenta. This fetal-placental infection results in fetal resorption, abortion, or neonatal death, depending upon the exact time in pregnancy that the adults are infected.

Eleven first-time-pregnant ferrets (Marshall Research Animals, North Rose, N.Y.) were infected with $6.75 \times 10^8$ plaque-forming units of VSV serotype Indiana, originally the gift of Robert M. McCombs then at Baylor College of Medicine (4). The virus was subsequently plaque purified two times in ferret kidney culture. Virus was isolated from ferret tissues homogenized in Hanks balanced salt solution containing 0.01% gentamicin. This material was clarified by centrifugation at $600 \times g$ for 15 min, and the supernatant fluid was assayed on HeLa cell monolayers. After viral adsorption, the monolayers were overlaid with nutrient agarose containing neutral red, 1:60,000. Neutralization titrations were performed by a plaque reduction method, and the 50% neutralization end point was determined by log-linear regression from serial dilutions. Specific fluorescein-labeled rabbit anti-ferret immunoglobulin G was prepared and tested as previously described (7). The specificity of antibodies derived from convalescent ferret serum, used in the indirect immunofluorescent localization of VSV antigen, was confirmed by the absence of fluorescence on control tissues that were either infected with the Long strain of respiratory syncytial virus or uninfected.

Table 1 shows the distribution of recoverable virus and the tissues containing viral specific antigen as determined by indirect immunofluorescence from two animals transplacently infected on day 41 of gestation and found dead about 36 h after birth and 60 h after maternal infection. A portion of the virus present in the organs could be due to circulating VSV; however, this was not tested. Similar fetal infections were obtained when the adults were infected via the intranasal, intramuscular, intracardiac, or intraperitoneal route.

Evidence of adult infection was observed at autopsy in the form of a lympho-plasmacytic infiltrate of the uterus and portal zones of the liver as well as splenic lymphoid hyperplasia. Further indications of infection were serum-neutralizing antibody titers of greater than 1:40,960 in each of four adult animals tested 30 days after infection.

VSV isolated from fetal liver homogenates by inoculating monolayers of embryonic ferret lung cells was plaque purified two times and reintroduced into pregnant ferrets via the intracardiac route. This virus also caused abortion. Virus recovered from aborted animals, as well as the initial stock virus, was verified to be VSV serotype Indiana by neutralization with National Institutes of Health reference mouse hyperimmune ascitic fluid (V-520-701-562).

Demonstration of this new property of VSV forces a reconsideration of the safety of women of childbearing age who work with this agent in the laboratory. Previous studies have shown
that as little as a 2-week period of work in a laboratory using VSV will cause seropositivity in 70% of the workers (1). Other studies have shown that in some areas of Central America up to 94% of the population has antibody to VSV (9). Although there are no data to suggest impaired fertility in populations or laboratory workers exposed to VSV, we feel that an epidemiological investigation of this point would be appropriate.

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LITERATURE CITED