Testimony
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The State of West Nile Virus Research at the National Institutes of Health

Statement of

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Mr. Chairman and Members of the Committee, thank you for the opportunity to appear before you today to report on the state of West Nile virus research at the National Institute of Allergy and Infectious Diseases (NIAID). Specifically, I will discuss our current research endeavors to address the diagnosis, prevention, and treatment of this disease, including our efforts to accelerate the development of a West Nile virus vaccine. In addition, I will describe the Institute's future plans to accelerate and expand research on West Nile virus within the context of the overall NIAID research program for emerging and re-emerging infectious diseases.

WHAT IS WEST NILE VIRUS?

I would like to provide a brief description of West Nile virus, how it is transmitted, and its potential effects on the human body. The virus belongs to a group of disease-causing viruses known as flaviviruses, which are carried by ticks and mosquitoes. Other flaviviruses include yellow fever virus, Japanese encephalitis virus, dengue virus, and Saint Louis encephalitis virus. West Nile virus represents an emerging infectious disease in the United States and has been isolated from more than 40 types of mosquitoes, primarily of the genus *Culex*, and from more than 110 species of birds.

West Nile virus is transmitted to humans by infected mosquitoes, which generally acquire the virus while taking a blood meal from an infected bird. Although the entire spectrum of clinical disease in the United States has not been fully documented, data from outbreaks in the United States and elsewhere indicate that most infections in humans (~80%) are asymptomatic. About 20% of infected individuals develop relatively mild symptoms that may include fever, headache, eye pain, nausea/vomiting and body aches, sometimes with skin rash and swollen lymph glands. If the virus crosses the blood-brain barrier, however, it can cause life-threatening encephalitis (inflammation of the brain) or meningitis (inflammation of the lining of the brain and spinal cord). The incubation period for West Nile virus disease ranges from about three to 14 days.

NIAID WEST NILE VIRUS RESEARCH

Because of the outbreaks and subsequent deaths due to West Nile virus infections since the virus was first detected in the United States in the summer of 1999, NIAID has reacted quickly to strengthen and enhance its West Nile virus research portfolio. This effort is part of NIAID's comprehensive emerging infectious disease program, which supports research on bacterial, viral, and other types of disease-causing microbes.

Research is underway at NIAID to develop a vaccine, antiviral medicines, and new diagnostic assays for the West Nile virus. Additionally, basic research is providing new clues about the virus itself, the disease in humans and animals, and how the virus is maintained in the environment. This knowledge is essential for the development of strategies to prevent, treat, and eventually control this disease. While we still have much to learn about the virus, the examples given below demonstrate the breadth and scope of NIAID's ongoing West Nile Virus research program and our commitment to maintaining and ultimately enhancing our role as a major player, in collaboration with the Centers for Disease Control and Prevention and the Food and Drug Administration, in combating this virus.
The major areas of NIAID's West Nile virus research include:

- *Basic research on the virus itself, on the disease in humans, and on its maintenance in nature* -- NIAID supports basic research to better understand the host, pathogen, and environmental factors that influence disease emergence. For example, basic research is helping scientists determine which flavivirus proteins contribute to the virus' ability to cause disease. Researchers also are investigating how protective immune responses are elicited within the central nervous system during acute flavivirus encephalitis. In addition, NIAID supports researchers who are investigating how West Nile virus disseminates throughout the environment. The Institute's International Centers for Infectious Disease Research (ICIDR) program is supporting research in Mexico to study whether migrating bird populations carry the virus from its presumed point of entrance into the Western Hemisphere (New York City) to points in Central and South America. The emergence of West Nile virus in these new areas, which harbor abundant mosquito populations, could provide conditions for a potentially severe epidemic.

  Furthermore, researchers are examining the ecology and persistence of mosquito-borne encephalitis viruses, including the effect of genetic variation on the virus' spread and virulence and how birds might be year-round reservoirs for the viruses that cause encephalomyelitis. In addition, they are comparing the genetics

of St. Louis encephalitis viruses from throughout California and different parts of the United States to determine the rate at which the virus is changing, and whether birds carry it between discrete geographic areas. The Institute also supports research to better understand the insects and ticks that transmit flaviviruses. Such an understanding will allow improved monitoring and surveillance, and enable the development and preliminary testing of strategies to control vectors of the virus.

- *Research to prevent and control spread of the disease* -- Since the first identified case in humans in the United States, NIAID has supported research to develop a candidate vaccine against West Nile virus. This candidate vaccine is constructed using a licensed yellow fever vaccine as a backbone for the insertion of genes of the envelope of West Nile virus and has undergone preclinical evaluations in hamsters, mice, monkeys, and horses. The company that developed the candidate vaccine, Acambis, is moving forward with Phase I trials, which are expected to begin in early 2003. NIAID intramural scientists have developed a West Nile virus vaccine candidate, which they have tested in monkeys with promising results. This vaccine uses an experimental dengue virus vaccine as a backbone. Other approaches include a West Nile virus DNA vaccine and one that uses expressed proteins. In addition, last year a hamster model of West Nile virus was developed, which closely mimics human disease. The animal model will help accelerate the development and testing of new vaccines as well as antiviral therapies in humans.

- *Research to treat the disease* -- NIAID supports research to establish a system to screen chemical compounds for possible antiviral activity against West Nile virus. Promising antiviral drug candidates will be tested in the hamster model. This resource allows scientists to evaluate a drug's safety and efficacy before moving on to possible human trials. Other research projects are investigating emerging diseases and developing candidate drugs to fight West Nile virus. More than 300 drugs have been screened, and several have moved forward for preclinical evaluation. Research on immunotherapeutics (treatments that modify the body's immune response) also is being explored.

- *Research to improve detection and rapid diagnosis* -- Research is underway to allow for more rapid detection of West Nile virus in samples from humans, including organs and tissues intended for transplantation, in other animals, or in vectoring mosquitoes. This research occurs mainly at small biotechnology companies attempting to develop new, commercially available diagnostic assays

Finally, the NIAID maintains the *World Reference Center for Arboviruses* at the University of Texas Medical Branch at Galveston. The Center has reference anti-West Nile virus sera and seed lots of various strains of the virus. This international program involves characterizing viruses transmitted to people and domestic animals by mosquitoes and other arthropods and researching the epidemiology of arboviruses of the United States and overseas. During the last 3 years, these reagents have been provided on request to investigators in the United States and internationally.

RESEARCH OPPORTUNITIES FOR THE FUTURE

The NIAID has identified a number of opportunities for accelerating or expanding research to improve the diagnosis, treatment, and prevention of West Nile virus. These areas include:

Basic Research:

- The development of additional animal models, including primate models, for studies of viral pathogenesis and testing of new vaccines and therapies
- Studies of correlates of immunity in the hamster model
- Immune enhancement of pathogenicity (i.e. effect of prior immunity to other flaviviruses)
- Characterization of severe and milder human disease and delineation of long-term central nervous system complications, including the effect of age on disease severity
- Molecular evolution of the virus
- Comparative virology between disease-causing flaviviruses

Diagnostics:

- Development of diagnostic tools with improved specificity to eliminate cross-reaction with other

flaviviruses

- Development of a single diagnostic test that could be used for multi-species analysis

Prevention:

- Evaluation of components of immune protection
- Characterization of mechanisms of cross-protection between flaviviruses
- Development and preclinical and clinical testing of candidate vaccines

Therapies:

- Design and development of new antiviral medicines
- Development and evaluation of immune-based therapies

Vector/Host/Ecology:

- Molecular epidemiology (especially as virus "evolves" and spreads)
- Basic epidemiology /natural history studies of the virus/host/vector and the establishment of important vector and host components of flavivirus cycling in North America
- Development and testing of new and alternative mosquito control methods
- Definition of viral epizootic/enzootic maintenance mechanisms
- Development and assessment of modern methods to predict emergence and extent of spread of flaviviruses
- Establishment/supplementation of overseas research programs in areas of intense flavivirus activity

FUTURE ACTIVITIES

New NIAID programs, such as the U.S.-based *Collaborations in Emerging Viral and Prion Diseases* and *Partnerships for Development of Novel Therapeutic and Vector-Control Strategies*, will increase research on West Nile virus. Through partnerships with industry, the discovery and development of novel antiviral agents against West Nile virus also will be expanded. Awards for these programs are expected in the early fall of 2002. In addition, many of the programs that have been recently developed and/or expanded to address biodefense in FY 2003, such as the *In Vitro Antiviral Screening Program* and the *Cooperative Research for the Development of Vaccines, Adjuvants, Therapeutics, Immunotherapeutics, and Diagnostics for Biodefense*, will support research on emerging infectious diseases such as West Nile virus.

CONCLUSION

Mr. Chairman, despite our ongoing research efforts and early successes, we still have much learn about West Nile virus. The NIAID will continue to expand its research portfolio to address all aspects of the virus to improve the diagnosis, prevention, and treatment of the disease. I hope that the information that I have provided here today has helped in the understanding of the virus and also has demonstrated NIAID's commitment to address this important public health issue.