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Influenza virus

Establishing the Link Between Viruses and Parkinson's Disease

Much of the current research on Parkinson's disease is centered on the role that genetic and environmental factors play in its development. A recent study at St. Jude's Children's Research Hospital in Memphis, Tennessee, establishes that certain flu viruses could be an environmental agent leading to neurological diseases such as Parkinson's. Parkinson's disease involves the loss of brain cells crucial to a variety of tasks, including movement, memory and intellectual functioning. The vast majority of Parkinson's disease cases currently have an unknown etiology.

Flu is primarily a respiratory disease, but indirect evidence links it to neurological problems, including a type of brain inflammation known as encephalitis. The association between flu and brain disorders including Parkinson's is controversial, although epidemiology strongly links influenza with an outbreak of encephalitic lethargic following the 1918 Spanish flu pandemic. A substantial number of these patients later developed Parkinson's symptoms.

Researchers at St. Jude found that mice infected with a particular strain of bird flu, the H5N1 avian influenza virus, suffered respiratory symptoms as well as weight loss. In addition, these animals developed neurological damage similar to that which is seen in Parkinson's disease. The influenza virus first infects the lungs, and then quickly infects neurons located in the stomach and intestine. The influenza virus then uses the connections of these neurons to travel into the brain where it first infects a small group of cells in the brain stem and then spreads — over a period of a few days — to infect the midbrain (including the dopaminergic neurons of the substantia nigra) and eventually the neurons in the cerebral cortex. The infection by the influenza neurons is transient and by three weeks there was no evidence of H5N1 in the nervous system. However, despite the

CONTINUED ON PAGE 2

In this issue:

Establishing the Link Between Viruses and Parkinson's Disease 1-2

Participate in a Parkinson's Disease Study. . . 3

Recognizing Caregivers in November 4

Managing Caregiver Fatigue 5

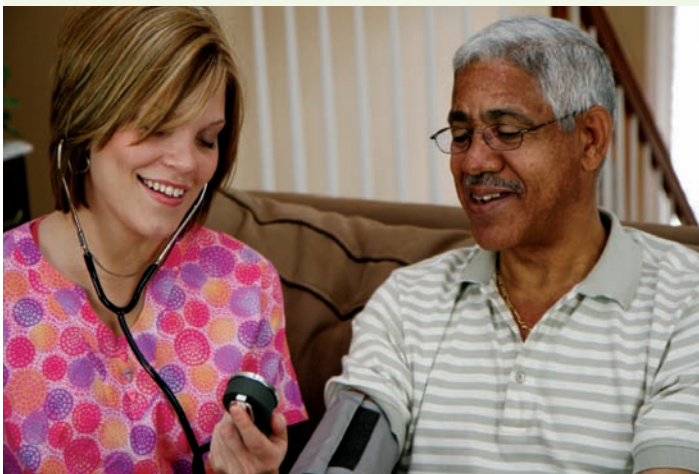
Ask the Doctor. 6-7

MRIs and Deep Brain Stimulation Devices 8

Veterans with Parkinson's Disease 9

Community Connections . . . 10

Support NPF 11



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fact that an active virus was no longer detected, the St. Jude researchers found a continued inflammation within the brain that lasted for months.

Dr. Richard Smeyne

The study didn't suggest that the virus directly causes Parkinson's, but it does strongly suggest that it leaves survivors more susceptible to the disease. "Around age 40, people start to experience a decline in brain cells. Most people die before they lose enough neurons to get Parkinson's. But we believe this H5N1 infection changes the curve. It makes the brain more sensitive to another hit, possibly involving other environmental toxins," said Dr. Richard Smeyne, Associate Member of St. Jude's Developmental Neurobiology Department and lead author of the study. Dr. Smeyne also serves on the National Parkinson Foundation's Clinical and Scientific Advisory Board.

In relation to Parkinson's disease, animals infected with influenza virus had a 17 percent loss of dopamine neurons in the substantia nigra. These are the same neurons lost in persons suffering from Parkinson's. Smeyne also reported that avian flu infection led to over-production of a protein found in the Lewy Bodies contained within brain cells of individuals with both Alzheimer's and Parkinson's diseases.

This research also supports the theory that a hit-and-run mechanism is at work in Parkinson's disease. The investigators believe the H5N1 infection sparks an immune response that persists long after the initial threat is gone, setting patients up for further devastating losses from a second hit, possibly from another infection, drug or environmental toxin. In this case, researchers think the flu virus is the first hit that sets up development of Parkinson's at a later time.

Haeman Jang, a graduate student in the lab of Dr. Smeyne and principal author of the study, said the research is "the first study with very direct experimental evidence that a virus that is in the environment can lead to this pathology. It offers new insight as to how viruses can invade the central nervous system."

Smeyne noted the work involved a single strain of the H5N1 flu virus, the A/Vietnam/1203/04 strain, which was isolated in 2004 from a patient in Vietnam and remains the most virulent of the avian flu viruses. The threat posed by other viruses, including the current H1N1 pandemic flu virus, is still being studied. St. Jude researchers launched this study nearly three years ago in response to the threat posed by avian flu.

"It is important for the public to know that this is a strain of the influenza virus that has never hit the United States, and is not easily transmitted from birds to humans, and therefore we want to be sure people do not panic when they read the news about it. We are hopeful that these findings will help us toward the cause and cure of Parkinson's disease." This point was stressed by Dr. Michael S. Okun, NPF's Medical Director, who also said that "this study is of paramount importance to the field and may help us break through and reach a new understanding of Parkinson's disease. The second hit hypothesis of Smeyne is intriguing and is inherently attractive to scientists in the field."

The findings were initially published in August 2009 in *The Proceedings of the National Academy of Sciences*: "Highly pathogenic H5N1 influenza virus can enter the central nervous system and induce neuroinflammation and neurodegeneration." Other authors in this paper include Robert Webster, David Boltz and Yun Jiao (St. Jude); and Katharine Sturm-Ramirez and Kennie Shephard (formerly of St. Jude). St. Jude conducted the study because it is a World Health Organization Collaborating Center for Studies on the Ecology of Influenza in Animals and Birds.

This work was supported by a grant from the National Parkinson Foundation (NPF), one of the largest private funders of Parkinson's disease research. Each year, NPF, under the direction of our Clinical and Scientific Advisory Board (CSAB), supports cutting-edge research conducted by the world's top neurological experts. NPF funds novel or critical research, led at our 43 Centers of Excellence, offering the promise of improving care for the estimated one million Americans living with the disease.