# TESTIMONY

**Testimony of**
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To the
Senate Health, Education, Labor, and Pensions Committee
and the
Governmental Affairs Subcommittee on Oversight of Governmental Management, Restructuring and the District of Columbia

The outbreak of West Nile Virus (WNV) infections in the United States has challenged government, medical and veterinary resources. The rapid geographic expansion and persistence of the virus in newly established enzootic areas in North America indicate WNV has become permanently established in the United States (1). Renewed efforts to understand human disease and the biology of the virus will be necessary as we are likely to continue to experience outbreaks of WNV for the foreseeable future.

I have divided my testimony into two areas. I will first address the clinical features of WNV infections in humans including our experience in 2002. I will then turn to the biology of WNV. Here I will describe additional studies of WNV that will be required to address the needs of populations at risk of infection, including domestic and wild animals.

The response of the Centers for Disease Control and Prevention and the Illinois Department of Health have been outstanding. Both federal and state agencies have provided needed information in a timely manner to physicians and other health care providers grappling with patients with WNV. Essential information has been presented on the Internet, allowing easy access to health care providers. In Illinois , we have been able to access up to date information on human and animal infections. CDCP and IDPH sites have offered valuable information for submission of specimens for testing and other essential information needed by health care providers. At Loyola University Medical Center various avenues of communication have been used to provide the latest information on WNV to attending and resident physicians, nurses, and allied health personnel. A “high index of suspicion” for WNV infection has been instituted to assure cases of infection are not overlooked. The Department of Neurology at Loyola University Medical Center has developed protocols to assure WNV infection is considered in the differential diagnosis of patients with neurological syndromes other than meningitis, encephalitis and meningoencephalitis.

Clinically, West Nile Virus infection usually results in an unapparent infection in humans (1). A serological survey for WNV antibodies conducted in New York City in 1999 found that approximately 20% of persons infected with WNV had developed West Nile fever. Most patients who developed symptoms often complain of the sudden onset of fever, malaise, anorexia or loss of appetite, nausea, vomiting, eye pain, headache, muscle pain, skin rash and lymphadenopathy (swollen lymph nodes). The risk of developing serious neurological disease is based on experience in previous WNV outbreaks in

Romania , Israel and New York City . In the Romanian outbreak of 1996, 1 in 140 to 320 infections led to disease of the nervous system. In New York , 1 in 150 infections resulted in neurological disease. The experience in Israel is similar to that seen in New York City . These findings suggest that the WNV strain circulating in the United States and Israel is associated with a higher rate of neurological infections. Meningoencephalitis, encephalitis and meningitis have been the predominant forms of neurological disease associated with WNV infection (2). Profound muscle weakness and muscle pain have been a prominent feature in WNV outbreaks in the United States (3).

Our experience suggests that nervous system infection with WNV during 2002 may have several unusual features. The profound myalgias encountered in New York City in 1999 and subsequent outbreaks in 2000 and 2001 have not been a prominent feature of our cases in 2002. We have also encountered involvement of the optic nerve and basal ganglia more frequently than expected. Whether or not our experience reflects a true change in the clinical features of WNV meningoencephalitis must await more extensive study of the clinical features of cases seen in 2002. If the clinical features of WNV meningoencephalitis are indeed changing, it will be important to recognize these changes as we confront future outbreaks of WNV infection.

Treatment for West Nile Virus infection has been limited to supportive measures to control cerebral edema, seizures, and systemic complications of the infection. Ribavirin in high doses and Interferon-a are effective in vitro (4). Control studies have not yet been completed for either agent. One patient has been treated with intravenous gamma globulin containing high antibody titers to WNV (5). The efficacy of intravenous gamma globulin cannot be determined from this one case.

Hyper immune gamma globulin with high antibody titers to WNV could offer an additional treatment for WNV neurological infections. Antiviral antibody therapy has been shown to be effective in experimental and human virus infections of the central nervous system. Antibody treatment of mice with Sindbis virus infection of the brain results in clearing of virus from neural cells. Humans with hypogammaglobulinemia who develop central nervous system enterovirus infections have been successfully treated with hyper immune gamma globulin. Gamma globulin therapy can be instituted without the long delays required for drug development. Individuals infected with West Nile Virus during the 2002 outbreak are likely to have high titers of antiviral antibodies in the serum. These patients could serve as donors for hyper immune gamma globulin that can then be stored for use in future outbreaks of WNV infection. The genetic stability of WNV suggest antibodies generated during the 2002 outbreak should be effective in neutralizing WNV in outbreaks in the near future.

West Nile virus presents a serious threat to human health for several reasons. Many, including some members of the news media, underestimated the magnitude of the problem at the beginning of the epidemic when only a small number of human cases had appeared. The current 424 human cases and 22 deaths in Illinois illustrate the difficulty in predicting the seriousness of these epidemics.

Experience over the last 4 years suggest that we are likely to see continued outbreaks of WNV infection. The spread of the virus across the United States will likely be followed by new outbreaks of WNV infection in humans and animals. Spread of the virus to Canada , Central and South America by migrating birds will place additional human populations at risk of disease. The WNV strain circulating in the United States appears to have a higher rate of neurological infections than those seen in Romania and other areas of the world. Viral evolution can result in changes in virulence, disease pattern, host cell range, and other properties of the virus. While it is true that viruses transmitted by

insects to mammals are constrained in their ability to mutate, the possibility of changes in the virus are real and require study. Transmission of WNV by unusual means such as blood and organ transplantation are of uncertain significance at the present time. However, since most patients with WNV infection are asymptomatic, these individuals would not provide a history to blood collection agencies that would preclude their donation of blood and blood products. It is important, therefore, to determine the risk of transmission from patients with asymptomatic infection to better assess the risk to the blood supply.

Although much is known about arthropod transmitted virus infections in humans, we also have much to learn. The epidemiology, wildlife enzootic cycles, and the pathogenesis of animal and human disease of WNV are important areas requiring further study. The enzootic cycle of virus circulation is a critical factor in the biology of virus transmission. A rural or sylvatic cycle of wild birds and ornithophilic mosquitoes and an urban cycle with domestic birds and mosquitoes feeding on humans and birds support WNV transmission. Illinois offers an excellent site to study wildlife factors involved in outbreaks of arthropod transmitted neurological diseases. The state has experienced significant outbreaks of both Saint Louis Encephalitis virus and WNV infection. Elucidation of the factors that support these outbreaks in Illinois may provide valuable information that will be applicable in other regions of the country.

The molecular biology of WNV also needs further study (6). The strain of WNV circulating in the United States originated in Israel . It has several unique properties. For instance, high avian mortality has only been encountered in outbreaks of WNV in the United States and Israel . The rate of neurological disease also appears to be higher in urban outbreaks of WNV compared to those in rural areas. The viral properties responsible for these and other features of WNV infection are only beginning to be understood. Continued efforts are needed to define viral factors associated with virulence, host cell range, and the possibility of viral persistence. The evolution of WNV strains in nature may help us understand how viruses “jump” to other species and present new threats to human health. The immune response to WNV infection is also an important area of future study that will be important in attempts to control virus replication in infected patients.

A multidisplinary approach will be needed if we are to understand the challenges of outbreaks of arthropod transmitted infections such as WNV. The Conversation Medicine Center of Chicago is a collaborative effort of Loyola University Medical Center , the Brookfield Zoo, and the University of Illinois that includes physicians, veterinarians, entomologists, field biologists and others. The Center is currently examining areas of research that would benefit from the collaborative expertise of its members. The enzootic cycle for WNV is one important area of interest. Isolation of WNV from squirrels and dogs suggest the virus is spreading to other mammalian species during the 2002 outbreak. Infection of other mammalian species has been noted in past outbreaks. In most species WNV infection does not result in titers of WNV sufficient to serve as a source of infection for mosquitoes or ticks. However, lemurs in Madagascar and several reptile species have been shown to develop virus titers in the blood that are sufficient to infect mosquitoes. Surveys need to be conducted to determine which species have been infected during the 2002 outbreak and if any support virus replication to levels sufficient to infect mosquitoes. If such species are found, the range of mosquito species infected with WNV may increase. Additional studies of WNV infection in mosquitoes, evolution of WNV strains in the laboratory and nature, and the factors associated with spread of infection to incidental hosts are currently being discussed. We are currently finishing a submission to study the pathogenesis of WNV infection in the brain in experimental animals. We believe the multidisplinary approach used by the Conservation Medicine

Center of Chicago and other such groups around the country offer the best opportunity to successfully address the challenges of WNV and other vector borne diseases.

The experience gained meeting the challenges of WNV outbreaks will improve our readiness to successfully address the challenges of bioterroism. Many of the same technological and epidemiological approaches used in the investigation of the WNV outbreak will be helpful in the event we are attacked using similar agents. I would also suggest consideration should be given to reopening surveillance laboratories, such as those supported by the Rockefeller Foundation. These laboratories closed during an era of increased international travel and increased risk of emerging infections, provided vital information for the study and control of insect borne viruses. Reestablishing surveillance laboratories that can warn the emergence of known viruses or new viruses will be invaluable in the future.

In closing, I wish to thank the committees for the opportunity to present my views. I look forward to answering any questions you may have at the hearing on September 24,2002

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