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Guest editorial

Neurovirology: evolution of a new discipline

Neurovirology has evolved as an interdisciplinary field incorporating aspects of virology, clinical and basic neurosciences, immunology, and molecular biology. Although the field relates primarily to the study of viral infections of the nervous system, it also includes the use of viruses as tracers of neuroanatomical pathways, as vectors for gene therapy, and as tools to delete specific neural cell populations in studies of developmental anatomy and neuropharmacology. As a distinct field, neurovirology has been identified only during the last 30 years (see Appendix). Clinical observations of rabies and its mode of transmission and the clinical pathological descriptions of poliomyelitis date back many years, but the origins of experimental virology lie in pathology. Ernest Goodpasture in the 1920s performed the first systematic studies to unravel the routes of viral invasion of nervous system infections by sacrificing experimental animals during the asymptomatic incubation period and examining them for sequential pathological changes (Goodpasture, 1929). These remarkable studies showed the spread of herpes viruses along sensory and motor nerves, and these pathological studies have largely been validated with subsequent, more sophisticated methods. Goodpasture also had the good fortune that, unlike rabies and polioviruses, herpesviruses cause striking extraneural histological changes and characteristic inclusion bodies that serve as footprints of the infection.

Animal virology extended beyond pathology with the widespread introduction of cell culture methods in the 1950s. Cell cultures in diagnostic virology showed that diseases such as encephalitis and meningitis were due to a panoply of different newly isolated viruses, primarily enteric viruses. Cell cultures also provided a better means of quantitation, so that growth of virus in tissues without histopathological changes could be accurately measured. The introduction of immunocytochemistry allowed tracing of infection to the cellular level. Initial studies of experimental animal infections with fluorescent antibodies showed the differences in pathogenesis with varied strains of virus, routes of inoculation, species of host, host age, or immunosuppression (Johnson and Mims, 1968). Studies of pathogenesis at a cellular level were subsequently improved with introduction of enzymatic immunocytochemical methods and with the localization of viral RNA and DNA by *in situ* hybridization, or, most recently, with *in situ* polymerase chain reaction on histological sections.

A more sophisticated level of immunology was added to neurovirology by the work of Mike Oldstone and his colleagues (Oldstone and Rall, 1993). The role of humoral and cellular immune responses in the clearance or failure of clearance of viral infections within the nervous system and the potential of immune responses to cause neurological diseases complicating viral infections have become areas of major interest. Pathogenesis was pursued to a molecular level by the work of Bernie Fields and collaborators (Fields, 1992). Using recombinants of multisegmented reoviruses they related specific structural proteins to neurovirulence, neurotropism, and neuroinvasiveness. Pathogenesis at a molecular level now has been further extended by other investigators with other viruses to show that single amino acid substitutions in specific proteins may alter neuropathogenesis.

A new area of interest rather abruptly appeared in the mid 1960s. Chronic neurological diseases without signs of inflammation were associated with infections by both conventional viruses and unconventional spongiform encephalopathy agents now referred to as prions (Prusiner, 1982). In 1966 kuru was transmitted (Gajdusek *et al*, 1966), and in 1968 Creutzfeldt-Jakob disease was transmitted (Gibbs *et al*, 1968). In 1969 measles virus was recovered from brains of patients with subacute sclerosing panencephalitis (Horta-Barbosa *et al*, 1969), and in 1971 JC virus was recovered from patients with progressive multifocal leukoencephalopathy (Padgett *et al*, 1971). Within 5 years viruses or virus-like agents were associated with four neurological diseases; there was a great optimism that diseases of major public health concern such as multiple sclerosis, Parkinson's disease, amyotrophic lateral sclerosis, Alzheimer's disease, and even schizophrenia would soon follow. These hopes have not materialized, although studies continue. Much more knowledge about the pathogenesis of these slow infections and about the nature of prions has accrued, but only progressive rubella panencephalitis has been added to the list of slow infections with previously known agents (Townsend *et al*, 1975).

In the last decade an even more dramatic and unexpected event has dominated neurovirology — emergence of the human immunodeficiency virus (HIV) with its associated neurological diseases. In initial years after the original description of acquired immunodeficiency syndrome (AIDS), neurological interest was limited to unusual opportunistic infections such as toxoplasmosis, cryptococcosis, and progressive multifocal leukoencephalopathy and the high rate of cerebral lym-

phomas. In 1985 this perspective changed with the recovery of virus from brain, cerebrospinal fluid, and peripheral nerve of patients with neurological disease (Levy *et al*, 1985; Ho *et al*, 1985), with the demonstration of HIV RNA and DNA in brain (Shaw *et al*, 1985), and with the documentation of intrathecal synthesis of anti-HIV antibodies in many patients (Resnick *et al*, 1985). Subsequent recognition that HIV invades the nervous system early in the majority of infected persons combined with the extraordinary spread of the epidemic has made HIV the most prevalent central nervous system infection in the world. The variety of clinical syndromes related to HIV infection involving both the central and peripheral nervous system is also quite extraordinary. They occur at all times during the infection from seroconversion to terminal AIDS and show a spectrum of pathological features including inflammatory, demyelinating and degenerative processes (Johnson *et al*, 1988). A few years ago some were incredulous that measles virus could produce three distinctly different diseases of the nervous system with different modes of pathogenesis, ie postinfectious encephalomyelitis, an autoimmune disease; inclusion body encephalitis with direct brain infection in immunodeficient patients; and subacute sclerosing panencephalitis with defective infection in the rare, otherwise normal child. Now we have a virus which has been associated with a dozen different clinical syndromes, and the story continues to unfold. Furthermore, the correlation of clinical and pathological disease to cellular localization of infection has raised intriguing questions. The preponderance of nervous system cells infected by HIV are macrophages and microglia and there is no evidence that the neurons that are decreased in number and have attenuated processes are directly infected. These findings have led to interesting new concepts in pathogenesis with disease mediated by virus proteins, cytokines, or other toxins possibly related to the infection of distant cells.

Neurovirology now is recognized as a discipline with a growing cadre of investigators and a unique body of knowledge. It now has its own journal as a statement of that stature. It is also a field that has expanded rapidly and will continue to grow. Growth is assured by the nature of viruses with their explosive replication and high mutational rates and by the changes in society with burgeoning human populations and jet speed mobility that enhance the opportunities for viruses to evolve, to be maintained among humans, and to spread worldwide. New viruses and viral infections will emerge. HIV is unique only in scope; in recent years we have seen the appearance of California encephalitis in the mid-west, massive epidemics of hemorrhagic conjunctivitis with a polio-like syndrome through Africa and Asia, and the emergence of new arenaviruses with agricultural encroachment on rodent habitats (Johnson, 1994). Within my 38 years in the field, I have seen scores of new viruses related to acute neurological diseases, the spectrum of disease related to viruses expand, and a new agent appear causing unprecedented numbers of infections with new syndromes and novel questions of pathogenesis. The evolution of neurovirology has been fast and fascinating; its future, to be chronicalled in this journal, should prove even more exciting.

Appendix

To my knowledge the term neurovirology was first coined in 1961 by Elizabeth Hartmann, the Director for Training Programs at the National Institute of Neurological Diseases and Blindness and a friend and mentor of trainees. In a Special Fellowship application which I titled 'The pathogenesis of viral infections of the nervous system' (which exceeded the 42 letter space limit) she 'whited-out' the title and typed in 'Neurovirology.' When I protested that no such word existed, Betsy replied with a laugh, 'If we have neuroanatomy, neurophysiology and neurochemistry, why not neurovirology?'

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