



NEWS RELEASE

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Research Team Develops Nonhuman Primate Model of Smallpox Infection

Scientists have made significant progress in developing an animal model of smallpox that closely resembles human disease, which will be necessary for testing of future vaccines and potential treatments.

The study, published in this week's online early edition of *Proceedings of the National Academy of Sciences*, is the first to demonstrate that variola virus, the causative agent of smallpox, can produce lethal disease in monkeys.

Smallpox, a devastating disease, was eradicated in 1979 through the efforts of the World Health Organization (WHO). Currently, infectious variola is known to exist only in two WHO-sanctioned repositories, one in Russia and the other at the Centers for Disease Control and Prevention (CDC) in Atlanta. However, there is concern that undisclosed reference stocks of the virus may exist, and the U.S. population is no longer routinely immunized against the disease. Due to its potential as an agent of bioterrorism, antiviral drugs and an improved smallpox vaccine are urgently needed.

Because the disease no longer occurs naturally, vaccine and drug candidates cannot be tested for their ability to prevent or treat smallpox in humans. Thus, licensing of future medical countermeasures for smallpox will depend upon animal studies. The U.S. Food and Drug Administration (FDA) has established an animal efficacy rule to facilitate the approval of vaccines and drugs for biological agents in cases where efficacy data in humans cannot be obtained.

In 1999, a study group convened by the U.S. Institute of Medicine recommended that variola research be conducted, and a research plan was approved by the WHO to develop an animal model of the disease. Peter B. Jahrling of the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) led the research team.

Jahrling and his colleagues exposed 36 cynomolgous monkeys to one of two variola strains, Harper and India 7124. Eight animals were challenged by a combination of aerosol plus intravenous inoculation—four with Harper strain and four with India strain. The remaining 24 animals were exposed only by the intravenous route to varying doses of the virus.

Both variola strains produced severe disease, with almost uniform lethality and end-stage lesions resembling the human disease, in monkeys exposed by the combined route of infection. According to the authors, death usually occurred within six days of inoculation. Similar results were seen in monkeys that received the same dose of either virus by the intravenous route alone.

Having demonstrated that it was possible to achieve lethal infection of primates using variola virus, the team next tried to determine whether lower doses of virus would produce a less accelerated disease course. In order to more closely mimic human smallpox, the animal model would include near uniform mortality, but a longer mean time to death. Using a ten-fold lower dose, however, also resulted in lower mortality overall, so further refinement of the model is indicated.

“Despite its limitations,” the authors wrote, “the intravenous variola primate model...has already provided valuable insight into the pathogenesis of this exquisitely adapted human pathogen.” In a related article in the same journal, Rubins and her colleagues examined the host gene expression patterns of hemorrhagic smallpox in these animals. Specifically, they documented fluctuations in cellular proliferation, interferon, and viral modulation of the immune response. A better understanding of the disease process that occurs with smallpox infection will aid in the development of diagnostic and therapeutic approaches.

“Aside from the technical accomplishments, what’s notable about these studies is the collaboration between multiple agencies—including the Department of Defense and the academic sector—to address the issues raised in the 1999 Institute of Medicine report on the need to retain live variola virus,” said co-author James W. LeDuc of the CDC, where the variola research was conducted. “This report has been the basis for the national smallpox research agenda, and these papers are the first significant publications to come from those efforts.”

In addition to Jahrling and LeDuc, the research team included Lisa E. Hensley, John W. Huggins, and Mark J. Martinez of USAMRIID, and Kathleen H. Rubins and David A. Relman of Stanford University.

USAMRIID, located at Fort Detrick, Maryland, is the lead medical research laboratory for the U.S. Biological Defense Research Program, and plays a key role in national defense and in infectious disease research. The Institute’s mission is to conduct basic and applied research on biological threats resulting in medical solutions (such as vaccines, drugs and diagnostics) to protect the warfighter. USAMRIID is a subordinate laboratory of the U.S. Army Medical Research and Materiel Command.

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