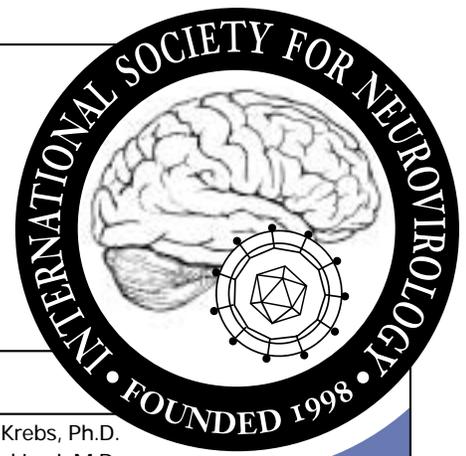


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Neal Nathanson Receives Pioneer in NeuroVirology Award for 2002

John Fazakerley, Ph.D., Edinburgh, Scotland

Neal Nathanson, M.D. has made an impressive contribution to the field of neurovirology and is a distinguished researcher in both viral pathogenesis and epidemiology. Dr. Nathanson is perhaps best known for his work on the epidemiology of polio, the role of immune responses in the neuropathology of experimental lymphocytic choriomeningitis virus infection, the molecular determinants of pathogenesis of the California serogroup bunyaviruses, determination of the neuropathogenesis of maedi-visna virus infection and studies on the neurotropism and neuropathology of HIV. His published work also includes studies on the pathogenesis of Langkat virus, West Nile virus, Eastern equine encephalitis virus, Japanese encephalitis virus, rat parvovirus, dengue virus, Tamiami virus, Tacaribe virus, Semliki Forest virus and rabies virus. This is an impressive list of neurotropic viruses, the range of which few can equal in the future.

His early definitive studies on the epidemiology of polio were followed by studies on the mechanisms of neuropathology, including age-related pathology, the role of immune responses, mechanisms of demyelination and the viral genetic loci determining disease. Additionally, his early studies on LCMV paved the way for other researchers, making work on the pathogenesis of maedi-visna virus all the more significant and valuable with the onset of the AIDS epidemic. His studies resulted in many reviews on these infections. Furthermore, his research on emerging infections and accumulated knowledge on related topics culminated in his definitive textbook 'Viral Pathogenesis'.

Dr. Nathanson studied medicine at Harvard Medical School, completed his internship and residency at the University of Chicago and completed his postdoctoral training at Johns Hopkins University School of Medicine. After a few years at Centers for Disease Control, he returned to

Johns Hopkins as the Head of the Division of Infectious Diseases in the Department of Epidemiology at the School of Hygiene and Public Health. Following his tenure at Hopkins, he devoted many years serving as the Chair of Microbiology at the University of Pennsylvania with a period as Vice Dean for Research and Training. From 1998 to 2000 he was Director of the Office of AIDS Research at the NIH. Currently, he is Vice Provost for Research at the University of Pennsylvania. Dr. Nathanson served as Editor of the *American Journal of Epidemiology*, *Epidemiological Reviews* and *Microbial Pathogenesis* and sat on many editorial boards and committees. He has been actively involved in a number of scientific societies and is a Past-President of the American Epidemiological Society. Over his 40 years in research, Dr. Nathanson mentored many scientists and post-doctoral students, several of whom have contributed greatly to the study of neurovirology and viral pathogenesis.



Neal Nathanson is a learned, distinguished, and esteemed scholar. His contributions to the field of neurovirology are numerous and significant. As an intellectual and visionary, Dr. Nathanson is a well-deserving recipient of the "Pioneer Award in Neurovirology" award.

2002 ISNV Election results

Drs. Peter G.E. Kennedy and Robert S. Fujinami have been elected as the next President and Vice President of the Society. Their terms of office will begin, as officers elect, on January 1, 2003 with three year terms of office commencing January 1, 2004.

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ISNV Highlight: Susan Weiss, Ph.D., University of Pennsylvania School of Medicine, Philadelphia, PA

EHUD LAVI, M.D. • Philadelphia, PA, USA

Dr. Susan Weiss received her undergraduate training in biology at Brandeis University in Waltham, Massachusetts and her Ph.D. at Harvard University, in the laboratory of Michael Bratt. Her Ph.D. thesis was on the messenger RNA and poly(A) of Newcastle disease virus. From 1976 to 1980 Dr. Weiss pursued a post-doctoral fellowship in molecular virology at the University of California in San Francisco with the Nobel Prize laureate Dr. J. Michael Bishop. Her project resulted in a publication in *Cell* on the purification, characterization and cell-free translation of the messenger RNAs of avian sarcoma-leukosis virus. In 1980, Dr. Weiss accepted a position as Assistant Professor in the Department of Microbiology at the University of Pennsylvania School of Medicine, where she rose through the ranks to full Professor in 1992. At the University of Pennsylvania, Dr. Weiss established a laboratory for studies of coronaviruses funded by several NIH grants. In addition, Dr. Weiss serves as co-director of an NIH-funded training program in neurovirology. Dr. Weiss interests are in the molecular biology and pathogenesis of coronavirus mouse hepatitis virus (MHV). MHV is a large RNA virus that

serves as an experimental model system of virus-induced CNS disease, especially demyelination. Initial studies in Dr. Weiss' laboratory included sequencing and characterization of a neurotropic MHV strain A59. Studies of the replicase gene of the virus resulted in better understanding of molecular mechanisms of MHV replication. Later on, the lab characterized the pathogenesis of MHV-A59 in mice and studied the interaction of the virus with cells of the CNS. The lab found that persistent infection of the virus upregulates MHV class I antigens on the surface of astrocytes and oligodendrocytes, cells which normally present very low levels of these molecules. Currently the main focus of the lab is to map the molecular determinants of MHV pathogenesis. The lab used targeted RNA recombination to introduce mutations into the spike gene of MHV and show that this envelope protein contains major determinants of pathogenesis including neurotropism and hepatotropism. Most recently, the lab has shown that background genes as well have a major influence on virulence of MHV in the CNS and the liver. The lab is also investigating the immune response to MHV-A59, and the mechanisms of viral

spread within cells of the CNS.



Recent papers published by Dr. Weiss

Luo Z, Matthews AM, Weiss SR (1999). Amino acid substitutions within the leucine zipper domain of the murine coronavirus spike protein cause defects in oligomerization and the ability to induce cell-to-cell fusion. *J Virol* **73**: 8152-9.

Phillips JJ, Chua MM, Lavi E, Weiss SR (1999). Pathogenesis of chimeric MHV4/MHV-A59 recombinant viruses: the murine coronavirus spike protein is a major determinant of neurovirulence. *J Virol* **73**: 7752-60.

Pinon JD, Teng H, Weiss SR (1999). Further requirements for cleavage by the murine coronavirus 3C-like proteinase: identification of a cleavage site within ORF1b. *Virology* **263**: 471-84.

Teng H, Pinon JD, Weiss SR (1999). Expression of murine coronavirus recombinant papain-like proteinase: efficient cleavage is dependent on the lengths of both the substrate and the proteinase polypeptides. *J Virol* **73**: 2658-66.

Phillips JJ, Chua M, Seo SH, Weiss SR (2001). Multiple regions of the murine coronavirus spike glycoprotein influence neurovirulence. *J Neurovirology* **7**: 421-31.

Phillips, J.J., Chua, M.M., Rall, G.F., Weiss, S.R. (2002). Murine coronavirus spike glycoprotein mediates degree of viral spread, inflammation and virus-induced immunopathology in the central nervous system. *Virology*, in press.

ISNV Highlight: Dr. Johnny He, Ph.D., Indiana University School of Medicine

WALTER J. ATWOOD, Ph.D. • Providence, RI



Dr. Johnny He received his undergraduate training in biochemistry at Sichuan University in Chengdu, China and his Ph.D. in the laboratory of Dr. Phillip Furmanski at New York University. His

Ph.D. thesis led to an important paper published in *Nature* on the functional consequences of lactoferrin binding to DNA. Dr. He then pursued post-doctoral work in molecular virology at the Aaron Diamond Research Center under the guidance of Dr. Ned Landau and later at

Harvard University under the guidance of Dr. Dana Gabuzda. His contributions during this time include important studies on the mechanism of Vpr induced G2 cell cycle arrest and the characterization of CCR3 and CCR5 as critical co-receptors for HIV-1 infection of microglia. In 1997 Dr. He accepted a position as Assistant Professor in the Department of Microbiology and Immunology at Indiana University School of Medicine. He also holds joint appointments in the Department of Medicine and in the Walther Oncology Center. Since moving to Indiana, Dr. He has established an active and well funded Neurovirology laboratory. His long term goals are to

understand the molecular mechanisms of HIV-1 infection and pathogenesis in the central nervous system. His laboratory is focused on defining the role that HIV-1 proteins, such as Tat, play in HIV-1 induced neuropathology. Dr. He and his colleagues have found that Tat binds to the low density lipoprotein receptor related protein (LRP) which promotes Tat uptake into neurons and subsequent translocation to the nucleus. They hypothesize that HIV-1 induced neuropathology is mediated by the ability of Tat to both activate neuronal genes and to antagonize LRP mediated physiological signals. To further test their hypothesis they have

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VZV Infection of the CNS: Vasculopathy, not Encephalitis

Donald H. Gilden, MD, Professor and Chairman, Department of Neurology, University of Colorado Health Sciences Center

One of the major contributions to the field of neurovirology made by Dr. Neal Nathanson, whose pioneering work is being honored this week, is his experimental research which recognized that a wide diversity of pathological lesions produced by acute virus infection of the nervous system depends upon whether infection is most prominent in neurons, glia, endothelial cells, leptomeninges, ependyma or blood vessels. Research has now shown that when varicella zoster virus (VZV), a neurotropic human herpesvirus, infects the CNS, primary disease is not a frank VZV encephalitis, but rather a vasculopathy that affects either large or small cerebral arteries and sometimes both. VZV large artery disease (also known as granulomatous arteritis) predominates in elderly immunocompetent adults and is characterized by acute focal deficit that develops weeks to months after contralateral trigeminal-distribution zoster (shingles), rarely without a history of zoster. Vasculopathy is usually restricted to 1-3 large arteries in the anterior circulation (mostly the carotid, anterior and middle cerebral arteries). Cases of clinically unifocal large-vessel vasculopathy have also been described in children with varicella (chickenpox), thus making VZV one cause of acute infantile hemiplegia. Pathological analysis of affected arteries of clinically unifocal vasculopathy after zoster or varicella reveals multinucleated giant cells, Cowdry A inclusion bodies and herpesvirus particles (hallmarks of human herpesvirus infection) as well as VZV



Fig. 1. Immunohistochemical analysis of cerebral artery from a patient with VZV vasculopathy. Note red staining VZV antigen after incubation of artery with rabbit antiserum against the VZV ORF 63 protein. x86.

DNA and antigen (Fig. 1) in affected vessels.

VZV infection of smaller cerebral blood vessels produces a syndrome of headache, fever, mental status changes and multifocal deficit, evident on neurological examination and by brain MRI imaging (Fig. 2), and a CSF mononuclear pleocytosis. Such small-vessel infection occurs most often (although not exclu-

sively) in immunocompromised individuals with zoster.

Most patients have AIDS or are immunosuppressed after organ transplantation or chemotherapy for cancer. At the University of Colorado Health Sciences Center,

VZV multifocal vasculopathy is the most common complication of zoster involving the brain. Disease is frequently chronic and may develop without zoster rash. Both ischemic and hemorrhagic infarcts are found in cortical, subcortical gray and white matter.

Although large-vessel disease develops after zoster or varicella, and small-vessel disease occurs after zoster, cases of small-vessel disease after varicella are less frequent and have not been adequately recognized. For example, in a neuropathological analysis of 32 fatal cases of varicella which excluded cases of Reye's syndrome (acute encephalopathy with fatty degeneration of the liver), intranuclear inclusions were restricted to areas

of previous necrosis, leading the investigators to comment that direct viral invasion was contiguous to areas where cerebral blood vessels or the blood-brain barrier were impaired, although the notion of a primary vasculopathy was not mentioned. Further, in a recent clinical study of four children with varicella who developed serious neurological disease, CT and MRI revealed bilateral basal ganglionic infarction in all brains. Recognition of VZV multifocal vasculopathy in varicella is strengthened by the detection of antibody to VZV in CSF, even in the absence of amplifiable VZV DNA in CSF. Essentially, both large unifocal and small multifocal vasculopathy can occur after either zoster or varicella.

The question arises whether primary VZV encephalitis exists at all, and earlier reports of clinical cases of encephalitis associated with varicella and zoster provide no definitive answer. MRI, which allows antemortem diagnosis of the focal nature of VZV vasculopathy, had not yet been developed, and none of the reports detailed histopathological findings.



Fig. 2. VZV multifocal vasculopathy. Proton-density brain MRI scan shows multiple areas of infarction in both hemispheres, particularly involving white matter and extending to gray-white matter junctions.

Furthermore, microscopic findings in one of the first cases of VZV "encephalomyelitis" that developed in a boy with leukemia in which VZV was isolated from brain revealed multiple areas of acute necrotic infarction, and four later cases of fatal VZV multifocal leukoencephalitis revealed multifocal abnormalities both on brain imaging and at autopsy, characteristic of multifocal VZV vasculopathy. In some instances, virus was

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Polyomaviruses and Human Diseases Basic and Clinical Perspectives

Human Polyomaviruses in the
Spotlight Pozzolatico, Florence, Italy
May 8-10, 2003

Pasquale Ferrante, MD, Milan, Italy
Kamel Khalili, Ph.D., Philadelphia, PA, USA

Polyomaviruses have received special attention due to their direct involvement in various human diseases, particularly neurological disorders, and their association with various cancers such as brain tumors and others. Rapid advance in the study of human polyomaviruses requires direct cross-communication between basic scientists who are involved in studying molecular biology and virology and this group of viruses, and clinicians who participate in diagnosis and treatment of virus-induced diseases.

The International Conference on Polyomaviruses and Human Disease: Basic and Clinical Perspectives provides a unique forum for reporting the latest discoveries related to basic and clinical

aspects of the polyomavirus-induced diseases and facilitates exchange of information required for the development of effective therapeutic strategies against virus replication and progression of the diseases. The two and a half day conference will cover three major polyomaviruses: JCV, BKV, and SV40, with more than forty oral presentations on molecular pathogenesis, genetics, epidemiology, pathology, diagnosis and treatment.

The symposium will offer the opportunity to discuss and clarify the role of polyomaviruses in a broad group of human diseases including tumors, as well as neurological illness such as progressive multifocal leukoencephalopathy, multiple sclerosis and human transplants.

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also found in cerebral parenchyma; however, in protracted cases, it is not surprising that virus spreads beyond cerebral vessels (the primary site of pathology) to brain parenchyma. Essentially, earlier reports of "VZV encephalitis," "VZV leukoencephalitis," and "post-varicella encephalitis" did not recognize the primary nature of the vasculopathy.

As the nomenclature of clinical unifocal and multifocal VZV vasculopathy becomes appreciated, it is important to recognize that syndromes of large- and small-vessel vasculopathy are not always distinct. Both may be involved and produce waxing and waning neurological symptoms and signs. In the future, it would be preferable to use the term "VZV multifocal vasculopathy" rather than "VZV encephalitis." Eliminating the term "VZV encephalitis" is justified because the symptoms and signs seen clinically and on brain imaging indicate a vasculopathy rather than an encephalitis. Immediate recognition by clinicians of a unifocal or multifocal vasculopathy after zoster or varicella should lead to improved diagnosis and rapid treatment.

Symposium in Honor of Volker ter Meulen

Brian Wigdahl, Ph.D., Hershey, PA, USA

An International Symposium on Viral Pathogenesis and Immune Control to celebrate the career of Dr. Volker ter Meulen was held at the Institute of Pharmacology and Toxicology of the University of Würzburg. The Symposium was organized by Sibylle Schneider-Schaulies and Thomas Hünig and reviewed recent insights into the molecular biology of viruses, virulence determinants, and viral interactions with cellular targets. Viral pathogenesis within the central nervous system (CNS) and strategies of the immune system to control and combat viral infections were also focal points for discussion. Presentations and discussion also centered on viral mechanisms employed to escape immune recognition. Dr. ter Meulen's contributions to the field of neurovirology spanned a period of more than thirty years and his seminal findings have greatly contributed to our current understanding of viral persistence and pathogenesis in the CNS. Dr. ter Meulen's studies on measles virus infection in the CNS have contributed greatly to our knowledge of how viruses are able to escape the immune response. Dr. ter Meulen received his M.D. from the University of Göttingen in 1960 and during a long and outstanding career at the University of Würzburg published more than 400 scientific articles in leading international journals. Dr. ter Meulen has received many awards including the Max Planck Research Prize and the 2000 Pioneer in NeuroVirology. Dr. ter Meulen's research and training career have had significant impact on the discipline of neurovirology.

ISNV Highlight from page 2 (Dr. He)

developed a unique doxycycline-regulated and brain-targeted Tat transgenic mouse model. This model should provide a wealth of important data regarding the mechanisms of Tat induced neuropathology associated with HIV-1 infection of the CNS. In addition, Dr. He is actively involved in characterizing interactions between HIV-1 and astrocytes both at the level of virus-host cell receptor interactions and at the level of Rev-mediated regulation of gene expression.

Recent papers published by Dr. He

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Li, J., Liu, Y., Park, I.W., and He, J. (2002) Expression of exogenous Sam68, the 68 kDa Src-associated protein in mitosis, is able to alleviate impaired Rev function in astrocytes. *Journal of Virology* 76:4526-4535.

Liu, Y., Li, J., Kim B.O., Pace B.S., and He, J. (2002) HIV-1 Tat protein-mediated transactivation of the HIV-1 LTR promoter is potentiated by a novel nuclear Tat-interacting protein of 110 kDa, Tip110. *Journal of Biological Chemistry* (In press, July 1 issue).